COVID-19 AND WOMEN'S HEALTH,
2nd Edition

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COVID-19 AND WOMEN'S HEALTH, 2nd Edition

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Table of Contents

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EDITORIAL
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Editorial: COVID-19 and Women's Health

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Editorial on the Research Topic

COVID-19 and Women's Health

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INTRODUCTION

The SARS-CoV-2 virus that causes COVID-19 emerged in Wuhan, China, in November 2019. Cases were officially recognized in December 2019 and, by February 2020, the virus had spread internationally. On 11 March 2020, the World Health Organization declared the outbreak a global pandemic.

COVID-19 has had a profoundly negative impact globally on physical and mental health, health care, and social functioning, across all age groups and medical conditions, although women may have been disproportionately affected.

What seemed initially to require a brief period of global lockdown, with at worst a return to the delivery of normal health services by autumn 2020, has resulted worldwide in ongoing restrictions in social activity and travel despite successful international vaccination programmes and infectious disease tracking and tracing.

Our Research Topic was launched on 5 May 2020 with a planned close on 8 September 2020, which was extended until 31 December 2020 due to a high number of submissions. These reflect people's experiences and associated health outcomes during the first and second waves of COVID-19.

OUTLINE OF CONTRIBUTIONS

Our Research Topic attracted keen interest from potential contributors worldwide. We accepted 39 manuscripts from the Americas ($N = 18$), Australasia ($N = 2$), Europe ($N = 12$), Africa ($N = 2$), and Asia ($N = 5$), covering a broad range of methodologies: a brief research report ($N = 1$), case reports/studies ($N = 2$), mini-reviews ($N = 5$), opinions ($N = 6$), original research ($N = 12$), perspectives ($N = 5$), reviews ($N = 5$), and systematic reviews ($N = 3$). Most of the manuscripts were in the fields of maternal health ($N = 18$) or maternal mental health ($N = 14$). Our comments below focus on the five top-viewed and downloaded papers we published.

By September 2020, a rapid narrative review by Mittal and Singh was published concerning gender-based violence during both current and prior pandemics (200,486 views, 7,699 downloads). Authors focused on the first wave of the pandemic and use of the quarantine as the primary measure to reduce disease spread, before the emergence of an effective vaccine. There was an alarming rise in gender-based violence, with risk factors including economic insecurity and alcohol consumption. Many services remained inadequate, as they had been pre-pandemic, and importantly, women remained both more disconnected from those services and from their prior support networks. A sobering aspect to this review was the observation that all of this has been observed before, as disruption of social norms tends to increase violence and gender-based violence, specifically. Interestingly, the overwhelming majority of people who viewed this paper reside in South Africa.

Davenport et al. (95,203 views, 8,288 downloads) undertook a rapid online survey via social media platforms of 900 pregnant or postpartum women in the earliest stages of the pandemic (i.e., April and May 2020), focusing on mental health and physical activity. Most women were from Canada, White, married, living in a single-family home, and had some post-secondary education. The authors documented a substantial increase in self-reported depression and anxiety, compared with pre-pandemic levels, recorded by validated screening questionnaires of depression/depressive symptoms. While two-thirds of women reduced their physical activity, 15% increased it, and those engaging in at least 150 mins per week of moderate-intensity physical activity, consistent with current physical activity guidelines, had significantly lower depression and anxiety scores—a potentially empowering message.

In their review, Thibaut and van Wijngaarden-Cremers (32,113 views, 5,458 downloads) showed that the pandemic was affecting the mental health of women more profoundly than men, as frontline workers, especially in the health and social sector, and as the primary care-givers in the home. There were echoes of financial challenges (including a higher likelihood of extreme poverty for young women) and mental health problems growing, as highlighted by the earlier published work of these authors and others. Importantly, the opportunity for positive change was emphasized, recognizing the major role of women at home and in the workplace; we were reminded of the example of the post-World War II era in which gender equality improved at home and in the workplace, and society became more resilient.[1]

When the pandemic first emerged, there was concern that pregnant women would be more susceptible to SARS-CoV-2 infection, as they had been with other coronavirus outbreaks, i.e., Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Although by February 2021, this was no longer thought to be the case, it was clear that when infected, pregnant women were more likely to develop severe disease and pregnancy complications (particularly preterm birth), especially in the third trimester. The Vale et al. review (18,777 views, 902 downloads) explored why this is the case. In brief, pregnancy is associated with physiological changes in the respiratory system—notably, vascular congestion and oedema of the upper respiratory tract, and a reduced expiratory reserve volume due to a raised diaphragm. Also, pregnancy is associated with immune adaptations, required to tolerate the fetus' paternal antigens, whilst preserving an adequate immune response against invading microorganisms. Of note, there is a natural increase in pro-inflammatory mediators in the first and third trimesters, that may augment the "cytokine storm" associated with COVID-19, leading to more severe disease. More changes during pregnancy that make pregnant women more susceptible to SARS-Cov-2 infection, in addition to an increased risk of developing more severe disease, are presented in this review.

While COVID-19 is clearly associated with more pregnancy complications, it is also clear that the pandemic itself has disrupted maternity services for all pregnant women, whether infected or not. This was highlighted by Oluoch-Aridi et al. (9,399 views, 1,338 downloads) through qualitative interviews in our fifth most viewed and downloaded publication. While the setting was informal settlements in Nairobi, Kenya, the messages are widely applicable to other health care settings. There was evidence that fear of infection was a barrier to care-seeking, but so was financial hardship a barrier to transportation. There were some improvements in quality of care, particularly outpatient care, in terms of shorter waiting times, as well as better hygiene measures and more responsive health personnel. However, the prohibition of friends and family accompanying women to health facilities was described as disrespectful, a breach of ethical guidelines, and a frank violation of human rights.

CONCLUDING REMARKS

Our Research Topic attracted a broad range of manuscripts from researchers across the globe, with more than half of studies focussed on women's health in general (rather than pregnancy/postpartum specifically), and as much interest in the indirect consequences of the pandemic as in the direct implications of SARS-CoV-2 infection itself. This represents a broad collection of global perspectives. The topic dovetails with two others. First, is the "Vaccination in pregnancy" topic that loses for submission of abstracts on 20 January 2022, and to full manuscripts on 31 January 2022 (https://www.frontiersin.org/research-topics/25767/vaccination-in-pregnancy). Second, is "SDG5 in a Post-COVID World -Achieving Gender Equity in Health," that closes for submission of abstracts on 08 February 2022, and to full manuscripts on 09 April 2022 (link to be added w/c Jan 31st). (https://www.frontiersin.org/research-topics/32121/sdg5-in-a-post-covid-world-achieving-gender-equity-in-health).

AUTHOR CONTRIBUTIONS

SK and LM outlined the general structure of the editorial. LM wrote the initial draft. All authors contributed to the article and approved the submitted version.

[1] https://www.theguardian.com/lifeandstyle/2018/feb/03/1940s-britains-wartime-women-gained-a-new-sense-of-power

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OPINION
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Mild and Asymptomatic Covid-19 Infections: Implications for Maternal, Fetal, and Reproductive Health

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INTRODUCTION

As of May 2020, more than five million people worldwide tested positive for SARS-CoV-2, among which around 80% display mild or no symptoms (1). There are currently around 4 million people worldwide in this category. According to these and other statistics, asymptomatic and mildly symptomatic infected pregnant women outnumber those infected women requiring hospitalization. For example, in a report from New York City about 43 pregnant women who tested positive for SARS-CoV-2 over the course of a 2 week period in March, 2020, the authors found that 86% of COVID-19 pregnant patients presented with mild or no viral-associated symptoms (2). Reports from China and Europe corroborate that asymptomatic and mildly symptomatic infected pregnant women outnumber those with severe symptoms. Current studies, however, focus on severe cases that required hospitalizations. These studies examine maternal and perinatal death rates, vertical transmission from mother to fetus, and obstetric and neonatal outcomes (3–7). There remains a gap in knowledge of the impact of the infection in a majority of asymptomatic or mildly symptomatic women. A recent review reported a high rate of elective preterm cesarean delivery (8). Maternal and fetal health throughout the trimesters should be examined carefully regardless of severity of symptoms. More evidence is required to guide obstetric practices.

Hoffmann et al. elucidated the mechanism of host cell entry of SARS-CoV-2. They determined that angiotensin converting enzyme 2 (ACE2) is the receptor that allows the binding of SARS-CoV-2 spike proteins and, through this binding process, enters host cells (9). The importance of ACE2 in SARS-CoV infection was established in the early 2000s. Li et al. first isolated the protein in SARS-CoV permissive cells and showed that ACE-2 antibodies blocked viral replication (10). A year later, a research group showed the correlation between susceptibility to SARS-CoV infection and the level of expression of ACE2 *in vitro* (11). The study supports the hypothesis that a higher expression of ACE2 leads to higher risk of SARS-CoV-2 infection. Furthermore, studies have shown that SARS-CoV infections downregulate ACE2 expression and promotes more severe disease progression (12–14). ACE2 is expressed in many organs including lung, stomach, kidney, heart, brain, and reproductive tissues (15, 16). Theoretically, once the virus establishes its primary infection through the respiratory system, it can spread to any other organs expressing ACE2 through the bloodstream and downregulate the local expression of ACE2. Studies investigating SARS-CoV-2 infection other than the respiratory system have started to emerge (17, 18). The public health implications of the spread of SARS-CoV-2 infection from the initial site of infection to the female reproductive organs, in both pregnant and non-pregnant reproductive age women, are the focus of this paper.

SARS-COV-2 INFECTION IN PREGNANCY AND MATERNAL HEALTH

Asymptomatic and mildly symptomatic pregnant women face two unique risks posed by SARS-CoV-2 infection due to changes in ACE2 expression to accommodate hemodynamic changes in pregnancy. The first risk involves the increased expression and activity of ACE2 during pregnancy and possible secondary uteroplacental infection. Increased expression of ACE2 during pregnancy was suggested by an animal study to play a functional role in maintaining a normal blood pressure despite an increase in plasma volume of 20–70% toward the end of pregnancy (16). ACE2 has been shown to metabolize angiotensin II (Ang II) to Ang-(1-7) (19). Ang II constricts blood vessels while Ang-(1-7) dilates vessels. Relative expression of Ang II and Ang-(1-7), heavily influenced by ACE2 expression, was proposed to maintain normal blood pressure. Another study confirmed this finding (19). The study compared mean blood pressure (MAP) and plasma Ang-(1-7) levels in ACE2 knockout (KO) and wild type (WT) pregnant mice and found a statistically significant increase in both MAP and plasma Ang (1-7) level in ACE2 KO mice (20). The same study also found an association between ACE2 deficiency and an impaired maternal gestational weight (20). The uterus and the placenta, with their enhanced expression and activity of ACE2 during pregnancy (16), may put pregnant women at an increased risk of establishing a secondary uteroplacental SARS-CoV-2 infection.

The second risk involves downregulation of ACE2 by the SARS-CoV-2 virus in pregnancy (14). In the study discussed above, in which the authors compared MAP and plasma Ang-(1-7) levels in ACE2 KO and WT pregnant mice, a statistically significant increase in both MAP and plasma Ang (1-7) level in ACE2 KO mice was found (20). This finding suggests another potential risk for the mothers, the potential risk of developing preeclampsia.

To evaluate the first risk of a secondary uteroplacental infection, studies should address the relationship between level of ACE2 expression in placenta and uterine tissues and tissue susceptibility to SARS-CoV-2 viral invasion. The second risk of developing preeclampsia needs to be assessed through human studies comparing the percentage of preeclamptic women in SARS-CoV-2 positive patients with preeclampsia in non-COVID-19 patients. A recent article suggested that a high plasma soluble ACE2 level might be protective for SARS-CoV-2 infection (21). The authors explained that this paradoxical observation might be due to the posttranslational events regulating protein levels and a balance between soluble and membrane-bound form. These results will need additional confirmation. Normal hemodynamics in placenta may be affected by viral-induced downregulation of ACE2 expression in COVID-19 pregnant women. A study showed a higher Ang II in placenta in ACE2 KO mice compared to WT mice (20). Previously, an increase in Ang II in both the maternal and fetal components of the placenta has been found in human transgenic rat model of preeclampsia (22). This increase in Ang II was also observed in the chorionic villi of the placenta of women with preeclampsia (23). The increased level of Ang II in placenta could lead to placental ischemia. A recent study of three women with confirmed SARS-CoV-2 infection who delivered by cesarean delivery described placental pathology (24). All three women had fever, one before delivery and the other two postpartum. Samples taken from the three placentas were negative for nucleic acid of SARS-CoV-2. Various degrees of fibrin deposition inside and in proximity to villi as well as local syncytial nodule increases were observed in all three placentas. One displayed massive placental infarction. No pathological placental changes due to SARS-CoV-2 was found in the three placentas. Such morphological studies of placenta should be extended to mildly symptomatic and asymptomatic women. To understand if the infection compromises blood flow to the placenta, placental tissue samples need to be collected from SARS-CoV-2 infected and healthy women. These samples should be evaluated for signs of ischemia. Furthermore, the use of ultrasound may demonstrate evidence of placental vascular compromise. A possible correlation between SARS-CoV-2 infection and incidence of placental ischemia needs to be understood through such studies.

In addition, whether there is a progressive increase in risk throughout the trimesters in developing cardiovascular and respiratory insufficiency should be addressed. Current published clinical experience is limited to women who developed symptoms in late third trimester and were delivered shortly after the diagnosis (8).

SARS-COV-2 INFECTION IN PREGNANCY AND FETAL HEALTH

In mildly and asymptomatic COVID-19 pregnant women, the dysregulation of ACE2-Ang-(1-7) and its receptor MasR axis may have implications for the fetus. This could occur at both the intrapartum period and long-term. A study in rats showed that maternal glucocorticoid treatment reduced levels of ACE2 and Ang-(1-7) in rat placenta, specifically in fetal part labyrinth zone where nutrient and waste exchange occurs in late pregnancy (25). The animal study further correlated this reduction in ACE2 and Ang-(1-7) with impaired intrauterine fetal growth. A recent review of both animal and human studies suggested that alterations in Ang-(1-7) axis, particularly within the kidney and brain during perinatal programming, could lead to increased risk of development of hypertension and cardiovascular disease (26). To assess if the infection is associated with restricted intrauterine fetal growth, studies need to monitor ACE2, Ang-(1-7) levels and the growth of fetus in both infected and healthy women. To evaluate if fetus born to infected mothers are at a higher risk of developing hypertension and cardiovascular diseases later in life compared to fetus born to healthy mothers, the infants need to be monitored for blood pressure and cardiovascular abnormalities into early and late adulthood.

SARS-COV-2 INFECTION AND REPRODUCTIVE HEALTH

Mildly symptomatic and asymptomatic COVID-19 women may have issues in planning for future reproduction. In particular, three issues, sexual transmission of the virus, the use of contraceptives and the risk of infertility, may be public health concerns. Recent studies have shown that no SARS-CoV-2 virus was detected in vaginal fluids or semen in infected individuals (27, 28). The sample size of both studies, however, is small. Larger-scale studies remain to be conducted to confirm this finding. Nevertheless, there is currently no evidence supporting sexual transmission of the virus. The usage of contraception should be examined for patients with an ongoing infection. For SARS-CoV-2 patients with an ongoing infection, whether estrogen and progesterone contained in contraceptive agents alters ACE2 expression and induces pregnancy-like risks is unclear. The dose-response effect of hormones contained in contraceptive agents on uterine and endometrial ACE2 expression should be studied. In addition, studies should address whether SARS-CoV-2 infections affect the overall efficacy of contraception, whether the contraception is via steroid hormones or by intrauterine devices.

COVID-19 infections may have implications for infertility patients. The enhanced expression of ACE2 in the placenta and uterus during early pregnancy (16) after infertility treatment may make the organs more susceptible to viral entry during mild or asymptomatic infections. The local placenta-uterus infection could induce inflammation and subsequent scarring that may compromise future fertility. In addition, ACE2 is found in human ovarian follicles and the endometrium (29, 30). As a consequence, patients with mild or asymptomatic SARS-CoV-2 infections may have difficulty with their ovarian ovulation induction protocols or with implantation of embryos in the endometrium. Among patients without previous history of infertility, whether mild or asymptomatic SARS-CoV-2 infections increases the infertility rates should be examined. Thus, for infertility, studies could include an examination of whether a secondary infection occurs at a higher rate in mild or asymptomatic infections, whether the infection affects ovulation induction or embryo implantation and whether a more general increase in rates of infertility is found in these patients.

DISCUSSION

The health risks of mild and asymptomatic SARS-CoV-2 infected women face in pregnancy have not been investigated in detail. As of May 2020, there have been more than 5 million confirmed cases worldwide with daily confirmed cases around 90,000[1,2]. Assuming that 80% of confirmed cases are asymptomatic and mildly symptomatic as recent reports suggested (31), there are already close to four million people worldwide in this category. There is an urgent need to understand what these risks might be and prepare families for current and future pregnancy challenges. So far, there have been no conclusive evidence on how the infection differentially affects pregnant women. They are in fact advised to take the same precautions as the general public. Public health initiatives should identify pregnant women infected with Covid-19 with antibody tests and monitor maternal and fetal health closely. Initiatives should also include non-pregnant women to be monitored for future reproductive issues.

There is a theoretical public health concern for SARS-CoV-2 to impact both a current pregnancy and future reproduction in mildly symptomatic and asymptomatic women. This theoretical issue is rooted in two findings that have been substantiated by several studies. The first is the association between the SARS-CoV-2 infection and disrupted ACE2 expression. Disrupted ACE2 expression is likely to lead to dysregulation in ACE2 Ang-(1-7) axis. The other finding is an association between dysregulated ACE2 Ang-(1-7) axis and impaired maternal and fetal health. Combining the two findings, we hypothesize that SARS-CoV-2 impairs cardiovascular adaptation of mothers, normal hemodynamic regulation of placenta, fetal growth and long-term cardiovascular health, as well as reproductive health of women in general.

The significance of ACE2 in the infection of SARS-CoV-2 is clear. Current evidences are mainly derived from animal studies. Future studies may consider distinguishing the function of soluble and membrane-bound form of ACE2 in viral invasion, early and late stages of the infection. Regardless of whether soluble and membrane bound forms of ACE2 play distinct roles, we think that ACE2 Ang-(1-7) axis is disrupted to different degrees during the infection. And this becomes a critical question that needs to be addressed in future studies.

As studies continue to shed light on the effect of the infection on different organ systems, they should engage the research community, clinicians, and the public to reassess the impact of the infection on reproduction. Based on evidence discussed here, we think that there are effects on mothers, placenta, and the fetus throughout the trimesters. In addition, we hypothesize that these effects may extend into future reproduction of mildly symptomatic and asymptomatic COVID-19 women. Given the risks associated with asymptomatic SARS-CoV-2 infections as well as inconclusive evidence surrounding vertical transmission, women of reproductive age may need to be advised about the theoretical risks to the mother and fetus until more is known.

[1]COVID-19 situation update worldwide, as of 6 May 2020. Available at: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases (accessed May 6, 2020).

[2]Daily confirmed COVID-19 cases. Available at: https://ourworldindata.org/grapher/daily-cases-covid-19 (accessed May 6, 2020).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Moms Are Not OK: COVID-19 and Maternal Mental Health

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Introduction: Depression and anxiety affect one in seven women during the perinatal period, and are associated with increased risk of preterm delivery, reduced mother-infant bonding, and delays in cognitive/emotional development of the infant. With this survey we aimed to rapidly assess the influence of the COVID-19 pandemic and subsequent physical distancing/isolation measures on the mental health and physical activity of pregnant and postpartum women.

Methods: Between April 14 and May 8, 2020, we recruited women who were pregnant or within the first year after delivery to participate in an online survey. This included questionnaires on self-reported levels of depression/depressive symptoms (Edinburgh Postnatal Depression Survey; EPDS), anxiety (State-Trait Anxiety Inventory; STAI-State), and physical activity. Current and pre-pandemic values were assessed for each.

Results: Of 900 eligible women, 520 (58%) were pregnant and 380 (42%) were in the first year after delivery. Sixty-four percent of women reported reduced physical activity with the onset of isolation measures, while 15% increased, and 21% had no change to their physical activity. An EPDS score $\geq$13 (indicative of depression) was self-identified in 15% of respondents pre-pandemic and in 40.7% currently (mean $\pm$ SD; 7.5 $\pm$ 4.9 vs. 11.2 $\pm$ 6.3, respectively; $p < 0.01$, moderate effect). Moderate to high anxiety (STAI-state score $\geq$40) was identified in 29% of women before the pandemic (mean STAI = 34.5 $\pm$ 11.4) vs. 72% of women currently (mean STAI = 48.1 $\pm$ 13.6; $p < 0.01$, large effect). However, women engaging in at least 150 min of moderate intensity physical activity (meeting current guidelines) during the pandemic had significantly lower scores for both anxiety and depression than those who did not ($p < 0.01$, large and small effect, respectively).

Discussion: This rapid response survey identifies a substantial increase in the likelihood of maternal depression and anxiety during the COVID-19 pandemic. This highlights the strong need for heightened assessment and treatment of maternal mental health. However, these data also suggest that physical activity, which has previously been shown to reduce depression and depressive symptoms in pregnancy, may be associated with better mental health during the pandemic.

Keywords: COVID-19, pregnancy, postpartum, mental health, physical activity

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INTRODUCTION

Since COVID-19 was first recognized in late 2019, the virus has rapidly spread throughout the world. In an effort to mitigate the devastating effects of this virus, varying levels of "stay at home" orders have been implemented in most countries around the world. This has resulted in the closure of schools, daycares, workplaces, and non-essential services. The impact of the physical (and social) isolation on mental health is anticipated to be high, and may disproportionately affect high risk populations.

Depression and anxiety affect one in seven women during the perinatal period, and are associated with increased risk of preterm delivery, reduced mother-infant bonding, and delays in cognitive/emotional development of the infant, which may persist into childhood (1–4). Prevention and treatment is critical yet it is estimated that 50% of women who are depressed remain undiagnosed during and following pregnancy (5). A cross-sectional study of 100 pregnant women from Italy found a moderate-to-severe psychological impact of the COVID-19 pandemic and highlighted the need for intervention to improve the mental health of this population (6). Furthermore, the COVID-19 pandemic is anticipated to decrease access to diagnosis and psychological or pharmacological treatment; this is likely exacerbating poor mental health (7). Even in the absence of clinical depression or anxiety, identifying therapies to reduce sub-clinical symptoms is important.

Obstetrical guidelines around the world recommend that all pregnant women without contraindication be physically active throughout pregnancy (8–11). This derives many health benefits including a 67% reduction in the odds of prenatal depression (odds ratio 0.33, 95% CI 0.21–0.53, $I^2 = 0\%$) (12), as well as postpartum depressive symptoms (standardized mean difference −0.34, 95% CI −0.50 to −0.19, $I^2 = 0\%$) (13). With this survey, we aimed to assess the influence of the COVID-19 pandemic and subsequent physical distancing/isolation measures on the mental health and physical activity of pregnant and postpartum women.

MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee at the University of Alberta (University of Alberta ethics protocol PRO00099671). Between April 14–May 8, 2020, we recruited women who were pregnant or within the first year after delivery to participate in an online survey. The survey was posted online via social media platforms (Twitter, Facebook, and Instagram) and shared publicly to facilitate snowball sampling. Participants were informed of the purpose, risks, and benefits of the survey, were told they could withdraw from the survey at any time, for any reason, and provided electronic informed consent. Women answered questions on demographics including their year of birth, level of education, and personal health history. They responded to questions regarding symptoms, testing, and diagnosis of COVID-19, and current physical distancing/isolation measures including current work status. Participants completed validated standard questionnaires of self-reported levels of depression/depressive symptoms (Edinburgh Postnatal Depression Survey; EPDS) and anxiety (State-Trait Anxiety Inventory; STAI-State). Self-reported physical activity was also collected. All measured were assessed for both current and pre-pandemic values.

The Edinburgh Postnatal Depression Scale (EPDS) is a self-reported screening questionnaire consisting of 10 questions which was initially used in the postnatal period; however, it is also commonly used during pregnancy (14). Clinical diagnosis of depression can only be determined by a trained health professional; however, a score of $\geq$13 on the EPDS is associated with a likely diagnosis of depression. The State-Trait Anxiety Inventory (STAI) is a commonly used self-report questionnaire to screen for the presence and severity of state (i.e., right now) and trait (how prone a person is to anxiety) anxiety (used with permission) (15). The STAI consists of 40 questions with equal numbers assessing both the state and trait subscales. A score of 40 or higher has been identified as the threshold to identify clinically significant symptoms of anxiety (16).

Physical activity was self-reported in two ways. First, participants provided an overall assessment of their achievement of 150 min of moderate intensity physical activity each week (i.e., current recommendations for pregnant and postpartum women). Secondly, participants reported on physical activity during the week. Volume of physical activity was determined as per previously published methods (12, 17). The intensity of each activity was assigned a metabolic equivalents (METs) score using the Compendium, and multiplied by the frequency and duration of the activities (18).

All data were checked for accuracy, and invalid data were removed. Pre-pandemic versus current mental health and physical activity metrics were compared using paired *t*-tests or Kruskal-Wallis-H tests as appropriate according to the normality of their distribution. Effect size was determined using Cohen's *d*. Women were stratified based on physical activity pattern during the pandemic to assess its influence on mental health using ANOVA. *Post-hoc* comparisons were assessed using Dunns Method. Statistical significance was defined as $p < 0.05$ and analyzed using SigmaStat (Systat Software Inc., USA).

RESULTS

Of 900 eligible women, 520 (58%) were pregnant and 380 (42%) were in the first year after delivery. One invalid record was removed. Participant's median age was 33 years (range 17–49 years; $n = 862$), 75.5% lived in cities ($n = 651$), and 69% ($n = 595$) lived in a single family home with an average of one child (range 0–5) living with them in the household. Most women were from North America ($n = 779$), were Caucasian ($n = 736$, **Table 1**), and had some postsecondary education ($n = 520$). At the time of the survey, 2.8% and 6.7% of women had a pre-existing clinical diagnosis of depression and anxiety, respectively (**Table 1**). Forty seven women had experienced symptoms of COVID-19, 13 of whom were tested and all had negative results. Ninety-three percent of women were currently engaged in physical distancing measures with 83% of women in self-isolation or isolation at home. Sixty-four percent of women reported reduced physical activity with the onset of isolation measures, while 15% increased and 21% had no change to their physical activity. The number of women meeting current prenatal physical activity recommendations prior to and during the pandemic are shown in **Table 2**.

An EPDS score $\geq$13 (indicative of depression) was self-identified in 15% respondents pre-pandemic and in 40.7% currently (mean $\pm$ SD; 7.5 $\pm$ 4.9 vs. 11.2 $\pm$ 6.3, respectively; $p <$ 0.01, Cohen's d 0.66; moderate effect). Moderate to high anxiety (STAI-state score $\geq$40) was identified in 29% of women before the pandemic (mean STAI = 34.5 $\pm$ 11.4) vs. 72% of women currently (mean STAI = 48.1 $\pm$ 13.6; $p < 0.01$, Cohen's d 1.08; large effect). However, women engaging in at least 150 min of moderate intensity physical activity (meeting current guidelines) during the pandemic had significantly lower scores for both anxiety (large effect) and depression (small effect) than those who did not ($p < 0.01$, see **Table 3**).

DISCUSSION

The findings of this survey illustrated a significant increase in self-reported levels of depression and anxiety, and substantial reductions in physical activity in pregnant women from before to during the COVID-19 pandemic. Depression and anxiety are well-established to have both acute (e.g., preterm delivery, attenuated fetal/neonatal growth) and long-term consequences (e.g., increased risk of future anxiety and depression, cognitive delays for the offspring) for the psychological and physical health of both mother and baby (2–4). Although, clinical diagnosis and treatment via psychological or pharmacological treatment remain front line therapies, the COVID-19 pandemic may reduce access and/or attendance to health care visits which could increase the risk of maternal/fetal health complications. The findings of this survey suggest that remaining physically active could be a helpful tool for pregnant and postpartum women. Specifically, engaging in at least 150 min of moderate intensity physical activity each week was associated with lower scores on screening tools for depression or anxiety. Thus, physical activity is an accessible measure to blunt the mental health crisis currently being experienced by pregnant and postpartum women.

Although estimates vary, depression and/or anxiety affect ~14% of pregnant and postpartum women (1). The consequences of undiagnosed and untreated depression are serious; nearly 20% of women with postpartum depression have considered hurting themselves and in the UK, the leading cause of maternal death in the year following delivery is suicide (19). Treatment of depression and anxiety is critical to support the health of both mother and child. However, many women are reluctant to take antidepressants even when prescribed (20, 21). In non-pregnant populations exercise has been found to be as effective in treating mild-to-moderate depression as anti-depressants and psychotherapy (22). Although this has not been evaluated in pregnant or postpartum women, recent systematic reviews and meta-analyses of randomized controlled trials have shown pre- and post-natal exercise reduces the odds

TABLE 1 | Participant characteristics.

	Number (% out of 900)
Ethnic background	
Caucasian	736 (81.8%)
Mixed Heritage	42 (4.7%)
Asian	36 (4%)
Hispanic or Latina	11 (1.2%)
African American	10 (1.1%)
Indigenous people	9 (1%)
South Asian	9 (1%)
Prefer not to say	58 (5.2%)
Region of residence	
Canada	655 (72.8%)
United Kingdom	73 (8.1%)
USA	53 (5.9%)
Australia	10 (1.1%)
India	7 (0.8%)
Brazil	6 (0.7%)
Germany	5 (0.6%)
China	4 (0.4%)
France	3 (0.3%)
Other/prefer not to say	84 (9.3%)
Relationship Status	
In a relationship but living together	837 (93%)
Single	21 (2.3%)
In a relationship but living apart	5 (0.6%)
Prefer not to say	37 (4.1%)
Employment status	No % due to multiple selections
Student	31
Self-employed	74
Part-time employment	89
Full-time employment	506
Homemaker/full time parent	103
Unemployed before COVID-19	16
Unemployed due to COVID 19	71
Prefer not to say	63
Pregnancy complications	
Gestational diabetes	37 (4.1%)
Hypertensive disorders of pregnancy	41 (4.6%)
Placenta previa	16 (1.8%)
Preterm labor	27 (3%)
Intrauterine growth restriction	11 (1.2%)
Multiple pregnancy (twins or higher)	22 (2.4%)
Depression	25 (2.8%)
Anxiety	60 (6.7%)
Prefer not to say	55 (6.1%)
No complications	655 (72.8%)
Pre-existing conditions	
Type 1 diabetes	5 (0.6%)
Type 2 diabetes	4 (0.4%)
Cardiovascular disease	6 (0.7%)
Respiratory disease	47 (5.2%)

TABLE 2 | Self-reported physical activity pre-pandemic and following the implementation of governmental recommendations for self-isolation/physical distancing associated with the COVID-19 pandemic.

Did you meet or exceed 150 min of moderate intensity physical activity each week?	*N* (%) Total = 714	METs per week
Prior to the implementation of physical isolation measures of COVID-19:		
Yes, most if not all of the time	205 (28.7%)	1,548 (1,120–2,342)
Yes, sometimes	211 (29.6%)	894 (567–1,372)*
Yes, but rarely	127 (17.8%)	580 (270–1,107)*#
No	171 (23.9%)	180 (0–516)*#†
Following implementation of physical isolation measures of COVID-19		
Yes, most if not all of the time	168 (23.5%)	1539 (967–2,301)
Yes, sometimes	195 (27.3%)	1005 (612–1,342)*
Yes, but rarely	136 (19%)	389 (180–767)*#
No	215 (30.1%)	90 (0–393)*#†

METs, metabolic equivalents.
Main effect of group on METs pre-pandemic: H = 260.206 with 3 degrees of freedom, $p < 0.001$, Cohen's d 1.507, very large.
Main effect of group on METs current: H = 342.357 with 3 degrees of freedom, $p < 0.001$, Cohen's d 1.914, very large.
**Different from most, if not all of the time, $p < 0.05$.*
#Different from sometimes, $p < 0.05$.
†Different from rarely, $p < 0.05$.

TABLE 3 | Current self-reported adherence to physical activity guidelines of at least 150 min of moderate to vigorous physical activity each week following the implementation of governmental recommendations for self-isolation/physical distancing associated with the COVID-19 pandemic.

Meets or exceeds physical activity guidelines	Edinburgh Postnatal Depression Score (EPDS) Median (25, 75%)	State-Trait Anxiety Inventory (STAI-State) Median (25, 75%)
Yes, most if not all of the time	8 (4, 14)	43 (32, 52)
Yes, sometimes	10 (5, 14)	47 (36, 56)*
Yes, but rarely	11 (8, 17)*	52 (42, 60)*
No	13 (8, 19)*#	53 (42, 62)*#

Main effect of group on EPDS: H = 36.900 with 3 degrees of freedom, $p < 0.001$, Cohen's d = 0.491, small.
Main effect of group on STAI-State: H = 47.415 with 3 degrees of freedom $p < 0.001$, Cohen's d = 0.568, large.
**Different from most, if not all of the time, $p < 0.05$.*
#Different from sometimes, $p < 0.05$.

of depression and depressive symptoms. The findings from the current study also suggest that pregnant or postpartum women who were able to engage in regular physical activity during the COVID-19 pandemic may have improved mental health compared to those who were not. We must also consider that certain barriers to physical activity may be increased in conjunction with COVID-19, such as the closure of indoor recreation centers and outdoor parks/greenspace. However, activities such as gardening, going for walks, household chores, and online fitness classes are feasible alternatives to promote wellness through movement and should be promoted as reasonable methods for increasing the physical activity of moms.

Due to the rapid development of COVID-19, pre-pandemic data were obtained through recall and were cross-sectional in nature, thereby precluding the ability to make causal inferences. As these data are correlative the underlying reason for the observed relationships cannot be determined and only associations could be identified. Indeed, a number of external factors may influence both likelihood of depression/anxiety and physical activity participation. These include fear of the virus, financial stresses, increased domestic workload, lack of motivation to exercise and social isolation, among many others. However, previous systematic reviews and meta-analyses from randomized controlled trials have demonstrated that rates of depression and depressive symptoms are reduced in pregnant and postpartum women randomized to an exercise intervention (compared to no exercise) (12, 13) supporting the observed relationship in the current study. Our approach utilized established and validated measures of self-reported screening tools for anxiety, depression, and physical activity to assess the psychological health of pregnant and postpartum women. These data were collected via online survey with social media as the primary avenue for promotion. As such, random sampling did not occur which may have introduced sampling bias into the survey. The number of individuals who saw the survey and chose not to participate could not be determined; however, it is plausible that women who had a pre-existing interest in physical activity and/or mental health would be more likely to respond to the survey. Furthermore, previous research has suggested that the quality of response may be reduced in online surveys (23, 24). Careless responding occurs when a participant fails to read or interpret the survey appropriately leading to incorrect responses. These types of responses can directly influence the results, thus the findings of this survey should be interpreted with consideration of these limitations. Our population was primarily from Canada (with a freely accessible health care system), Caucasian, were married, living in a single-family home, and had some post-secondary education. While we did not capture a more diverse population, the high rates of anxiety and depression are concerning as this group would not typically be considered at elevated risk of mental health disorders. Thus, these data likely under-estimate the true mental health crisis for pregnant and postpartum women as a result of the COVID-19 pandemic. Although the change in prevalence and symptom severity of anxiety and depression from pre-pandemic to current times may be subject to recall bias, the unexpectedly high rates of current mental health issues warrant an urgent call to action.

CONCLUSION

This rapid response survey identifies a substantial increase in self-reported maternal depression and anxiety from pre- to during-pandemic. These data highlight the strong need for heightened assessment and treatment of maternal mental health. However, these data also suggest that remaining active during the pandemic is associated with a reduced likelihood of anxiety and depression. These data highlight a potential intervention for all pregnant and postpartum women to improve or maintain mental health during this extremely stressful period where access to diagnosis and treatment is more challenging.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee at the University of Alberta (University of Alberta ethics protocol PRO00099671). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MD: had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, statistical analysis, and study supervision. MD and RK: study concept and design. All authors: acquisition, analysis, or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

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What Sex-Disaggregated Metrics Are Needed to Explain Sex Differences in COVID-19?

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Between early December 2019 and June 28 2020, there have been around 9.9 million confirmed cases of COVID-19 and 498,895 related deaths in 187 countries (1). In nearly all countries where sex-disaggregated data are available, men who are diagnosed with COVID-19 appear more likely than women to experience severe disease and eventually die from it (2), although the relative and absolute difference in reported case fatality rates between women and men varies between countries. This finding has attracted attention in the scientific community, and media more broadly (3). Current hypotheses to explain this observation center around differences, to men's disadvantage, in the prevalence of pre-existing chronic disease comorbidities and lifestyle risk factors, such as personal hygiene, smoking and alcohol consumption, immunological differences, and genetic factors (4).

The volunteer-led Global Health 50/50 initiative is tracking the availability of sex-disaggregated COVID-19 data on the numbers of confirmed cases and deaths. As of June 28 2020, they report data from 133 countries, representing 99% of global confirmed cases and >99% of reported deaths. Of these, 40% ($n = 53$) report sex-disaggregated data on *both* cases and deaths and 37% ($n = 49$) report *either* cases or deaths (**Figure 1**). At the time of writing, the 60% of countries that do not report sex-disaggregated data on both metrics contain more than half (53%) of the reported global burden of COVID-19 deaths and account for half of the global population. Although Global Health 50/50 does not capture all countries where COVID-19 cases have been identified, including some reporting sex-specific data, these data suggest a significant gap in sex-disaggregated COVID-19 surveillance data.

Overall and sex-disaggregated data on the numbers of confirmed cases and deaths are undoubtedly useful for assessing the magnitude of the pandemic. However, the data available to date make it difficult to accurately quantify sex differences in COVID-19 infection and mortality rates. For instance, testing criteria in many countries prioritize healthcare workers (the majority of whom are women), potentially resulting in more cases being identified in women who are at otherwise relatively low mortality risk. On the other hand, other key workers who have a high

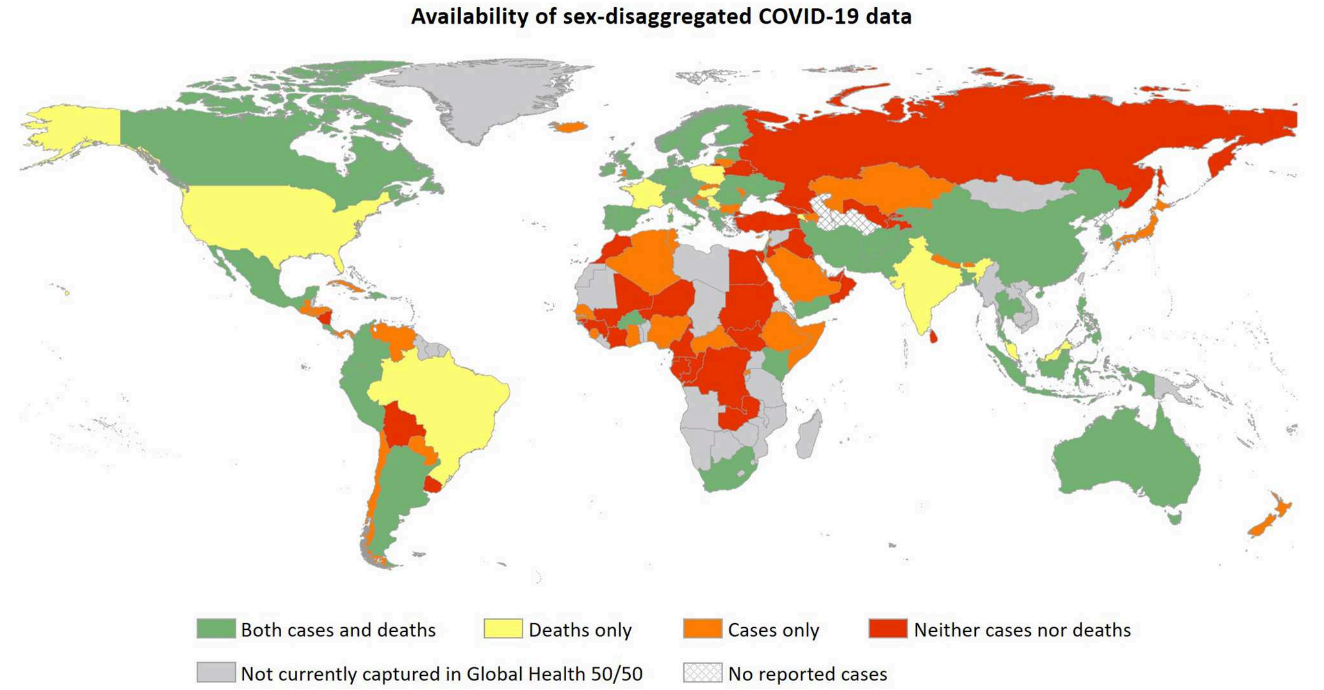

FIGURE 1 | Availability of sex-disaggregated data on confirmed COVID-19 cases and deaths in countries represented in the Global Health 50/50 COVID-19 sex-disaggregated data tracker on June 15 2020 (https://globalhealth5050.org/covid19/).

risk of exposure to COVID-19 infection (e.g. social workers), and are disproportionately likely to be female (5), are, unfortunately, not prioritized. If sufficiently large, these sex differences in testing may limit the comparability of case fatality rates in women and men. Another nuance to the current data in countries experiencing a high burden of COVID-19 is that reported deaths often only include those occurring in hospital. Without an accurate count of all COVID-19-attributable deaths, disaggregated by sex (and ideally age and ethnicity), care should be taken when quantifying sex differences.

Other sex-disaggregated surveillance data that would facilitate a better understanding of how COVID-19 differentially affects women and men include hospital and intensive care unit (ICU) admissions and lengths of stay, as well as the provision of invasive ventilation and other types of organ support. Such data would enable better determination of the extent to which the risk of severe disease is lower for women, or whether women do experience severe disease but are more likely to survive. This has important prognostic implications and would increase understanding of disease progression in women and men as well as the longer-term needs of COVID-19 survivors, many of whom may experience respiratory, cardiovascular and/or renal complications, either as acute events or due to pre-existing conditions becoming exacerbated. This could result in a substantial deterioration in mental and physical health, as is commonly seen in survivors of sepsis (6).

As we continue to broaden our understanding of COVID-19, we must also be cognizant of the need for well-designed sex and gender COVID-19 research that represents all patients. To do this well, a proactive intersectionality-informed approach to research design and data analysis is crucial (7). Data from Italy and the UK suggest that the overall prevalence of comorbidities in those who die from COVID-19 is similar for women and men (8, 9). However, the *type* of comorbidities varies, with pre-existing heart failure, hypertension, dementia and autoimmune diseases being more common in women, and ischemic heart disease, liver disease and chronic kidney disease more common in men. This likely reflects known, and in part age-related, sex differences in the prevalence of these comorbidities in the general population, but it does raise important questions around whether clinical management of COVID-19 should incorporate a sex lens. Moreover, based on experiences from previous infectious disease epidemics, we must plan to record and examine the pregnancy status of COVID-19-infected women so that pregnancy and perinatal outcomes of COVID-19 can be more fully understood early on. All this must be done against the backdrop of intersecting factors, including gender, age, ethnicity, and socioeconomic status.

The COVID-19 pandemic has illuminated well-known, yet all too often neglected, health disparities based on sex, gender, race, ethnicity, and socioeconomic status (10, 11). For sex, we know from other disease areas that differences in clinical presentation, disease progression and treatment outcomes between women and men have historically been overlooked and that this has cost lives (12). This must not be repeated. In the current pandemic, it is imperative that sex-disaggregated data are collected and effectively analyzed from the outset so that policies that appropriately address the needs of both women and men can be developed.

If any countries with sex-disaggregated data are not currently represented in the Global Health 50/50 database and would like to be, please contact info@globalhealth5050.org.

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Endometriosis and the Coronavirus (COVID-19) Pandemic: Clinical Advice and Future Considerations

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INTRODUCTION

The COVID-19 pandemic has led to a dramatic shift in the clinical practice of women's health and routine care for endometriosis has been severely disrupted. Endometriosis is defined as an inflammatory disease characterized by lesions of endometrial-like tissue outside the uterus that is associated with pelvic pain and/or infertility (1). It affects ∼10% of reproductive age women worldwide, is diagnosed by surgical visualization or by radiological imaging, and is managed with hormone treatments or by laparoscopic removal of lesions (2–4).

At the time of writing, under the guidance of international gynecological organizations (5–7), many centers temporarily ceased offering outpatient appointments, diagnostic imaging for non-acute pelvic pain, surgery for endometriosis, and fertility treatments. In the absence of routine care pathways and uncertainty about when health services will be available again, endometriosis sufferers are likely to feel vulnerable and that resultant stress and anxiety may contribute to a worsening of symptoms. The pandemic poses several important questions for healthcare providers on how best to deliver care within these restrictions. Herein, we present clinical advice on the management of endometriosis during the COVID-19 pandemic and future considerations (**Table 1**).

ARE ENDOMETRIOSIS PATIENTS A HIGH-RISK POPULATION OF BECOMING INFECTED WITH SARS-CoV-2 OR DEVELOPING MORE SEVERE COVID-19 DISEASE SYMPTOMS?

To date, there is no evidence that those with endometriosis are at increased risk of becoming infected with SARS-CoV-2 or developing COVID-19 disease[1]. A rare subgroup of those with endometriosis have thoracic endometriosis (lesions within the pleural cavity or on the diaphragm). The exact prevalence is unknown but some case series suggest that up to 12% of those with endometriosis have extra-pelvic endometriosis, with the thorax being the most common site (8). In general, there is a paucity of literature labeling this form of endometriosis as a risk factor for respiratory or systemic illness beyond catamenial pneumothorax (9). As such, it is challenging to know whether this group is at increased risk of becoming infected with SARS-CoV-2 or developing COVID-19. Similarly, there is no evidence that COVID-19 will hasten the progression/development of endometriosis. Nonetheless, the pandemic will likely contribute to a reduction in quality of life secondary to a delay in diagnosis and/or the management of endometriosis owing to the temporary closure of outpatient services, (including complementary therapies), postponement of planned surgical or fertility treatments, and an eventual increase in the waitlist for services once they resume. The extent of the impact will depend on the duration of service postponement and regional resource variations (e.g., access to operating theater time when surgeries resume).

MANAGEMENT OPTIONS AVAILABLE DURING THE COVID-19 PANDEMIC

We encourage individuals in need of help to seek a clinical assessment with their general practitioners (GP), gynecologists, physiotherapists, and/or complementary medical providers through telehealth avenues or in-person when services resume exercising caution to follow local risk-reduction practices. Referral to a gynecologist with expertise in endometriosis may also be appropriate to offset the new diagnostic and therapeutic challenges faced during this time. Those with an established diagnosis who are seeking help, regardless of their intentions to pursue surgical management, should discuss with their clinician the potential to modify their current medication regimen. Some with suspected endometriosis may accept a clinical diagnosis in the absence of imaging or laparoscopy and empirical medical therapy can be initiated (2). In those given a clinical diagnosis, and who don't respond to medical therapy, non-invasive imaging could be the first investigation arranged when it is safe to do so to evaluate for features that can reliably be identified such as deep endometriosis, ovarian endometriomas, and pouch of Douglas obliteration; whilst recognizing that at present superficial peritoneal endometriosis is not reliably detected using imaging (10, 11). Non-endometriosis pathologies may also be diagnosed. Knowledge of these entities has the potential to change clinical management, so awareness of them is important. However, if a patient is responding well to empiric treatment and does not intend to alter management, it may be reasonable to proceed without imaging. Laparoscopy as a diagnostic tool should be avoided unless the intention is to simultaneously surgically treat any endometriosis that is found (12). This could be considered in those who are experiencing failed medical management, have endometriosis-related infertility seeking to avoid or unable to access assisted reproductive technologies, or simply prefer to undergo surgery instead of using medical management.

Initially, caution in the use of non-steroidal anti-inflammatory drugs (NSAIDs), commonly used for endometriosis-related pain, was being advised (13). At present, the World Health Organization states that there is no evidence of severe adverse events, acute health care utilization, decreased long-term survival, or diminished quality of life in patients with COVID-19, as a result of the use of NSAIDs (14). As such,

TABLE 1 | Advice summary for endometriosis care during the COVID-19 pandemic and future considerations.

Be aware of the risks of the COVID-19 pandemic on endometriosis patients

- Reduction in quality of life secondary to
  - Delayed diagnosis and treatment due to
    - the closure of outpatient clinical services (consultations, diagnostic imaging, allied health appointments) and
    - the eventual increase in the waitlist for services once they resume.
  - The high degree of uncertainty of surgical or fertility interventions

Treatment options for patients with endometriosis

- Postponement of elective surgery and fertility therapy should be guided by medical colleges and societies and made by governing bodies
- Continue current management if symptoms are stable or contact a healthcare provider for changes to medication if symptoms are not well-managed
- Patients should seek telehealth appointments over in-person visits
- Patients with pain due to endometriosis may still consider the use of NSAIDs or other over-the-counter analgesic medications
- Empirical medical therapy with hormonal medications is appropriate in the absence of an imaging or surgical diagnosis
- Patients should consider the numerous complementary and alternative pain management strategies available via telehealth services

Use of the emergency department

- Patients should use telehealth services as much as possible before resorting to visiting the emergency department

Future considerations for endometriosis management

- Resumption of surgery and fertility therapy should be guided by medical colleges and societies and made by governing bodies
- When surgery resumes, serious consideration should be given to:
  - Screening for COVID-19 pre-operatively
  - Adopting appropriate PPE behaviors
  - Mitigating release of aerosolized gas by modifying surgical techniques
- Telehealth services should be considered as a viable method of assessment once routine outpatient services resume
- Self-management strategies should continue to be highly encouraged as adjuncts to traditional management
- Preoperative triaging tools including advanced clinical algorithms and imaging strategies should be implemented to avoid diagnostic laparoscopy and multiple/repeated surgical procedures.

[1] *People Who Are at Higher Risk for Severe Illness | Coronavirus | COVID-19 | CDC*. Available online at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html (accessed April 18, 2020).

those with endometriosis-related pain who use NSAIDs can continue to do so as needed, ensuring appropriate dosing according to medication labels and/or healthcare providers, bearing in mind that long-term use of NSAIDs come with its own set of side-effects including peptic ulceration and adverse impact on ovulation (2). Beyond traditional medical therapies, problem-focused interventions such as education, modifying work/school/social life, taking advantage of virtual and telephone support provided by national endometriosis organizations, improving sleep hygiene, low-intensity physical activity (including pelvic exercises, yoga), dietary changes, application of heat, and medical cannabis should be considered, either with the assistance of a healthcare provider via telehealth or independently by patients themselves (15). Similarly, emotion-focused strategies, which include relaxation/mindfulness, acceptance of chronic illness (e.g., via Acceptance and Commitment Therapy with the help of a clinical psychologist through telehealth), reducing catastrophizing, and improving a balance toward positive attitude can be considered (15). These strategies are not unique to the COVID-19 pandemic and are recognized as an integral part of the usual multidisciplinary management of endometriosis.

Patients should be aware that, if they experience acute exacerbations of their chronic pain, they may warrant urgent medical assessment, as such cases, especially those with suspected endometrioma or severe acute recalcitrant exacerbation of pain, may require urgent surgery. However, most pain exacerbations are not life- or organ-threatening and with appropriate counseling and support, a face-to-face consultation in the emergency department may be avoided. Some GPs may find it challenging to confidently reassure patients that they are safe to avoid an emergency department visit, so urgent telehealth consultation with a gynecologist or pain specialist may be helpful. That said, we do not advocate for the avoidance of the emergency department out of fear, so patients and providers should continue to judiciously and safely use this service when warranted.

ADVICE ON RESUMING PRE-PANDEMIC "REGULAR" CARE FOR ENDOMETRIOSIS

As restrictions begin to lift, healthcare services, including surgery for endometriosis, will resume. The decision about *when* clinical care should resume will be determined by medical colleges and societies, in compliance with governing bodies informed by emerging viral disease pandemic experts. The provision of appropriate medical and surgical care should resume with an emphasis on safety for patients, healthcare staff, and society. The American College of Surgeons (16), the Royal College of Obstetricians and Gynaecologists (17), and a collaborative effort by nine women's health care societies (18) outline important guidance for resuming surgical practice and reintroducing these procedures. Though endometriosis is a non-malignant disease, we believe it must be treated with high priority due to the major impact it has on quality of life (19). That said, facilities should employ a prioritization policy committee, including a gynecologist with expertise in managing the various facets of endometriosis (surgery, pain management, fertility treatment), to ensure an appropriate strategy is developed across all specialties. Amongst several strategies (16), previously canceled and postponed endometriosis surgeries should be prioritized. An objective priority scoring tool could also be implemented [e.g., MeNTS instrument (20)]. Based on the procedure, disease type, and patient factors that go into this scoring tool, endometriosis surgery would be relatively low risk. Objectively judging the impact of a 2- or 6-week delay on disease outcome is challenging as timing surgical management (e.g., immediate vs. delayed) has never been evaluated (21). It is unlikely for there to be a change in the surgical difficulty/risk with a 2- or 6-week delay (22). For urgent/emergency surgeries that have continued through the COVID-19 pandemic, there has been discussion about the safety of surgery based on theoretical evidence that aerosolization of the virus can occur with ultrasonic/electrosurgery (23). During this time, a minimally invasive surgical approach is being recommended (24) and felt to be lower risk (20). This COVID-19 specific recommendation aligns with the typical approach to endometriosis preceding the pandemic. Benefits include improved visibility of subtle endometriosis lesions (and therefore targeted treatment), decreased blood loss, reduced post-operative pain levels, and shorter in-hospital stay post-operatively. We support the joint statement by several gynecologic surgical societies, where expert opinion recommendations on intraoperative precautions have been put forward (25).

Adequate preoperative screening and diagnosis of SARS-CoV-2 will be an important consideration for the resumption of endometriosis surgery (26). Though most patients undergoing surgery for endometriosis are relatively young and healthy, we must be cognizant of the increased risk in those with perioperative SARS-CoV-2 infection. It has recently been noted that post-operative pulmonary complications occur in half of the patients with perioperative SARS-CoV-2 infection and are associated with high mortality (27).

At this time, we do not believe that the COVID-19 pandemic warrants a sustained change in the overall medical approach to the management of endometriosis (e.g., avoid surgery and favor medical management). Regardless of a pandemic, we encourage healthcare providers to comprehensively counsel patients on the therapeutic options available for each individual with endometriosis. The possible risks and realistic scheduling obstacles secondary to COVID-19 must be part of this conversation, but patients should still retain their autonomy to choose the option that is best for them.

FUTURE CONSIDERATIONS

We believe that the COVID-19 pandemic can lead to sustained improvements in the care for those with endometriosis. Firstly, there may be an ongoing openness to telehealth (28). This could dramatically minimize the geographic barriers to care that many women experience, and facilitate the development of endometriosis networks of expertise, which is recommended by the World Endometriosis Society (2). Telehealth may also be an appropriate alternative for patients with pain that limits their ability to travel to their healthcare provider in some settings. Secondly, there may be increased awareness to self-management strategies that have always existed, yet were under-utilized (e.g., mindfulness, physical exercise, and diet) until COVID-19 resulted in them becoming valuable tools for patients (15). Finally, the current situation mandates a more discerning approach to surgery now and in the future, so that we "operate sparingly and operate well." This approach can be guided by preoperative triaging tools including advanced clinical algorithms and imaging strategies (29) to avoid multiple repeated surgical procedures.

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All authors meet justification criteria of authorship as per ICMJE: substantial contributions to conception and design or acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Gender-Based Violence During COVID-19 Pandemic: A Mini-Review

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Purpose: Quarantine is necessary to reduce the community spread of the Coronavirus disease, but it also has serious psychological and socially disruptive consequences. This is known as the quarantine paradox that also includes a surge in the cases of gender-based violence. However, there exists a clear gap of rigorous literature exploring the issue. Hence, the current paper attempts to understand gender-based violence as an aspect of the COVID-19 lockdown. It reviews the pattern of rise in gender violence cases and the resultant psychological and social issues and attempts to create awareness by initiating a discourse urging for change in the response towards the victims of gender-based violence. The paper further attempts to suggest measures to mitigate the issues arising out of gender violence during quarantine.

Method: The current paper reviews the literature on the rise of gender-based violence in the times of current and past pandemics. The paper also reviews the published reports in scientific as well as mass media literatures focusing on the rise of gender-based violence during the imposed lockdown, its consequences, and the measures taken by the governments to tackle the issue.

Results: The present review reveals that similar to the previous pandemics and epidemics, there has been an alarming rise in the incidents of gender-based violence during the COVID-19 pandemic. The present review further reveals various other risk factors that have been found attributive to the surge of gender-based violence such as economic insecurity and alcohol consumption. The results of the review indicate that despite its global prevalence, gender-based violence has been one of the most neglected outcomes of pandemics. Moreover, the legislatures and services available for such victims are often inadequate and, thus, worsening their situation.

Conclusion: Pandemic situations have been found to be associated with advancements in the medical field. However, a part and parcel of this situation is the age-old practice of quarantine that has several negative outcomes. This also includes a surge in gender-based violence that raises serious concerns about the safety of women. As the legislatures provided and measures taken by the governments are falling short in dealing with the issue, a number of non-government organizations are stepping up to provide necessary services to these victims.

Keywords: quarantine, gender-based violence, pandemic, domestic violence, COVID 19

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PANDEMIC AND GENDER-BASED VIOLENCE

Quarantine has been an effective measure of controlling infection since the 14th century. The medieval societies were able to establish a link between the emergence of symptoms and the duration of time. The origin of the term is rooted in the health practice related to plague back in 1377 AD when ships were isolated for 30 days and land travelers for 40 days in the sea port of Ragusa (1). However, the earliest record of quarantine can be traced back to 532 AD (2). Since then, the practice of quarantine has been utilized to reduce the spread of contagious diseases. With the declaration of COVID-19 as a global pandemic, there is a mounting pressure on the governments to take measures to reduce the community spread of the disease. Hence, in the absence of a vaccine or effective treatment, going into quarantine for varying periods of time is being adopted as an option by most countries. This has led to a drastic alteration in the day-to-day lifestyle of the individuals. Most of the work is being done from home, and efforts are being made to maintain social distance. These measures are crucial to the protection of healthcare systems. However, just like one coin has two sides, the positive efforts to tackle COVID-19 have negative consequences associated with them. These negative consequences include the risk of losing jobs, economic vulnerabilities, and psychological health issues resulting from isolation, loneliness, and uncertainty, among others. This can be regarded as the quarantine paradox. History has witnessed the weakening of the states in the face of pandemics and outbreaks. The Antonine plague of 161 AD had economically weakened the Roman Empire (3). The Byzantine empire too had suffered weakening of the economic infrastructure during the Justinian plague (4). Past researches indicate that the risk of serious psychological consequences increases with the increase in the duration of the quarantine (5). According to Hawryluck et al. (6) and Reynolds et al. (7), a longer duration of quarantine was found to be associated with increased symptoms of PTSD. Lee et al. (8) reported that the risk of developing PTSD symptoms persisted despite home quarantine. Another downside of quarantine is the increase in cases of gender-based violence that is frequently ignored (9). Gender-based violence is a form of violence targeting a person based on the gender of an individual. It is a complex phenomenon that includes combinations of sexual, physical, and emotional violence and neglect or deprivation (10). CEDAW (Committee on Elimination of Discrimination Against Women) has defined gender-based violence as a form of violence that disproportionately affects women. Some common forms of gender-based violence include sexual violence, violence against women, domestic violence, and harmful traditional practices, such as female genital mutilation. For the present paper, the term gender-based violence has been used to denote different aspects of domestic violence against women.

According to an article published in a national newspaper of India, The Hindu, the National Commission for Women (NCW) recorded a twofold rise in the cases of gender violence (11). Several researches indicate a rise in family violence and sexual violence during and after any large crisis or disaster [e.g., (12, 13)].

RELATION BETWEEN GENDER-BASED VIOLENCE AND CRISIS SITUATIONS

Violence has generally been found to increase in the face of pandemics. For instance, Rose (14) reported an erosion of social norms and increase in violence in Bologna, Italy, in the context of plague and natural disaster. According to UNFPA (15), pandemics often lead to breakdowns of social infrastructures thus compounding the already existing weaknesses and conflicts. As a result, the existing gender inequality is worsened by the pandemic situations. It also increases the exposure of children and women to harassment and sexual violence when they try to procure necessities such as water, food, and firewood. Several researches report that gender-based violence is more prevalent in HIV hyper-endemic countries [e.g., (10, 16)]. Researchers have observed a link between the prevalence of HIV epidemic and gender-based violence in India as well (17, 18). A report about rapid gender analysis on COVID-19 by CARE and International Rescue had expected gender-based violence to rise amid pandemic and quarantines. Hence, the report had also recommended to prepare and build on existing services for the victims of gender-based violence. The report further emphasized on the need to strengthen online services to provide psychological support and legal aid services (19). According to Menendez et al. (20), often women do not have rights over their sexual choices. Consequently, they experience sexual violence and the risk of exposure to the virus through the male carrier. Okur (21) emphasized that sexual and gender-based violence increases during crisis situations due to breakdown in law. Thus, the victims often do not receive the adequate support, and the perpetrators get exempted from punishment. Also, according to the WHO global ethics unit (22), gender roles affect all aspects of an endemic including interpersonal violence. It also emphasized the need of various services to minimize the risk of violence when people are quarantined at home or in institutions. Hence, the present research shall focus on the gender-based violence, because despite being a global phenomenon, it is highly underreported due to stigma and social pressures. Moreover, there is a lack of studies focusing on the prevalence of gender-based violence during disasters. Consequently, those responding to disasters are often not aware of the possibility of surge in the cases of gender-based violence. Therefore, they often do not prepare to deal with, thereby making the situation worse. In fact, according to John et al. (23), these are the lessons never learnt. Therefore, we have a limited understanding toward how the victims of gender-based violence respond to the situation of the current pandemic. Hence, the present research reviews the linkages between gender violence and pandemic and also attempts to identify the potential policy responses to moderate the issue.

In the past, crises have been linked with a surge in cases of gender violence (24–27). A surge in intimate partner violence was observed during other disasters such as Earthquake in Haiti in 2007, Hurricane Katrina in 2005, and Eruption of Mount Saint Helens in the 1980s due to unemployment, family, and other stressors (28). Even during the South Asian Tsunami of 2004, a surge in gender-based violence was observed. Fisher (29) emphasized that in the aftermath of Tsunami, several incidents of violence against women and sexual assault were reported in Sri Lanka. According to researchers, pandemics cannot be considered an exception to this (9). Sikira and Urassa (30) reported an increase in wife battering in the face of the HIV pandemic due to suspicion of extramarital affairs. Recent outbreaks such as Ebola, Cholera, Zika, and Nipah have also led to an increase in the cases of domestic violence (31). During the Ebola virus outbreak, women and girls were especially vulnerable to violence because of the inability to escape their abuser. Moreover, the victims of violence were not recognized and were often left unattended (32). According to Yasmin (33), cases of rape, violence against women, and sexual assault also increased during the Ebola outbreak in West Africa.

There are a number of reasons for such increase in gender violence cases. Arthur and Clark (34) also identified economic dependence as a cause for domestic violence. During quarantine, as more women were in informal jobs and got laid off, this led to them experiencing a greater impact as they became economically dependent on their male counterparts. According to Alon et al. (35), lesser women than men are in telecommutable jobs, thus making it difficult for them to adapt to the changing conditions. This increased economic dependence not only increases their risk of gender-based violence but also makes it difficult to leave their perpetrators. Pandemics like influenza, swine flu, and SARS have been found to result in psychological issues such as anxiety, substance abuse, PTSD, and sleep disturbances that often tend to continue even after the pandemic (36, 37). According to a research by Zhang et al. (38), increased prevalence of depressive symptoms could be observed among COVID 19 patients. A significant rise in anxiety levels of the COVID-19 patients as well as the general public was reported by the findings of the study. In return, these mental health issues and related factors such as alcoholism tend to lead to a rise in gender-based violence (39–42). Several researchers have reported that the sales of alcohol have skyrocketed during pandemic [e.g., (43, 44)]. Polakovic (43) reported a rise of 55% in the consumption of alcoholic beverages in the United States. Evidence also suggests that increase in male migration reduces gender violence due to reduced exposure to the potential perpetrators (45). When under quarantine, women individuals are in close proximity to the male members with limited to no freedom to go out, thus leading to an increase in gender violence at home. Pandemics also increase economic vulnerabilities because of the rise in unemployment, or, in the risk of unemployment. Several studies link economic insecurities to increased gender-based violence. Economic insecurity has been found to be linked to adopting poor coping strategies that are inclusive of substance abuse (46–48). These, in turn, have been found to be associated with various forms of gender-based violence (49). However, interesting gender differences can be observed in this context. Bhalotra et al. (50) reported that increase in male unemployment was associated with increase in interpersonal violence against women where an increase in women unemployment was associated with a decrease in violence against them. According to Schneider et al. (51), such an outcome could be because of male backlash resulting from feelings of emasculation and inadequacy at not being able to serve the role of a breadwinner of the family. According to Bradbury-Jones and Isham (52), it could also be because of the distorted power dynamics at home resulting in abuse and gender violence that escapes the scrutiny of anyone from outside. The problem of gender-based violence during the pandemic further worsens because the police are unable to tackle the issue of gender-based violence. According to a report, gender-based violence in Liberia could have also increased because the police were overwhelmed and unable to defend the victims (53). Richards (54) reported that economic strain, substance abuse, and isolation all tend to increase the risk of domestic violence. Based on the above literature review, it is evident that understanding of gender violence is a key priority in order to achieve gender equality globally.

Past researches have established a strong link between different forms of gender-based violence and psychological issues. Thus, it is all the more important to tackle the issue of rising gender-based violence in the face of COVID-19. It has been reported that women who experience one form of gender-based violence are more likely to experience other forms of gender violence (55). According to Campbell (56), intimate partner violence is associated with PTSD, depression, chronic pain, sexually transmitted diseases, etc. Woods (57) reported that PTSD symptoms could be observed in both abused and post-abused women. Jackson et al. (58) established a link between traumatic brain injury and woman battering. They reported that the frequency of being hit in the head was significantly correlated with severe cognitive symptoms. Walker (59) reported that victims of domestic violence experience a sequelae of psychological symptoms that include anxiety, depression, avoidance, reexperiencing of traumatic events, and hyper-arousal.

COVID-19 AND GENDER VIOLENCE

COVID-19 seems to be similar to the pandemics in the past since this too has resulted in an increase in cases of domestic violence. According to Bradbury-Jones and Isham (52), the lockdown imposed to deal with COVID-19 has granted greater freedom to abusers. Several media reports indicate a surge in cases of domestic violence in various countries. According to Kagi (60), though a drop was observed in the overall crime rates in Australia, the domestic abuse rates increased by 5%. Some charities in Australia also raised concerns about COVID-19 misinformation being used by the offenders to further control and abuse the victims of domestic violence (61). Allen-Ebrahimian (62) reported that China witnessed a three-fold increase in the cases of domestic violence after imposing quarantine. Different states in the United States also reported an increase of about 21–35% in domestic violence (63). Even the UK has been facing concerns due to rising family violence. There has also been an apparent increase in the number of domestic homicides (64). The Refuge website recorded an increase of 150% in the calls about domestic abuse (65). An article in The Indian Express draws attention to the fact that a vast majority of people in Mumbai do not have household water connections. With rising summer temperatures, people spending more time at homes during lockdowns, and emphasis on handwashing, there comes the need for household water. Consequently, many women are turning to underground water market operating under the cloak of darkness. Moreover, women have been spending more time queuing up for water and often approach the market in the wee hours of mornings where they often face verbal and sexual harassment (66). Despite this increase in incidents of gender-based violence, Jagori, a Delhi-based NGO, has witnessed a drop in calls on its helpline numbers by 50%. This could be because of the fear of getting discovered by their offenders at home according to Jaya Velankar, Director Jagori (67). According to Bradbury-Jones and Isham (52), the lockdown imposed to deal with COVID-19 has granted greater freedom to abusers. It has become easier for the abusers to enforce control tactics by limiting the access of the victims to phones, internet, and other people. van Gelder et al. (68) also emphasized that the lockdown limits familiar support options. In an article published by BU today (69), Rothman who is a professor of Community Health Sciences raised concerns about declaring sale of guns to be essential services in some states of the United States. This increases the likelihood of fatal interpersonal violence. Fielding (70) pointed out that the victims of abuse may even be scared to visit a hospital for treatment of their injuries due to the fear of contracting the COVID-19 disease.

TACKLING GENDER-BASED VIOLENCE DURING COVID-19

The first step to tackle the issue of rising gender violence in the times of pandemic is the acknowledgment of the issue, which has been ignored during the pandemics in the past (71). Campbell (28) emphasizes that expanding community partnerships and spreading awareness about the importance of reporting incidents of abuse are crucial to reducing the number of such cases. According to Bradbury and Isham (52), one way to deal with the issue of domestic violence is by constantly asking if people feel safe at home. However, it is very crucial that the people asking these questions have the time and emotional resources. It is often possible that the victims may communicate in subtle and indirect ways, which can be easily missed. They also emphasize the importance of online and telephonic services for those seeking therapeutic interventions, counseling, or any other kind of support. Gerster (72) emphasizes that neighbors of families with violence can also help to reduce domestic violence by initiating conversation with them. Researchers also emphasize the need to train healthcare workers to recognize the signs of violence to tackle the issue of gender-based violence (73, 74). Van Gelder et al. (68) emphasize the role of the media to raise awareness about the issue of gender violence during pandemic as well as about the practices that can replace the conventional in-person support. These may include offering supportive statements, promoting safety guidelines via advertisements, bystander approaches, and accessing help on behalf of the victim after obtaining consent. They also call for increase in service availability and funding for protection needs and shelters during quarantine. Hatchimonji et al. (71) called for coupling physical distancing with social support to ensure that it does not exacerbate gender violence. There is also a strong need to strengthen the helpline services which victims of gender violence can utilize without alerting their offenders. Antonio Guteres, the United Nations Secretary General, also emphasized the need for the countries to prioritize support by setting up emergency warning systems for individuals facing family violence (75). Mazza et al. (76) have emphasized on the need of a trained multidisciplinary staff including psychologists, psychiatrists, and social and legal services to prevent acts of domestic violence and ensure accurate assessment of various domains of the abuse.

Some countries have in fact tried to adapt to the situation of quarantine resulting from COVID-19 by implementing several practices to reduce gender-based violence. For instance, France has set up warning systems at groceries and pharmacies to enable victims of gender and family violence to alert the authorities (77). They may also alert the staff about the required help by using code words that have been introduced. Domestic Violence Resource Center Australia has also issued specific guidance for family and friends to support those in family violence situations (78). UNFPA (United Nations Population Fund) and UN Women have published guidelines that can be utilized by various governments to include gender considerations into their responses (15, 79). National Domestic Violence Hotline, USA, has also been offering service via online texting chat so that victims of domestic violence can seek help (80). In Beijing, a judicial court has been using cloud-based platforms and online court hearings to deal with cases of gender-based violence in the times of pandemic (81). Nair and Banerjee (82) emphasized the need for the combined efforts of health professionals with print and digital media to avoid misinformation and educate people about abuse prevention.

In a conversation with staff of AALI (Association for Advocacy and Legal Initiative, Lucknow, India), it was revealed that the actions being taken by the authorities in India are insufficient to deal with the issue of gender violence during COVID-19. NGOs have requested to publicize the phone numbers of the protection officers by sticking them outside their offices to make them more accessible to the victims. The AALI staff member also expressed concern over a lack of sense of urgency when dealing with domestic violence cases under lockdown. The effectiveness of the helplines is reduced if it is not followed by necessary action and is merely recorded as data. The National Commission of Women (NCW), India and NGOs such as Jagori have compiled information pertaining to the One Stop Centers, protection officers, and other support services on their websites. Aman: global Voices for Peace in the Home, which is a network of over 146 organizations and individuals working on the issue of violence against women across 18 states in India, has written a letter to the National Commission of Women, India with collective recommendations to respond to the situation of women facing violence under lockdown. The recommendations include making the helpline numbers such as 181 and 1,091 functional; publicizing the support services and resources available; utilizing Nirbhaya funds (Nirbhaya Fund is a corpus fund of Indian rupee 10 billion created by the Government of India to support the activities and initiatives of the government and NGOs working towards protecting the dignity and ensuring safety of women in India.) to increase the availability of resources available to NGOs offering legal aid, counseling, and shelter to women facing violence; developing special protocols to provide support to trans women, disabled women, and migrant women who are even more marginalized and have negligible access to support; and forming a panel of lawyers offering legal information to women over phone, among others. The Aman network has also recommended to build a temporary shelter in the Kashmir Valley, as there are no shelter homes built under the Protection of Women under the Domestic Violence Act, 2005.

The outcome of gender-based violence is long lasting for its victims, and rampant for the responses that are often inadequate. Hence, it is crucial to maintain a sense of urgency in cases of gender-based violence even during crisis situations. Based on the above literature review, it can be maintained that there is a need for a holistic response model to deal with the issue of gender-based violence during current and possible future pandemics. Health professionals, media, and community efforts must be combined to effectively deal with the issue of gender-based violence. Moreover, continuous and rigorous efforts are required to put an end to the stigma associated with gender-based violence.

CONCLUSION

The spread of the novel Coronavirus has created a myriad of problems for the people to grapple with. In the absence of a vaccine and effective treatment for this virus, the governments are forced to impose quarantines to reduce the spread of the disease. However, this has resulted in a paradox of social distancing, which includes issues such as economic instability, mental health problems, and isolation. Although there have been researches exploring the impact of COVID-19, there is a lack of rigorous literature highlighting these issues from the perspective of gender. This also involves the issue of rising gender violence during the pandemic. COVID-19 has not only led to an increase in the cases of gender-based violence but has disconnected them from their support networks. To reduce the prevalence of the issue, it is crucial to acknowledge the extent of gender-based violence, reimagine government policies, and support networks to make it easier for the victims to access them and, lastly, create awareness about the issue as well as the resources available to tackle it.

AUTHOR CONTRIBUTIONS

SM and TS contributed to the conception, structure of the paper, contributed to analysis, and interpretation of available literature. SM contributed to the development initial draft. TS reviewed and critiqued the output for important intellectual content. All authors contributed to the article and approved the submitted version.

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General Mental Health State Indicators in Argentinean Women During Quarantine of up to 80-Day Duration for COVID-19 Pandemic

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Introduction: Argentinean quarantine during the COVID-19 pandemic is one of the most long-lasting worldwide. We focused on the first 80-days of this quarantine on Argentinean women. Our aims were to analyze differences in general mental health state (MHS) indicators, by the (1) sites of residence with different prevalence of COVID-19 cases, and (2) quarantine duration; (3) to assess multiple relationships between each general MHS indicator and potentially affecting factors.

Methods: We used a cross-sectional design with convenience successive sampling ($N = 5{,}013$). The online survey included a socio-demographic questionnaire (elaborated *ad hoc*) with standardized and validated self-reported questionnaires (General Health Questionnaire, Kessler Psychological Distress Scale) measuring the MHS indicators: self-perceived health, psychological discomfort, social functioning and coping, and psychological distress.

Results: Worse self-perceived health and higher psychological discomfort affected significantly more women residing in sites with high prevalence of COVID-19 cases, compared to those residing in sites with intermediate prevalence, but effect sizes were small. Mean scores of all general MHS indicators were significantly worse for longer quarantine sub-periods (up to 53, 68, and 80-day duration) than for shorter sub-periods (up to seven, 13, and 25-day duration). Being a younger age, having mental disorder history, and longer quarantine durations were associated to worsening MHS, while the lack of previous suicide attempt has a protective effect.

Discussion: Our findings show that a worse MHS during quarantine may not be attributed to the objective risk of contagion (measured greater or less), and under quarantine, women MHS—as indicated by group central tendency measures—got worse as time went by. This strongly suggests that special attention needs to be paid to younger women and to women with history of mental disorder. Along with physical health, mental health must be a priority for the Government during and after quarantine and the COVID-19 pandemic.

Keywords: coronavirus, women's mental health, psychological distress, COVID-19, coping, social functioning, self-perceived health, quarantine

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INTRODUCTION

The outbreak of the COVID-19 (coronavirus disease) started in Wuhan, China, on 31st December 2019. This virus promptly spread around the world, leading to the current COVID-19 pandemic declared on 11th March 2020 (1). On 1st August, 17,396,943 persons have become infected and 675,060 deaths have occurred globally due to the COVID-19 (2). On the same date, there were a total of 195,543 confirmed cases of COVID-19 and 3,596 fatal cases due to this disease in Argentina (3). In addition, there are a wide range of health concerns, beyond those physical effects directly attributable to the virus itself (4), which should be recognized in order to allow developing and implementing responses possible. Among such health concerns are mental health issues.

Due to the pandemic, hundreds of countries have adopted old-style sanitary measures—e.g., isolation, quarantine, social distancing, and community containment. As effective vaccine against COVID-19 is still unavailable, these measures play a critical role in containing the disease spread-rates (5). However, quarantine and social distancing-related measures due to the COVID-19 pandemic may produce undesirable mental health effects in the general population (6–8), such as anxiety, depressive symptoms, stress, and insomnia (8), among others. In addition, it is suspected that prolonged quarantine duration is likely to exacerbate these effects (6).

The negative mental health impacts of quarantine may vary by context and by groups. To the best of our knowledge, there are no studies focusing on the mental health effects of quarantine in women during the current pandemic of COVID-19, except for studies on particular women sub-groups, such as during pregnancy or within the first year after delivery (9, 10). Notwithstanding, women are one of the groups which may be particularly vulnerable to suffer from higher negative impacts on mental health from both the pandemic and the social distancing measures (11). Indeed, during the current pandemic, a nationwide survey among Chinese people showed that women had significantly higher psychological distress than their men counterparts (12). In view of all the aforementioned, research focusing on women mental health is a pressing request.

In Argentina, mandatory quarantine was established for all inhabitants—except for workers on essential services—since 20th March 2020 and for a duration of 2-weeks. Nonetheless, several quarantine extensions were afterward necessary. On 30th July, eight quarantine extensions had occurred, corresponding to a quarantine duration of 133-days and counting. Whether a negative mental health impact of quarantine is dependent on duration, lengthy Argentinean quarantines should indicate certain insights about it. In this paper, we focused on the first 80-days of this quarantine.

The aims of this research are 3-fold: to analyze differences in general mental health state (MHS) indicators (in terms of self-perceived health, psychological discomfort, social functioning and coping, and psychological distress), in Argentinean women, by (1) sites of residence with different prevalence of COVID-19 cases (per 100,000 inhabitants), and (2) quarantine duration; (3) to assess multiple relationships between each general MHS indicator and potentially affecting factors (age, sites of residence by prevalence of COVID-19 cases, mental disorder history, suicide attempt history, and quarantine duration) in the entire sample.

METHODS

Sample and Procedure

This study used a cross-sectional design. Sampling was one of convenience, with successive samples, and included 5,013 Argentinean women from 18 years of age [M_{age} = 25.71, standard error [s.e.] ± 0.12; Median = 23; Range = 18–75], residing in one of the 23 Argentinean provinces, the Buenos Aires City (CABA) or momentarily stranded abroad due to travel bans and airport closures due the COVID-19 pandemic (**Table S1**). Data were collected since 17th March (i.e., 3 days before quarantine became mandatory in Argentina, but when quarantine was already strongly recommended by the Government to all Argentinean inhabitants) until 4th June 2020 (i.e., during mandatory Argentinean quarantine, up to the 5th quarantine extension announced by the Government, inclusive). Collection procedure was carried out via online, using Lime Survey software (UNC official license). This study was advertised in social networks with a brief mention to the general aim, general inclusion criteria (being women, Argentinean, being 18 years of age or older, currently reside in Argentina), and the link for the online survey. Upon accessing the survey, participants were initially presented with the information sheet and informed consent form approved by the Ethics Committee of the Institute of Psychological Research, Faculty of Psychology, National University of Córdoba (CEIIPsi-UNC-CONICET; comite.etica.iipsi@psicologia.unc.edu.ar).

Instruments

Sociodemographic questionnaire. We developed a brief *ad hoc* questionnaire on sociodemographic data and other factors potentially affecting the current MHS. With this instrument we asked the participants about: age; current site of residence (options available between: each one of the 23 Argentinean provinces, the CABA or momentarily stranded abroad); mental disorder history (yes or no); suicide attempt history (yes, no, ideation); date (automatically recorded by the online survey system).

General Health Questionnaire (GHQ-12) (13). We used the Argentinean validation (Cronbach's alpha = 0.80) of the GHQ-12 (14). This is a 12-item measure, which evaluates the general dimension of *self-perceived health* and allows for discrimination in two sub-dimensions (6 items each): (a) unspecific psychological well-being/discomfort (hereinafter named as *psychological discomfort*), and (b) social functioning and coping. In the GHQ-12, the higher the score, the worse is the self-perceived health. In this research, we informed scores on the general dimension and on the two sub-dimensions. We used the dichotomous scoring (0-0-1-1), whose range of scores is between 0 and 12 for the entire scale and is between 0 and 6 for each sub-dimension. For this form of scoring, the cutoff scores for the entire scale indicating common mental disorders are 4 or

5 (13). We adopted the higher cutoff score (i.e., 5) for the entire scale. There are no cutoff scores for the sub-dimensions.

Kessler Psychological Distress Scale (K-10) (15). We used the Argentinean validation (Cronbach's alpha = 0.88) of the K-10 (16). This is a 10-item global dimensional measure of non-specific psychological distress (hereinafter named as *psychological distress*), which evaluates symptoms related to depression and anxiety, indicating the risk to suffer psychological distress but does not specify the disorder. The range of the K-10 scores is between 0 and 50, where a higher score indicates a higher psychological distress. This scale discriminates with precision between community cases and non-cases of DSM-IV disorders (17). Since there are no cutoff scores specific to the Argentinean population, we adopted the cutoff score of 20 (18) for deciding between cases and non-cases of any depressive and/or anxiety disorder. In addition, we used the following classification of the psychological distress: low (scores between 10 and 15), moderate (scores between 16 and 21), severe (scores between 22 and 29), and very severe (scores between 30 and 50) (19).

Data Analysis

We performed all data analysis with RStudio version 3.6.2 (20). We considered $p \leq 0.05$ as statistically significant. We report exact *p*-values, except for *p*-values under 0.001, where we report as < 0.001. Likewise, 95% confidence interval (CI) is informed when corresponded. Skewness and kurtosis were calculated in all indicators of general MHS, since it were in the range of acceptable values [−1 to +1 for skewness and −3 and +3 for kurtosis; (21)] (see **Supplementary Material**), parametric tests were applied.

For analyses corresponding to the first aim, we established the following categories of prevalence of COVID-19 confirmed cases per 100,000 inhabitants, based on official available data from 10th June (22): low (up to 10 confirmed cases per 100,000 inhabitants), intermediate (between 11 and 25 confirmed cases per 100,000 inhabitants), intermediate to high (between 26 and 50 confirmed cases per 100,000 inhabitants), and high (> 50 confirmed cases per 100,000 inhabitants). Then, we grouped the sites of residence into these categories of prevalence of COVID-19. However, each site of residence corresponded to one of three of these categories, but none corresponded to the intermediate to high category (**Table S2**). Thus, prevalence categories grouping all our samples were as follow: *low* ($n = 952$ participants from the provinces of Jujuy, Salta, Tucumán, Santiago del Estero, Formosa, Misiones, Entre Ríos, Catamarca, San Juan, San Luis, La Pampa, and Chubut), *intermediate* ($n = 1{,}938$ participants from the provinces of Corrientes, Santa Fe, Mendoza, La Rioja, Córdoba, Neuquén, and Santa Cruz), and *high* ($n = 2{,}123$ participants from the provinces of Buenos Aires, CABA, Chaco, Río Negro, Tierra del Fuego, and currently stranded abroad). As stated in the first aim, we analyzed differences in each general MHS indicator (i.e., self-perceived health, psychological discomfort, social functioning and coping, and psychological distress) by the sites of residence with different prevalence of COVID-19 cases. Additionally, we explored differences in age, in proportions of mental disorder history (presence), and in proportions of suicide attempt history (presence, absence, ideation) by the sites of residence with different prevalence of COVID-19 cases.

For addressing the second aim, we divided the entire sample into six groups according to the sub-periods of quarantine duration: (a) participants answering during 17–23 March 2020, i.e., first week of data collection before the quarantine extension, named as first *week pre-quarantine extension* ($n = 1{,}490$) and corresponding to a quarantine duration of up to 7-days; (b) participants answering during 24–29 March 2020, named as second *week pre-quarantine extension* ($n = 495$) and corresponding to a quarantine duration of up to 13-days; (c) participants answering during 30 March-10 April 2020, i.e., sub-period after the first quarantine extension, named as first *extension* ($n = 766$) and corresponding to a quarantine duration of up to 25-days; (d) participants answering during 11 April-08 May 2020, i.e., sub-period after the second quarantine extension and including the third extension, named as *second/third extensions* ($n = 594$) and corresponding to a quarantine duration of up to 53-days; (e) participants answering during 09–23 May 2020, i.e., sub-period after the fourth quarantine extension, named as *fourth extension* ($n = 652$) and corresponding to a quarantine duration of up to 68-days; (f) participants answering during 24 May-04 June 2020, i.e., sub-period after the fifth quarantine extension, named as fifth *extension* ($n = 1{,}016$) and corresponding to a quarantine duration of up to 80-days. As stated in the second aim, we analyzed differences in each general MHS indicator (i.e., self-perceived health, psychological discomfort, social functioning and coping, and psychological distress) by quarantine duration. Additionally, we explored differences in age, in proportions of mental disorder history (presence), and in proportions of suicide attempt history (presence, absence, ideation) by quarantine duration.

For addressing the first and second aims of this research, we applied one-way between-groups ANOVA (when the criterion variable was numerical) or test for equality of proportions (when the criterion variable was categorical). When significant differences were found, Tukey's *post hoc* test or pairwise comparisons of proportions (Test of equal or given proportions with two-sided alternative hypothesis) were applied, correspondingly.

For addressing the third aim, we run multiple linear regressions rather than ANCOVA because the emphasis of this aim was on the dependent outcome variable. We considered the following potentially affecting factors: age, sites of residence by prevalence of COVID-19 cases, mental disorder history, suicide attempt history, and quarantine duration. We considered these based on both the literature (6) and findings from a previous analysis we have carried out in another sample of Argentinean population of both sexes (López Steinmetz et al. under review). Prior to running regression analyses, we assessed multicollinearity by using the variance inflation factor (VIF), the mean VIF, and the tolerance statistics, and we adopted the following criteria for interpreting these outcomes: a) if the largest VIF is > 10, then there is cause of concern, b) if the average VIF is substantially > 1, then the regression may be biased, c) tolerance below 0.1 and below 0.2 indicates a serious and a potential problem, respectively (23). For the initial model, the VIF values were all well below 10, the tolerance statistics were all well above 0.2, and the average VIF was close to 1

(**Table S3**), indicating that there was no collinearity within our data. Thus, for each general MHS indicator (i.e., self-perceived health, psychological discomfort, social functioning and coping, and psychological distress), we tested (with the *lm* function) a starting model including all the predictors mentioned above (i.e, age, sites of residence by prevalence of COVID-19 cases, mental disorder history, suicide attempt history, and quarantine duration) for the entire sample. We used a stepwise method of regression where decisions about the order in which predictors are entered into the model are based on a purely mathematical criterion (23). Specifically, for each MHS indicator, we performed a stepwise model selection in both directions (i.e., forward and backward) by using the exact Akaike's Information Criterion (AIC). To do this, we used the *stepAIC* function from the *MASS* package. This function performs stepwise model selection by using the exact AIC to compare fitted models, where the smaller the AIC indicates a better fit. For each general MHS indicator, we tried only additive models. For the model best fitting each MHS indicator, we reported 95% confidence interval (CI), the coefficient of determination (r^2), and the adjusted R-squared (adj r^2). Likewise, for providing a measure of error prediction, we calculated the error rate by dividing the residual standard error (RSE) by the mean outcome variable.

For analyses corresponding to the three aims, we computed effect sizes (ES) by using the *effectsize::cohens_f* function from the *sjstats* package. We adopted the Cohen's effect size conventions, for one-way ANOVA: $f = 0.10$ small, $f = 0.25$ medium, and $f = 0.40$ large; for multiple regression: $f = 0.02$ small, $f = 0.15$ medium, and $f = 0.35$ large.

RESULTS

Differences in General Mental Health State by Sites of Residence With Different Prevalence of COVID-19

Regarding general MHS by sites of residence with different prevalence of COVID-19 cases, statistically significant differences were found in self-perceived health [$F_{(2)} = 5.15$, $p = 0.006$; ES = 0.05, 90% CI: 0.02–0.07] and in psychological discomfort [$F_{(2)} = 5.66$, $p = 0.003$; ES = 0.05, 90% CI: 0.02–0.07]. In both MHS indicators, these differences were observed between the high and the intermediate prevalence of COVID-19 cases. In self-perceived health, differences were also meaningful between the low and the intermediate level of prevalence of COVID-19 cases (**Table 1**). In all sites, the mean scores of self-perceived health were above the cutoff score indicating common mental disorders (**Table 2**). In addition, a significant difference was found in social functioning and coping by sites of residence with different prevalence of COVID-19 cases [$F_{(2)} = 3.17$, $p = 0.04$; ES = 0.04, 90% CI: 0.00–0.06], but this difference does not remain significant in the *post hoc* test (**Table 1**). Likewise, no significant differences were found in psychological distress [$F_{(2)} = 0.35$, $p = 0.71$; ES = 0.01, 90% CI: 0.00–0.03; **Table 1**]. In all sites, the mean scores of psychological distress were above the cutoff score for deciding between cases and non-cases of any depressive and/or anxiety disorder; mean scores in all sites indicated severe psychological distress (**Table 2**).

The age of participants significantly differed between sites of residence with different prevalence of COVID-19 cases [$F_{(2)} = 3.64$, $p = 0.03$], although with a small

TABLE 1 | Multiple comparisons of means[a] in general mental health state (MHS) scores and mean age by sites of residence with different prevalence of COVID-19 cases.

MHS indicators and age	Sites of residence by prevalence levels of COVID-19 cases[b]	Dif	95% CI		*p* adj[c]
			Lower	Upper	
Self-perceived health	Intermediate-High	−0.32	−0.58	−0.07	**0.008**
	Low-High	−0.002	−0.32	0.31	1.00
	Low-Intermediate	0.32	−0.0004	0.64	**0.05**
Psychological discomfort	Intermediate-High	−0.19	−0.33	−0.05	**0.003**
	Low-High	−0.03	−0.20	0.14	0.90
	Low-Intermediate	0.16	−0.01	0.33	0.08
Social functioning and coping	Intermediate-High	−0.13	−0.28	0.01	0.08
	Low-High	0.03	−0.15	0.21	0.92
	Low-Intermediate	0.16	−0.02	0.34	0.09
Psychological distress	Intermediate-High	−0.21	−0.82	0.40	0.69
	Low-High	−0.06	−0.81	0.70	0.98
	Low-Intermediate	0.16	−0.61	0.92	0.88
Age	Intermediate-High	0.43	−0.21	1.08	0.25
	Low-High	0.89	0.09	1.69	**0.02**
	Low-Intermediate	0.46	−0.35	1.27	0.38

Dif, Difference; 95% CI, 95% Confidence Interval; Lower—Upper, Lower and upper limits of 95% confidence intervals; p adj, Adjusted p-value; Low, up to 10 confirmed cases of COVID-19 per 100,000 inhabitants; Intermediate, between 11 and 25 confirmed cases of COVID-19 per 100,000 inhabitants; High, > 50 confirmed cases of COVID-19 per 100,000 inhabitants.

[a]*Multiple comparisons of means were carried out with Tukey post hoc test.*

[b]*Categories based on available official data published by the Argentinean Government on 10th June 2020 (22): low (up to 10 confirmed cases per 100,000 inhabitants), intermediate (between 11 and 25 confirmed cases per 100,000 inhabitants), intermediate to high (between 26 and 50 confirmed cases per 100,000 inhabitants), and high (> 50 confirmed cases per 100,000 inhabitants). No sites corresponded to the intermediate to high category of prevalence.*

[c]*Exact p-values are informed, except for p-values under 0.001, which are informed as < 0.001. Statistically significant p-values are highlighted in bold.*

TABLE 2 | Mental health state, age, mental disorder history, and suicide attempt history by sites of residence with different prevalence of COVID-19 cases.

Mental health-related variables[a]	Sites of residence by prevalence of COVID-19 cases[b] Low (n = 952)	Intermediate (n = 1,938)	High (n = 2,123)
Self-perceived health	5.83 (± 0.11)	5.51 (± 0.08)	5.83 (± 0.07)
Psychological discomfort	3.43 (± 0.06)	3.27 (± 0.04)	3.46 (± 0.04)
Social functioning and coping	2.40 (± 0.06)	2.24 (± 0.04)	2.37 (± 0.04)
Psychological distress	26.40 (± 0.27)	26.25 (± 0.19)	26.46 (± 0.18)
Age	26.27 (± 0.27)	25.81 (± 0.21)	25.38 (± 0.18)
Mental disorder history (presence or absence)	25.73% presence, 74.26% absence	27.29% presence, 72.70% absence	26.80% presence, 73.20% absence
Suicide attempt history (presence, absence, ideation)	9.24% presence, 55.25% absence, 35.50% ideation	8.87% presence, 57.38% absence, 33.75% ideation	7.39% presence, 57.18% absence, 35.42% ideation

Low, up to 10 confirmed cases per 100,000 inhabitants; Intermediate, between 11 and 25 confirmed cases per 100,000 inhabitants; Intermediate to high, between 26 and 50 confirmed cases per 100,000 inhabitants; High, > 50 confirmed cases per 100,000 inhabitants.

[a] *For the variables self-perceived health, psychological discomfort, social functioning and coping, psychological distress, and age, mean and standard error are informed, while for mental disorder history and suicide attempt history, distributions by percentages are informed.*

[b] *Categories based on available official data published by the Argentinean Government on 10th June 2020 (22). No sites corresponded to the intermediate to high category of prevalence.*

effect size (ES = 0.04, 90% CI: 0.01–0.06). However, the difference was only meaningful between sites with low and high prevalence of COVID-19 cases, but not between sites with low and intermediate prevalence, nor between intermediate and high prevalence of COVID-19 cases (**Table 1**). Likewise, by sites of residence with low, intermediate, and high prevalence of COVID-19 cases, no differences were found in proportions of participants having mental disorder history [X-squared$_{(2)}$ = 0.79, p = 0.67] nor in proportions of participants with suicide attempt history [X-squared$_{(2)}$ = 4.23, p = 0.12], without suicide attempt history [X-squared$_{(2)}$ = 1.30, p = 0.52] or with suicidal ideation history [X-squared$_{(2)}$ = 1.52, p = 0.47]. Mean age of participants and proportions of participants having mental disorder history and suicide attempt history by sites of residence are shown in **Table 2**.

Differences in General Mental Health State by Quarantine Sub-periods

Regarding general MHS by quarantine sub-periods, statistically significant differences were found in all the indicators measured, i.e., in self-perceived health [$F_{(5)} = 16.18$, $p < 0.001$; ES = 0.13, 90% CI: 0.10–0.15], in psychological discomfort [$F_{(5)} = 19.69$, $p < 0.001$; ES = 0.14, 90% CI: 0.11–0.16], in social functioning and coping [$F_{(5)} = 8.69$, $p < 0.001$; ES = 0.09, 90% CI: 0.06–0.11], and in psychological distress [$F_{(5)} = 9.59$, $p < 0.001$; ES = 0.10, 90% CI: 0.07–0.12]. Several differences were observed between sub-periods before quarantine extensions and sub-periods after quarantine extensions (**Table 3**). In general, mean scores of MHS during sub-periods before quarantine extensions were lower than the mean scores after the extensions, mainly, during sub-periods corresponding to the second/third, fourth, and fifth extensions of quarantine (**Table 4**; **Figures 1–4**). In all of the quarantine sub-periods, mean scores of self-perceived health were above the cutoff score indicating common mental disorders. Likewise, in all of the sub-periods, mean scores of psychological distress were above the cutoff score for deciding between cases and non-cases of any depressive and/or anxiety disorder. For all sub-periods, mean scores indicated severe psychological distress (**Table 4**).

The age of participants significantly differed by quarantine sub-periods [$F_{(2)} = 89.90$, $p < 0.001$], with a medium effect size (ES = 0.30, 90% CI: 0.27–0.32) (**Table 3**). In general, the mean age of the sub-group of participants was higher for all quarantine extensions (i.e., four of the six sub-periods analyzed) compared to quarantine prior extensions (**Table 4**). On the other hand, there were no significant differences in participants with mental disorder history [X-squared$_{(5)}$ = 8.30, p = 0.14] nor with suicide attempt history [X-squared$_{(5)}$ = 3.67, p = 0.60] by quarantine sub-periods. However, there were significant differences in participants without suicide attempt history [X-squared$_{(5)}$ = 33.62, $p < 0.001$] and with suicidal ideation history [X-squared$_{(5)}$ = 37.18, $p < 0.001$] by quarantine sub-periods. For the absence of suicide attempt history, these differences were only meaningful between the first week of pre-quarantine extension (lower proportions of participants without suicide attempt history) and the first, fourth, and fifth extensions (higher proportions of participants without suicide attempt history). For suicidal ideation history, these differences were only meaningful between the first week pre-quarantine extension (higher proportions of participants with suicidal ideation history) and the first, second/third, fourth, and fifth extensions (lower proportions of participants with suicidal ideation history). Results on pairwise comparisons of proportions in participants both without suicide attempt history and with suicidal ideation history are shown in **Table 5**. Proportions of participants having mental disorder history and suicide attempt history by quarantine sub-periods are shown in **Table 4**.

Regression Models for General Mental Health State Indicators

The initial regression model for each general MHS indicator included the predictors: age, sites of residence by prevalence of COVID-19 cases, mental disorder history, suicide attempt history, and sub-periods of quarantine duration. The minimum suitable model best fitting the data was the same as the model from the start, i.e., included all the predictors, for the MHS indicators self-perceived health [$F_{(11 \text{ and } 5001)} = 52.44$, $p < 0.001$, Residuals: −7.88 to 9.12; AIC = 11941.75], psychological discomfort [$F_{(11 \text{ and } 5001)} = 31.87$, $p < 0.001$, Residuals: −4.39 to 4.13; AIC = 5911.25], and social functioning and coping [$F_{(11 \text{ and } 5001)} = 56.49$, $p < 0.001$, Residuals: −3.63 to 5.45;

TABLE 3 | Multiple comparisons[a] of means in general mental health state (MHS) scores and age by quarantine sub-periods.

MHS indicators and age	Quarantine sub-periods	Dif	95% CI		*p* adj[b]
			Lower	Upper	
Self-perceived health	1. First week pre-extension–2. Second week pre-extension	0.06	−0.45	0.57	1.00
	1. First week pre-extension–3. First extension	0.17	−0.26	0.61	0.86
	1. First week pre-extension–4. Second/third extensions	0.95	0.48	1.43	**< 0.001**
	1. First week pre-extension–5. Fourth extension	0.91	0.45	1.37	**< 0.001**
	1. First week pre-extension–6. Fifth extension	0.93	0.53	1.33	**< 0.001**
	2. Second week pre-extension–3. First extension	0.11	−0.45	0.68	0.99
	2. Second week pre-extension–4. Second/third extensions	0.89	0.30	1.49	**< 0.001**
	2. Second week pre-extension–5. Fourth extension	0.85	0.26	1.43	**< 0.001**
	2. Second week pre-extension–6. Fifth extension	0.87	0.33	1.41	**< 0.001**
	3. First extension–4. Second/third extensions	0.78	0.24	1.32	**< 0.001**
	3. First extension–5. Fourth extension	0.73	0.21	1.26	**0.001**
	3. First extension–6. Fifth extension	0.76	0.29	1.23	**< 0.001**
	4. Second/third extensions–5. Fourth extension	−0.04	−0.60	0.51	1.00
	4. Second/third extensions–6. Fifth extension	−0.02	−0.53	0.48	1.00
	5. Fourth extension–6. Fifth extension	0.02	−0.47	0.51	1.00
Psychological discomfort	1. First week pre-extension–2. Second week pre-extension	−0.06	−0.33	0.21	0.99
	1. First week pre-extension–3. First extension	0.04	−0.19	0.28	0.99
	1. First week pre-extension–4. Second/third extensions	0.52	0.27	0.78	**< 0.001**
	1. First week pre-extension–5. Fourth extension	0.50	0.25	0.75	**< 0.001**
	1. First week pre-extension–6. Fifth extension	0.52	0.31	0.74	**< 0.001**
	2. Second week pre-extension–3. First extension	0.10	−0.20	0.41	0.92
	2. Second week pre-extension–4. Second/third extensions	0.58	0.26	0.90	**< 0.001**
	2. Second week pre-extension–5. Fourth extension	0.56	0.25	0.88	**< 0.001**
	2. Second week pre-extension–6. Fifth extension	0.59	0.30	0.88	**< 0.001**
	3. First extension–4. Second/third extensions	0.48	0.19	0.77	**< 0.001**
	3. First extension–5. Fourth extension	0.46	0.18	0.74	**< 0.001**
	3. First extension–6. Fifth extension	0.48	0.23	0.73	**< 0.001**
	4. Second/third extensions–5. Fourth extension	−0.02	−0.32	0.28	1.00
	4. Second/third extensions–6. Fifth extension	0.004	−0.27	0.27	1.00
	5. Fourth extension–6. Fifth extension	0.02	−0.24	0.29	1.00
Social functioning and coping	1. First week pre-extension–2. Second week pre-extension	0.12	−0.17	0.41	0.83
	1. First week pre-extension–3. First extension	0.13	−0.12	0.38	0.66
	1. First week pre-extension–4. Second/third extensions	0.43	0.16	0.70	**< 0.001**
	1. First week pre-extension–5. Fourth extension	0.41	0.14	0.67	**< 0.001**
	1. First week pre-extension–6. Fifth extension	0.41	0.18	0.63	**< 0.001**
	2. Second week pre-extension–3. First extension	0.01	−0.31	0.33	1.00
	2. Second week pre-extension–4. Second/third extensions	0.31	−0.03	0.65	0.10
	2. Second week pre-extension–5. Fourth extension	0.28	−0.05	0.62	0.15
	2. Second week pre-extension–6. Fifth extension	0.28	−0.02	0.59	0.10
	3. First extension–4. Second/third extensions	0.30	−0.01	0.61	0.06
	3. First extension–5. Fourth extension	0.27	−0.02	0.57	0.10
	3. First extension–6. Fifth extension	0.27	0.01	0.54	**0.04**
	4. Second/third extensions–5. Fourth extension	−0.02	−0.34	0.29	1.00
	4. Second/third extensions–6. Fifth extension	−0.03	−0.32	0.26	1.00
	5. Fourth extension–6. Fifth extension	−0.001	−0.28	0.28	1.00
Psychological distress	1. First week pre-extension–2. Second week pre-extension	−0.16	−1.38	1.06	1.00
	1. First week pre-extension–3. First extension	−1.16	−2.21	−0.12	**0.02**
	1. First week pre-extension–4. Second/third extensions	0.92	−0.22	2.06	0.20
	1. First week pre-extension–5. Fourth extension	0.91	−0.19	2.01	0.17

(Continued)

TABLE 3 | Continued

MHS indicators and age	Quarantine sub-periods	Dif	95% CI		*p* adj[b]
			Lower	Upper	
	1. First week pre-extension–6. Fifth extension	1.24	0.29	2.20	**0.003**
	2. Second week pre-extension–3. First extension	−1.00	−2.36	0.35	0.28
	2. Second week pre-extension–4. Second/third extensions	1.08	−0.35	2.51	0.26
	2. Second week pre-extension–5. Fourth extension	1.07	−0.33	2.47	0.25
	2. Second week pre-extension–6. Fifth extension	1.40	0.12	2.69	**0.02**
	3. First extension–4. Second/third extensions	2.08	0.80	3.37	**< 0.001**
	3. First extension–5. Fourth extension	2.07	0.82	3.33	**< 0.001**
	3. First extension–6. Fifth extension	2.41	1.29	3.54	**< 0.001**
	4. Second/third extensions–5. Fourth extension	−0.01	−1.34	1.32	1.00
	4. Second/third extensions–6. Fifth extension	0.33	−0.89	1.54	0.97
	5. Fourth extension–6. Fifth extension	0.34	−0.84	1.52	0.96
Age	1. First week pre-extension–2. Second week pre-extension	0.93	−0.30	2.17	0.26
	1. First week pre-extension–3. First extension	5.28	4.22	6.34	**< 0.001**
	1. First week pre-extension–4. Second/third extensions	5.80	4.65	6.96	**< 0.001**
	1. First week pre-extension–5. Fourth extension	4.02	2.90	5.14	**< 0.001**
	1. First week pre-extension–6. Fifth extension	5.61	4.64	6.58	**< 0.001**
	2. Second week pre-extension–3. First extension	4.34	2.97	5.72	**< 0.001**
	2. Second week pre-extension–4. Second/third extensions	4.87	3.42	6.32	**< 0.001**
	2. Second week pre-extension–5. Fourth extension	3.08	1.66	4.50	**< 0.001**
	2. Second week pre-extension–6. Fifth extension	4.67	3.37	5.98	**< 0.001**
	3. First extension–4. Second/third extensions	0.53	−0.78	1.83	0.86
	3. First extension–5. Fourth extension	−1.26	−2.53	0.01	0.05
	3. First extension–6. Fifth extension	0.33	−0.81	1.47	0.96
	4. Second/third extensions–5. Fourth extension	−1.79	−3.14	−0.44	**0.002**
	4. Second/third extensions–6. Fifth extension	−0.20	−1.43	1.03	0.99
	5. Fourth extension–6. Fifth extension	1.59	0.39	2.79	**0.002**

Dif, Difference; 95% CI, 95% Confidence Interval; Lower—Upper, Lower and upper limits of 95% confidence intervals; p adj, Adjusted p-value; Low, up to 10 confirmed cases of COVID-19 per 100,000 inhabitants; Intermediate, between 11 and 25 confirmed cases of COVID-19 per 100,000 inhabitants; High, > 50 confirmed cases of COVID-19 per 100,000 inhabitants. 1. First week pre-extension = First week of quarantine before extension, including participants answering during 17–23 March 2020; 2. Second week pre-extension = Second week of quarantine before extension, including participants answering during 24–29 March 2020; 3. First extension = Sub-period after the first quarantine extension, including participants answering during 30 March to 10 April 2020; 4. Second/third extensions = Sub-period after the second quarantine extension and including the third extension, with participants answering during 11 April to 08 May 2020; 5. Fourth extension = Sub-period after the fourth quarantine extension, including participants answering during 09–23 May 2020; 6. Fifth extension = Sub-period after the fifth quarantine extension, including participants answering during 24 May to 04 June 2020.

[a] *Multiple comparisons of means were carried out with Tukey post hoc test.*

[b] *Exact p-values are informed, except for p-values under 0.001, which are informed as < 0.001. Statistically significant p-values are highlighted in bold.*

AIC = 6248.35; **Table 6**]. This model explained 10.34% of variance in the participants' self-perceived health according to r^2 (10.14% according to adjusted r^2), with a RSE of 3.29, corresponding to 57.58% error rate. For psychological discomfort, the model explained only 6.55% of variance according to r^2 (6.34% according to adjusted r^2), with a RSE of 1.80, corresponding to 53.30% error rate. For both self-perceived health and psychological discomfort, the largest effect sizes corresponded to the predictors: suicide attempt history and sub-periods of quarantine duration (**Table 7**). For social functioning and coping, the model explained 11.05% of variance according to r^2 (10.86% according to adjusted r^2), with a RSE of 1.86, corresponding to 80% error rate. The largest effect sizes corresponded to the predictors: suicide attempt history and age (**Table 7**). Overall, being a younger age, having mental disorder history, and longer quarantine durations were correlated to worst self-perceived health, higher levels of psychological discomfort, and worst social functioning and coping; while lack of previous suicide attempt and residing in sites with intermediate prevalence of COVID-19 cases had a protective effect on these MHS indicators. Residing in sites with a low prevalence of COVID-19 also had a protective effect on psychological discomfort (**Table 6**).

For psychological distress, the best fitting model included almost all of the predictors as the model from the start, except sites of residence by prevalence of COVID-19 cases [$F_{(9 \text{ and } 5003)} = 132.10$, $p < 0.001$, Residuals: −22.87 to 25.67; AIC = 20143.82; **Table 6**]. This model explained 19.20% of variance in the participants' psychological distress according to r^2 (19.06% according to adjusted r^2) with a RSE of 7.45, corresponding to 28.25% error rate. Being a younger age, having mental disorder history, having suicide attempt

TABLE 4 | Mental health state, age, mental disorder history, and suicide attempt history by quarantine sub-periods.

Mental health-related variables[a]	Quarantine sub-periods					
	1. First week pre-extension (*n* = 1,490)	**2. Second week pre-extension (*n* = 495)**	**3. First extension (*n* = 766)**	**4. Second/third extensions (*n* = 594)**	**5. Fourth extension (*n* = 652)**	**6. Fifth extension (*n* = 1,016)**
Self-perceived health	5.25 (± 0.08)	5.31 (± 0.15)	5.43 (±0.13)	6.21 (± 0.15)	6.16 (± 0.13)	6.19 (± 0.11)
Psychological discomfort	3.15 (± 0.05)	3.08 (± 0.08)	3.19 (± 0.07)	3.67 (± 0.08)	3.65 (± 0.07)	3.67 (± 0.06)
Social functioning and coping	2.11 (± 0.05)	2.23 (± 0.08)	2.24 (± 0.07)	2.54 (± 0.08)	2.52 (± 0.08)	2.51 (± 0.06)
Psychological distress	26.08 (± 0.21)	25.92 (± 0.37)	24.92 (± 0.29)	27.00 (± 0.36)	27.00 (± 0.32)	27.33 (± 0.26)
Age	22.47 (± 0.10)	23.40 (± 0.24)	27.74 (± 0.38)	28.27 (± 0.40)	26.48 (± 0.37)	28.08 (± 0.33)
Mental disorder history (presence or absence)	25.91% presence, 74.09% absence	24.04% presence, 75.96% absence	26.76% presence, 73.24% absence	27.44% presence, 72.56% absence	25.46% presence, 74.54% absence	29.92% presence, 70.08% absence
Suicide attempt history (presence, absence, ideation)	7.92% presence, 51.54% absence, 40.54% ideation	9.29% presence, 53.53% absence, 37.17% ideation	8.49% presence, 59.79% absence, 31.72% ideation	9.76% presence, 58.08% absence, 32.15% ideation	7.21% presence, 60.74% absence, 32.05% ideation	8.17% presence, 61.02% absence, 30.81% ideation

1. First week pre-extension = First week of quarantine before extension, including participants answering during 17–23 March 2020; 2. Second week pre-extension = Second week of quarantine before extension, including participants answering during 24–29 March 2020; 3. First extension = Sub-period after the first quarantine extension, including participants answering during 30 March to 10 April 2020; 4. Second/third extensions = Sub-period after the second quarantine extension and including the third extension, with participants answering during 11 April to 08 May 2020; 5. Fourth extension = Sub-period after the fourth quarantine extension, including participants answering during 09–23 May 2020; 6. Fifth extension = Sub-period after the fifth quarantine extension, including participants answering during 24 May to 04 June 2020.

[a]*For the variables self-perceived health, psychological discomfort, social functioning and coping, psychological distress, and age, mean, and standard error are informed, while for mental disorder history, and suicide attempt history, percentages are informed.*

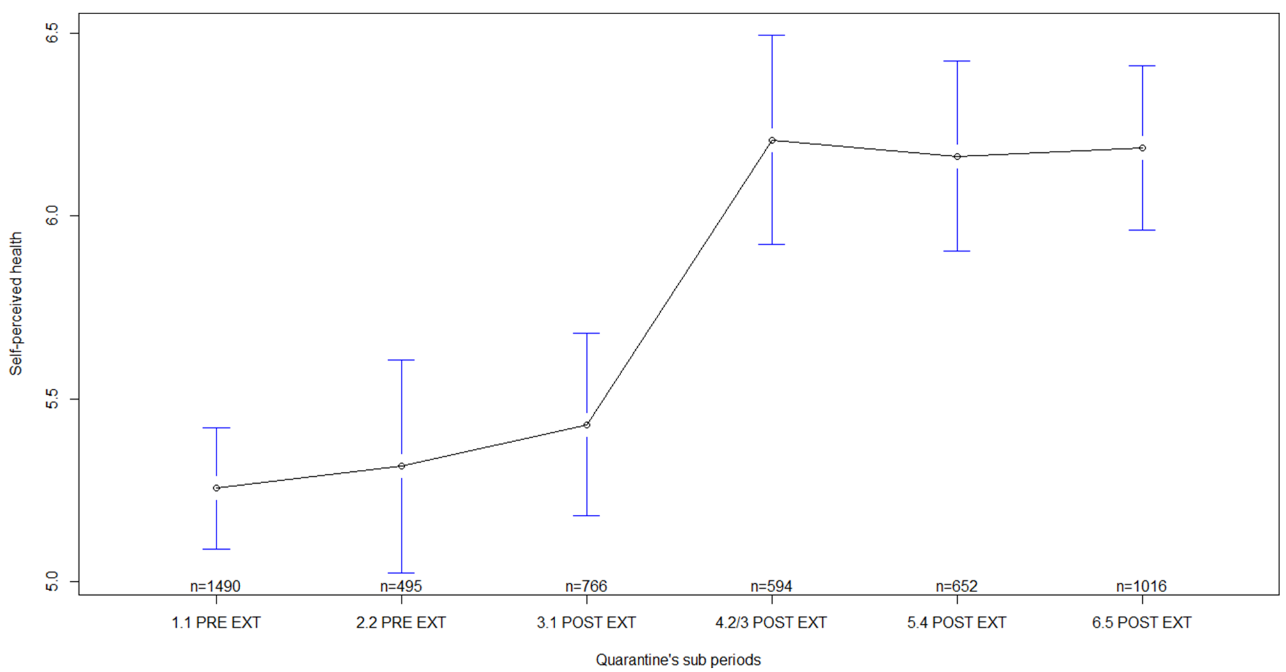

FIGURE 1 | Self-perceived health by quarantine sub-periods. Mean plot with 95% confidence interval. Self-perceived health as measured by the General Health Questionnaire (scores from the entire scale), in which higher scores indicate worse self-perceived health. 1.1 PRE EXT = First week of quarantine before extension, including participants answering during 17–23 March 2020; 2.2 PRE EXT = Second week of quarantine before extension, including participants answering during 24–29 March 2020; 3.1 POST EXT = Sub-period after the first quarantine extension, including participants answering during 30 March to 10 April 2020; 4.2/3 POST EXT = Sub-period after the second quarantine extension and including the third extension, with participants answering during 11 April to 08 May 2020; 5.4 POST EXT = Sub-period after the fourth quarantine extension, including participants answering during 09–23 May 2020; 6.5 POST EXT = Sub-period after the fifth quarantine extension, including participants answering during 24 May to 04 June 2020.

history, and longer quarantine durations were correlated to higher levels of psychological distress; while lack of previous suicide attempt had a protective effect on this MHS indicator. The largest effect sizes corresponded to the predictors: suicide attempt history and mental disorder history (**Table 7**).

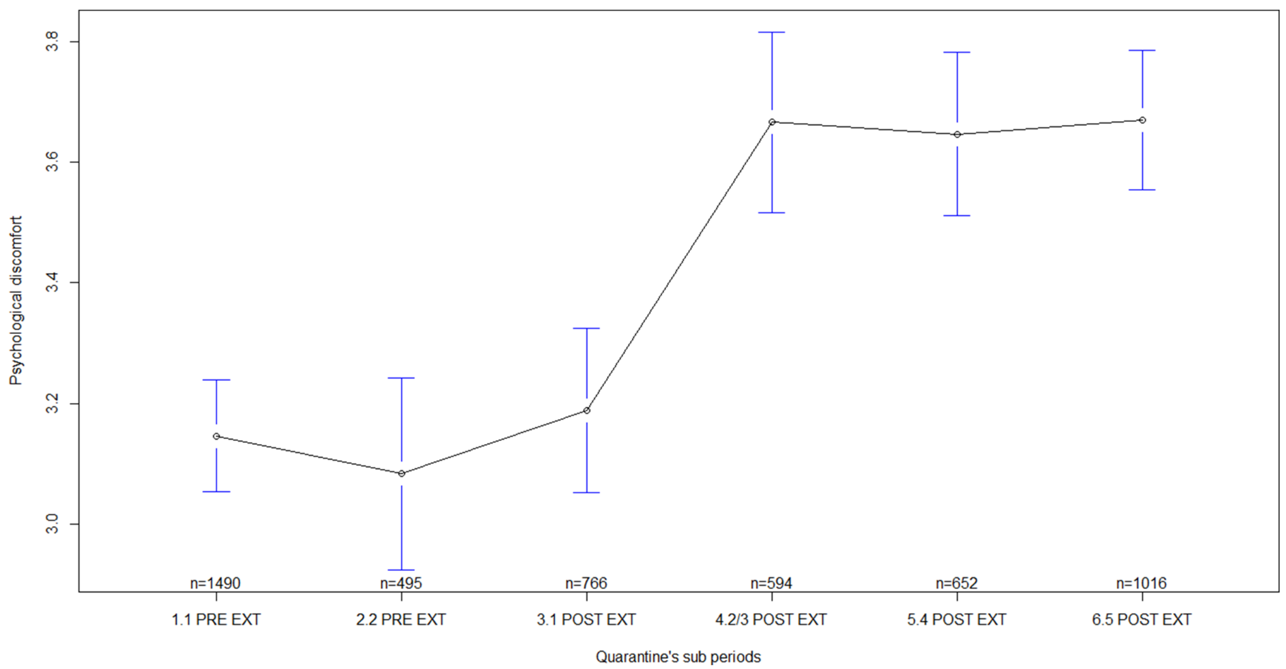

FIGURE 2 | Psychological discomfort by quarantine sub-periods. Mean plot with 95% confidence interval. Psychological discomfort as measured by the General Health Questionnaire (scores from the sub-scale measuring unspecific psychological well-being/discomfort), in which higher scores indicate higher psychological discomfort. 1.1 PRE EXT = First week of quarantine before extension, including participants answering during 17–23 March 2020; 2.2 PRE EXT = Second week of quarantine before extension, including participants answering during 24–29 March 2020; 3.1 POST EXT = Sub-period after the first quarantine extension, including participants answering during 30 March to 10 April 2020; 4.2/3 POST EXT = Sub-period after the second quarantine extension and including the third extension, with participants answering during 11 April to 08 May 2020; 5.4 POST EXT = Sub-period after the fourth quarantine extension, including participants answering during 09–23 May 2020; 6.5 POST EXT = Sub-period after the fifth quarantine extension, including participants answering during 24 May to 04 June 2020.

DISCUSSION

Differences in General Mental Health State by Sites of Residence With Different Prevalence of COVID-19

In the first aim of this research, we analyzed differences in general MHS indicators, in Argentinean women, by sites of residence with different prevalence of COVID-19 cases. Worse self-perceived health and higher psychological discomfort affected significantly more women residing in sites with high prevalence of COVID-19 cases, compared to those residing in sites with intermediate prevalence of this disease. At a first glance, it could be presumed that mental health impacts on women during quarantine may be attributed to the objective risk of contagion (greater or less measured in an area). However, our findings do not support this assumption due to a number of reasons. First, these MHS indicators are worse in sites with low prevalence of COVID-19 compared to sites with intermediate prevalence of this disease. Second, rather than differences are meaningful between sites with high and low prevalence of COVID-19, mean scores are equal (in self-perceived health) or quite similar (in psychological discomfort) between these sites. Third, the remaining MHS indicators, i.e., social functioning and coping and psychological distress, do not differ by sites of residence with low, intermediate, and high prevalence of COVID-19. Fourth, when statistical significant differences were found, effect size measures were very small. Fifth, in sites of residence with low as well as with intermediate and high prevalence of COVID-19, mean scores of self-perceived health and of psychological distress overcome the cutoff scores for mental disorders. Some of these findings are consistent with what we have previously found on college students, whose differences in psychological discomfort by regions of residence were only meaningful between the most populated and center regions, which correspond to sites with high and intermediate prevalence of COVID-19 cases, respectively, but not between the remaining sites of residence (López Steinmetz et al. under review). Unlike COVID-19 cases, mental health affections seem to be equally distributed throughout the whole country, which may suggest that the prevalence of the latter may be higher than the former. In line with our findings, a study carried out in China found that the specific location of residence, within or outside the epicenter of the pandemic, do not seem to be significantly associated to more or less mental health problems; instead of the specific location, the direct exposure to COVID-19 seems to be relevant (24).

Differences in General Mental Health State by Quarantine Sub-periods

Regarding the second aim of this research, the mean scores of all general MHS indicators in women are significantly worse for

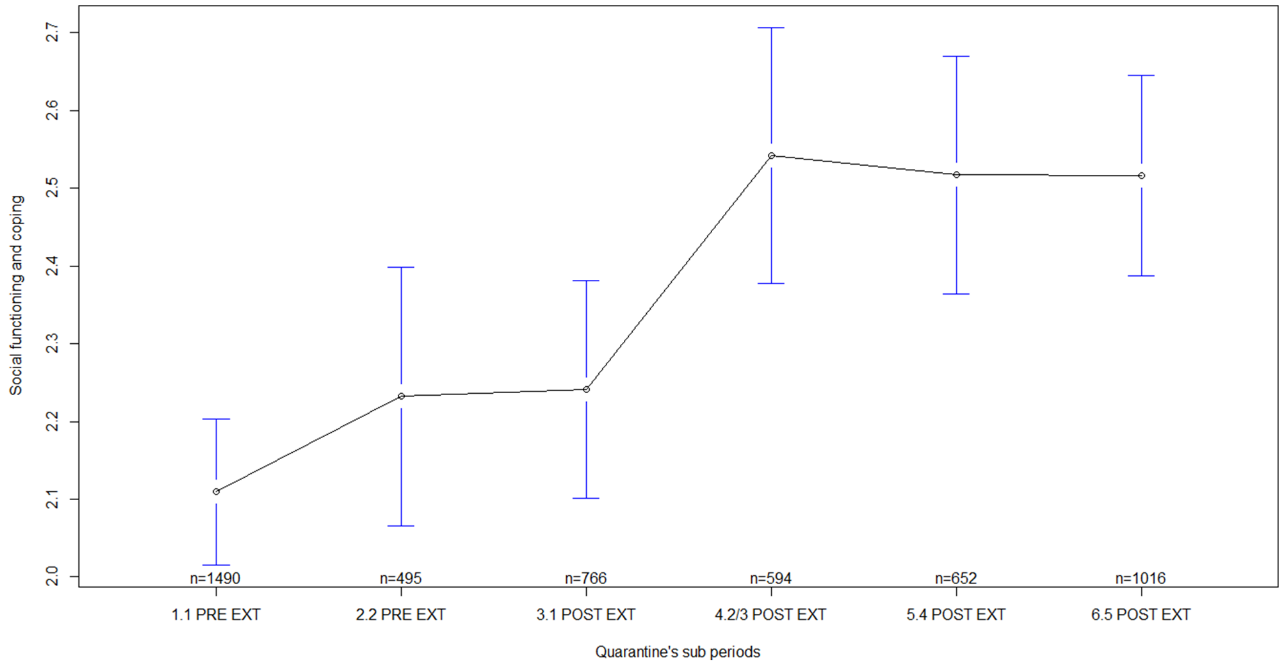

FIGURE 3 | Social functioning and coping by quarantine sub-periods. Mean plot with 95% confidence interval. Social functioning and coping as measured by the General Health Questionnaire (scores from the sub-scale measuring social functioning and coping), in which higher scores indicate worse social functioning and coping. 1.1 PRE EXT = First week of quarantine before extension, including participants answering during 17–23 March 2020; 2.2 PRE EXT = Second week of quarantine before extension, including participants answering during 24–29 March 2020; 3.1 POST EXT = Sub-period after the first quarantine extension, including participants answering during 30 March to 10 April 2020; 4.2/3 POST EXT = Sub-period after the second quarantine extension and including the third extension, with participants answering during 11 April to 08 May 2020; 5.4 POST EXT = Sub-period after the fourth quarantine extension, including participants answering during 09–23 May 2020; 6.5 POST EXT = Sub-period after the fifth quarantine extension, including participants answering during 24 May to 04 June 2020.

longer quarantine sub-periods (up to 53, 68, and 80-day duration, i.e., second/third, fourth, and fifth extensions, respectively) than for shorter sub-periods (up to seven, 13, and 25-day duration, i.e., first and second week of pre-quarantine extension, and first extension, respectively), and these differences are somewhat largest for self-perceived health and psychological discomfort than for social functioning and coping and psychological distress. This worsening pattern that we have found on mental health as time went by does not seem to be privative of women, since we have also observed it in college students (López Steinmetz et al. under review) and in the general population of both sexes (López Steinmetz et al. under review). Although this worsening pattern is not observed solely in women, the possibility exists that negative mental health impact may be worse in women than in men (25, 26). In line with our results, a current study has also found that mental health state worsens as the time spent in lockdown has progressed (27). On the contrary, findings of a study carried out in China by Wang et al. (26) reported a significant reduction on post-traumatic stress disorder symptoms along with no significant longitudinal changes in stress, anxiety, and depression 4 weeks after the COVID-19 outbreak. Unfortunately, in the Chinese study, the authors did not indicate if both measures—during the initial outbreak and 4 weeks later—or just one of them was under social isolation sanitary measures. In addition, it is important to note that the results of the cited study was conducted prior to the COVID-19 infection reaching the state of pandemic and although it is announced as a longitudinal study, the majority of data (1,405 participants of $N = 1,738$) analyzed in such study are in fact transversal samples, as our samples are. Our results are in line with findings based on previous quarantine-related situations reporting that longer durations of quarantine are associated with increased psychological symptoms (28–30). However, it is important to note that most of these previous studies investigating the impact of quarantine duration focused on people quarantined because they became infected by a particular disease, or belong to particular occupational groups, such as nurses and other healthcare workers. However, it was demonstrated that healthcare workers tend to be at high risk of developing mental illness than other occupational groups during current (31) and previous (32) epidemics and pandemics. Bearing all these in mind, our findings are novel since they bring additional insights on mental health impact of quarantine duration in non-infected women of the general population.

Finally, in the additional exploratory analyses corresponding to aim 2, we noticed some differences in the composition of participants' sub-group regarding with age—where greater mean age of sub-groups corresponded to longer quarantine durations—and also regarding suicide attempt history—where greater proportions of participants without suicide attempt history and lower proportions of participants with suicidal ideation history responded during longer quarantine durations. On the one hand, these results indicate that, since we have

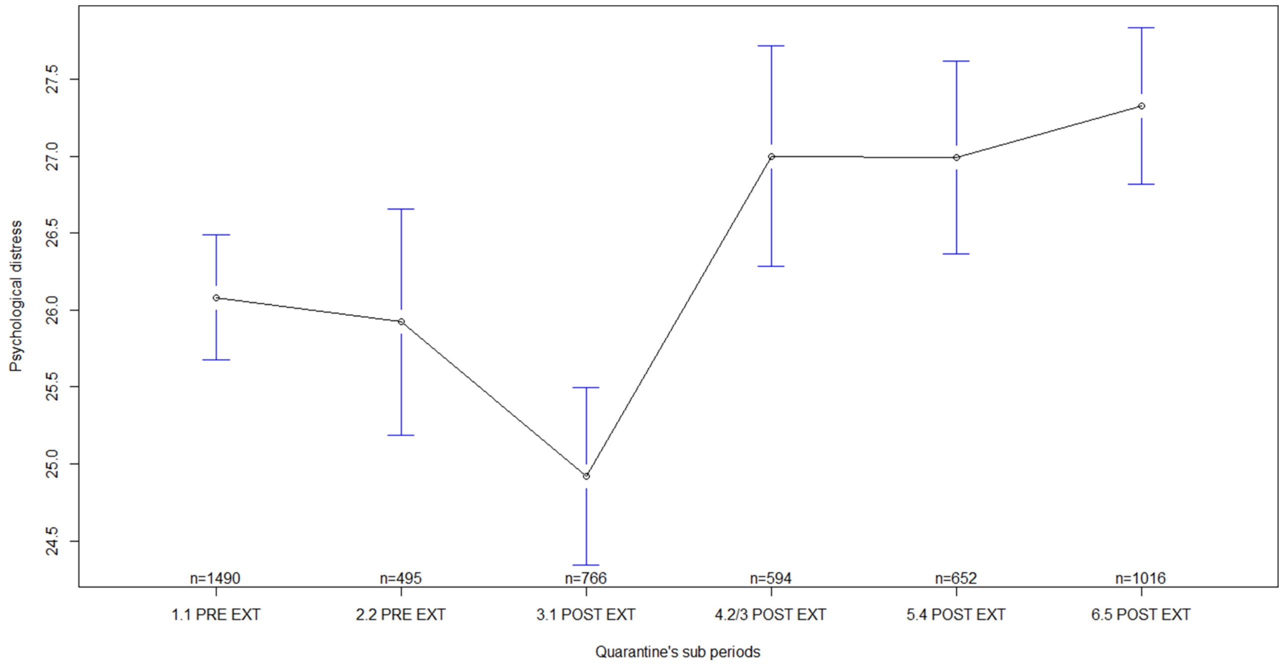

FIGURE 4 | Psychological distress by quarantine sub-periods. Mean plot with 95% confidence interval. Psychological distress as measured by the Kessler Psychological Distress Scale, in which higher scores indicate higher psychological distress. 1.1 PRE EXT = First week of quarantine before extension, including participants answering during 17–23 March 2020; 2.2 PRE EXT = Second week of quarantine before extension, including participants answering during 24–29 March 2020; 3.1 POST EXT = Sub-period after the first quarantine extension, including participants answering during 30 March to 10 April 2020; 4.2/3 POST EXT = Sub-period after the second quarantine extension and including the third extension, with participants answering during 11 April to 08 May 2020; 5.4 POST EXT = Sub-period after the fourth quarantine extension, including participants answering during 09–23 May 2020; 6.5 POST EXT = Sub-period after the fifth quarantine extension, including participants answering during 24 May to 04 June 2020.

TABLE 5 | Pairwise comparisons of proportions in participants without suicide attempt history (lower triangle) and with suicidal ideation history (upper triangle) by quarantine sub-periods.

	Pairwise comparisons of proportions[a] (*p*-values[b])					
Quarantine sub-periods	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**
1. First week pre-extension	–	1.00	**0.001**	**0.005**	**0.003**	**< 0.001**
2. Second week pre-extension	1.00	–	0.53	0.76	0.73	0.17
3. First extension	**0.003**	0.29	–	1.00	1.00	1.00
4. Second/third extensions	0.09	1.00	1.00	–	1.00	1.00
5. Fourth extension	**0.001**	0.17	1.00	1.00	–	1.00
6. Fifth extension	**< 0.001**	0.08	1.00	1.00	1.00	–

1. First week pre-extension = First week of quarantine before extension, including participants answering during 17–23 March 2020; 2. Second week pre-extension = Second week of quarantine before extension, including participants answering during 24–29 March 2020; 3. First extension = Sub-period after the first quarantine extension, including participants answering during 30 March to 10 April 2020; 4. Second/third extensions = Sub-period after the second quarantine extension and including the third extension, with participants answering during 11 April to 08 May 2020; 5. Fourth extension = Sub-period after the fourth quarantine extension, including participants answering during 09–23 May 2020; 6. Fifth extension = Sub-period after the fifth quarantine extension, including participants answering during 24 May to 04 June 2020.

[a] *Pairwise comparisons of proportions were carried out with Test of equal or given proportions, alternative hypothesis two-sided.*

[b] *Exact p-values are informed, except for p-values under 0.001, which are informed as < 0.001. Statistically significant p-values are highlighted in bold.*

not included covariates in ANOVAs, differences on MHS by quarantine durations and further analyses (i.e., multiple linear regressions) should be interpreted with caution. Although this is true, on the other hand, all these results indirectly indicate that when worse mean scores on MHS were recorded (i.e., during longer quarantine durations): (a) older participants were responding to the survey, and (b) higher proportions of participants without suicide attempt history and lower proportions of participants with suicidal ideation history were responding to the survey. Thus, if younger age results as being a predictor of worse MHS and if the absence of suicide attempt history results as being a protective factor for MHS this would not be due to differences in the composition of participants' sub-group.

TABLE 6 | Summary of the linear regression models better fitting[a] each general mental health state (MHS) indicator ($N = 5{,}013$).

MHS indicator	Predictors	Estimate	Std. Error	*t*-value	*p-value*[b]	95% CI	
						2.5%	97.5%
Self-perceived health	Intercept	7.63	0.16	46.19	**< 0.001**	7.31	7.96
	Age	−0.07	0.01	−12.00	**< 0.001**	−0.08	−0.06
	Prevalence of COVID-19: intermediate	−0.31	0.10	−2.98	**0.003**	−0.51	−0.11
	Prevalence of COVID-19: low	−0.21	0.13	−1.57	0.12	−0.47	0.05
	Mental disorder history: yes	0.31	0.11	2.87	**0.004**	0.10	0.53
	Suicide attempt history: no	−1.51	0.10	−14.63	**< 0.001**	−1.71	−1.30
	Suicide attempt history: yes	−0.13	0.18	−0.70	0.48	−0.48	0.23
	Quarantine sub-periods: 2. 2nd pre-ext.	0.19	0.17	1.09	0.28	−0.15	0.52
	Quarantine sub-periods: 3. 1st ext.	0.64	0.15	4.30	**< 0.001**	0.35	0.93
	Quarantine sub-periods: 4. 2nd/3rd ext.	1.45	0.16	8.82	**< 0.001**	1.13	1.77
	Quarantine sub-periods: 5. 4th ext.	1.33	0.16	8.16	**< 0.001**	1.01	1.65
	Quarantine sub-periods: 6. 5th ext.	1.46	0.14	10.63	**< 0.001**	1.19	1.73
Psychological discomfort	Intercept	4.10	0.09	45.26	**< 0.001**	3.92	4.28
	Age	−0.03	0.003	−8.66	**< 0.001**	−0.03	−0.02
	Prevalence of COVID-19: intermediate	−0.19	0.06	−3.27	**0.001**	−0.30	−0.07
	Prevalence of COVID-19: low	−0.14	0.07	−1.96	**0.05**	−0.29	0.0003
	Mental disorder history: yes	0.17	0.06	2.90	**0.004**	0.06	0.29
	Suicide attempt history: no	−0.57	0.06	−10.04	**< 0.001**	−0.68	−0.46
	Suicide attempt history: yes	−0.14	0.10	−1.40	0.16	−0.33	0.05
	Quarantine sub-periods: 2. 2nd pre-ext.	−0.01	0.09	−0.06	0.95	−0.19	0.18
	Quarantine sub-periods: 3. 1st ext.	0.22	0.08	2.73	**0.007**	0.06	0.38
	Quarantine sub-periods: 4. 2nd/3rd ext.	0.72	0.09	8.01	**< 0.001**	0.54	0.90
	Quarantine sub-periods: 5. 4th ext.	0.67	0.09	7.54	**< 0.001**	0.50	0.85
	Quarantine sub-periods: 6. 5th ext.	0.73	0.07	9.75	**< 0.001**	0.59	0.88
Social functioning and coping	Intercept	3.53	0.09	37.73	**< 0.001**	3.35	3.72
	Age	−0.04	0.003	−12.78	**< 0.001**	−0.05	−0.03
	Prevalence of COVID-19: intermediate	−0.12	0.06	−2.09	**0.04**	−0.24	−0.01
	Prevalence of COVID-19: low	−0.07	0.08	−0.88	0.38	−0.22	0.08
	Mental disorder history: yes	0.14	0.06	2.26	**0.02**	0.02	0.26
	Suicide attempt history: no	−0.94	0.06	−16.11	**< 0.001**	−1.05	−0.83
	Suicide attempt history: yes	0.01	0.10	0.11	0.91	−0.19	0.21
	Quarantine sub-periods: 2. 2nd pre-ext.	0.19	0.10	1.98	**0.05**	0.002	0.38
	Quarantine sub-periods: 3. 1st ext.	0.42	0.08	4.95	**< 0.001**	0.25	0.58
	Quarantine sub-periods: 4. 2nd/3rd ext.	0.73	0.09	7.82	**< 0.001**	0.55	0.91
	Quarantine sub-periods: 5. 4th ext.	0.66	0.09	7.11	**< 0.001**	0.47	0.84
	Quarantine sub-periods: 6. 5th ext.	0.73	0.08	9.34	**< 0.001**	0.58	0.88
Psychological distress	Intercept	31.99	0.36	89.11	**< 0.001**	31.29	32.70
	Age	−0.18	0.02	−13.90	**< 0.001**	−0.20	−0.15
	Mental disorder history: yes	2.32	0.25	9.34	**< 0.001**	1.83	2.80
	Suicide attempt history: no	−5.09	0.23	−21.80	**< 0.001**	−5.54	−4.63
	Suicide attempt history: yes	1.31	0.41	3.20	**0.001**	0.51	2.12
	Quarantine sub-periods: 2. 2nd pre-ext.	0.13	0.39	0.34	0.73	−0.63	0.89
	Quarantine sub-periods: 3. 1st ext.	0.16	0.34	0.49	0.62	−0.50	0.83
	Quarantine sub-periods: 4. 2nd/3rd ext.	2.22	0.37	6.02	**< 0.001**	1.50	2.95
	Quarantine sub-periods: 5. 4th ext.	2.11	0.35	5.97	**< 0.001**	1.42	2.80
	Quarantine sub-periods: 6. 5th ext.	2.63	0.31	8.44	**< 0.001**	2.02	3.24

Std. Error, Standard error; 95% CI, 95% Confidence Interval; Prevalence of COVID-19 (Sites of residence by prevalence of COVID-19 cases): Low, up to 10 confirmed cases of COVID-19 per 100,000 inhabitants; Intermediate, between 11 and 25 confirmed cases of COVID-19 per 100,000 inhabitants; High, > 50 confirmed cases of COVID-19 per 100,000 inhabitants; Mental disorder history: yes, Presence of mental disorder history; no, Absence of mental disorder history; Suicide attempt history: yes, Presence of suicide attempt history; no, Absence of suicide attempt history; Quarantine sub-periods: 1. 1st pre-ext., First week of quarantine before extension, including participants answering during 17–23 March 2020; 2. 2nd pre-ext., Second week of quarantine before extension, including participants answering during 24–29 March 2020; 3. 1st ext., Sub-period after the first quarantine extension, including participants answering during 30 March to 10 April 2020; 4. 2nd/3rd ext., Sub-period after the second quarantine extension and including the third extension, with participants answering during 11 April to 08 May 2020; 5. 4th ext., Sub-period after the fourth quarantine extension, including participants answering during 09–23 May 2020; 6. 5th ext., Sub-period after the fifth quarantine extension, including participants answering during 24 May to 04 June 2020.

[a] *Best fitted model according to multiple linear regressions: stepwise selection (direction: both) by using the exact Akaike's Information Criterion (AIC) to compare additive fitted models.*

[b] *Exact p-values are informed, except for p-values under 0.001, which are informed as < 0.001. Statistically significant p-values are highlighted in bold.*

TABLE 7 | Summary of Cohen's effect size for models better fitting each general mental health state (MHS) indicator (*N* = 5,013).

MHS indicator	Predictors	*f*	90% CI	
Self-perceived health	Age	0.16	0.14	0.19
	Cases per inhabitant	0.05	0.02	0.07
	Mental disorder history	0.09	0.07	0.12
	Suicide attempt history	0.21	0.18	0.23
	Sub-periods of quarantine duration	0.19	0.16	0.21
Psychological discomfort	Age	0.11	0.08	0.13
	Cases per inhabitant	0.05	0.02	0.07
	Mental disorder history	0.08	0.05	0.10
	Suicide attempt history	0.14	0.11	0.16
	Sub-periods of quarantine duration	0.18	0.15	0.20
Social functioning and coping	Age	0.19	0.16	0.21
	Cases per inhabitant	0.04	0.01	0.06
	Mental disorder history	0.09	0.07	0.12
	Suicide attempt history	0.23	0.21	0.26
	Sub-periods of quarantine duration	0.16	0.13	0.18
Psychological distress	Age	0.22	0.20	0.24
	Mental disorder history	0.23	0.20	0.28
	Suicide attempt history	0.34	0.31	0.36
	Sub-periods of quarantine duration	0.15	0.13	0.17

f, Cohen's f (partial); 90% CI, 90% Confidence Interval.

Regression Models for General Mental Health State Indicators

When assessing the effects on each specific MHS indicator of potentially affecting factors, we found that—in general terms—being a younger age, having mental disorder history, and longer quarantine durations are associated to worsening mental health in women, while a lack of previous suicide attempt has a protective effect on all the MHS indicators measured. Residing in sites with intermediate prevalence of COVID-19 cases also provided a protective effect for self-perceived health, psychological discomfort, and social functioning and coping in women. Regarding age, prior to the current pandemic, literature reported that young people were one of the most vulnerable age groups for developing mental health disorders (33, 34). With the current mass quarantine for the COVID-19 pandemic, schools and college closures have been conducted in hundreds of countries, such as Argentina, affecting more females than males (35). Such closures along with other activity cessations (e.g., group sports activities) disallow young people to access social support organizations e.g., peer support groups, and may in turn cause additional negative mental health impacts (36), thus increasing the vulnerability in developing mental disorders. In line with our findings, a younger age and female gender were previously indicated as pre-quarantine predictors associated with negative psychological impacts (6, 37).

It is important to note that school closures not only disrupt the lives of students, but also of their families (38). This would mean a challenge for parents, who must acquire and perform additional functions, such as emerging educators. Pandemic-related sanitary measures like quarantine, place parents as the first-line of responders for children's survival, care, and learning (39). However, in Argentina these additional roles are overloaded mainly to women, who became full-time caregivers, are overworked, experienced more fatigue than before the quarantine, and sleep less than necessary (40). It may be presumed that this is the case not only in Argentina. In non-quarantine-related situations, women still undertake twice as much routine housework as men do, and more unbalanced divisions of housework were associated to greater depression and less marital satisfaction in women (41). However, across the transition to parenthood, for working-class women, the division of child-care could be more relevant in predicting distress than the division of housework (42). Nonetheless, there are evidences to expect that increased family demands are likely to be primarily shouldered by women (43). In addition, quarantine situations have the potential of exacerbating intimate partner violence, which is most frequently suffered by women than by men (44, 45). Women who have undergone intimate partner violence are, in turn, at a greater risk of multiple mental health and physical conditions (46).

Conclusions

All the aspects described above suggest that women are a special vulnerable group for developing mental disorders during quarantine. As longer quarantine durations (6, 28–30) and its extensions (47) were demonstrated as having a negative impact on mental health, and some of these effects may be long-lasting (48), there is an imperative need that the Government provides funding sources for developing sanitary programs targeted at the mental health of women. Our results suggest that special attention needs to be paid to younger women and also to women having a history of mental disorder. Along with physical health, mental health and psychological needs must start to be a priority for the Government during and after quarantine and the COVID-19 pandemic. In sanitary events such as epidemics and pandemics, the amount of people resulting with mental health affections is usually higher than people affected by the physical disease, and negative mental health effects tend to persist longer than the epidemic or pandemic; however, mental health or psychological needs have never been a priority during this kind of sanitary events (49, 50). As having a worsening mental health was demonstrated as being an adverse effect of pandemic-related sanitary measures (7, 11), which affects more in groups at particular risk, such as women (11), and although these negative mental health outcomes may not be entirely prevented, it should be addressed early. In this regard, findings of our study may be useful for public health officials and government officials who must decide upon sanitary measures and public policies; however, they need to be interpreted with caution and considered within the context of several limitations. First, this study was cross-sectional. However, we implemented successive sampling, which allowed us to monitor group central tendency measures through quarantine sub-periods; although prospective research is warranted. Second, our sample was one of convenience and it is unclear to what extent our results could be representative of the Argentinean women population. Nevertheless, it is important to note that we have analyzed a large sample (> 5,000), including data from participants throughout the whole country. Third, the sample was limited to a single country, thus, findings can only be interpreted within the context of Argentinean women. Fourth, our sample only includes women having access to the internet; thus, low-income women may be underrepresented. Likewise, we did not capture additional relevant factors such as family/household demands and domestic violence, which should be addressed in further research. Fifth, mental disorder was assessed as a binary variable, which does not adequately describe the complexity of mental health in the population, and the screening tools used provide limited information. Sixth, additional variables, such as physical comorbidities, pregnancy and postpartum conditions, should be included in further research, since these might have an influence on general mental health state. Despite these limitations, we believe that our findings remain valuable for developing evidence-based sanitary measures and help shed light for further research on women mental health impacts during the current quarantine, which is a pressing public health concern.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

This study involved human participants and was reviewed and approved by Ethics Committee of the Institute of Psychological Research, Faculty of Psychology, National University of Córdoba (CEIIPsi-UNC-CONICET; comite.etica.iipsi@psicologia.unc.edu.ar). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL has elaborated the research project, designed the online protocol of this research, participated in the data collection, made data analyzes, and wrote the manuscript. SF has participated in the data collection, made bibliography searches, and revised the manuscript for English grammar. CL and MD have participated in the data collection and carried-out bibliography searches. JG has participated in the data collection and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2020.580652/full#supplementary-material

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CASE REPORT
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Post Partum Death in a Patient Diagnosed With COVID-19

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Background: There are few case reports describing maternal mortality and intensive care of the pregnant patient with COVID-19 infection.

Case: A 27-year-old patient at 34 weeks of gestation was admitted for the evaluation of cough, fever, tachypnea, and oligohydramnios. The day of admission she underwent cesarean delivery for a non-reassuring fetal heart rate tracing. Over the next 6 days her clinical condition deteriorated, she developed multi organ system failure, and died despite aggressive supportive care.

Conclusion: Although mortality related to COVID-19 in pregnancy has been rarely reported to date, we describe a case of progressive clinical deterioration postpartum despite aggressive supportive care. Management strategies specific for pregnant women have not been developed. In timing delivery, the obstetrician must consider the possibility that the inflammatory response associated with CD may increase the risk for multiorgan system failure in parturients with COVID-19 while recognizing that risks to the fetus may be higher in patients with COVID-19 than in other critically ill parturients. Vertical transmission of infection to the neonate did not occur in our case and has not been demonstrated in other pregnancies with COVID-19 disease.

Keywords: corona virus disease (COVID-19), maternal mortality, respiratory failure, infectious disease, vertical transmission

INTRODUCTION

Corona virus disease has evolved into the worst worldwide pandemic since the influenza outbreak of 1918 (1). Although case series describe the disease course in pregnant women (2–5), there are few published reports of maternal death (6–8). We report such a case that occurred in Skopje, Macedonia in a woman who was symptomatic for COVID-19 at the time of delivery, became progressively more ill over the next 6 days, and died despite aggressive supportive care. The patient's family provided consent for publication of this report and accompanying images.

CASE

A 27-year-old G2P1 woman at 34 weeks gestation was admitted with a 4-day history of sore throat, cough, fever, and shortness of breath at the University Hospital of Gynecology and Obstetrics, Skopje, North Macedonia. Her past medical and obstetrical history was unremarkable, and her current pregnancy had been without incident until oligohydramnios was discovered on a routine screening ultrasound examination the day before admission. Her social history revealed that a father in law who resided with her was positive for COVID-19, and she resided in a community where COVID-19 was widespread.

Physical examination revealed a slightly dyspneic and febrile woman with a BP 115/70 mmHg, pulse 80 beats per minute, respiratory rate of 32 breaths per minute, an oxygen saturation of 94% on room air, temperature 38.1°C, and a BMI of 23.4 kg/m^2. Although her pulmonary examination was clear to auscultation, she could not hold her breath for >3 s. Initial laboratory findings (**Table 1**) showed a lymphopenia and no other significant abnormality. Her chest radiograph on the day of admission showed severe bilateral coalescent consolidative opacities suggestive of pneumonia (**Figure 1A**). Given the patient's presentation, naso, and oropharyngeal swabs were obtained for SARS-CoV-2RT-PCR test. She was placed in isolation and contact precautions were initiated using World Health Organization (WHO) guidelines (7). The test was reported positive 12 h later using WHO procedures for quantitative RT-PCR testing. An initial fetal evaluation with trans-vaginal and abdominal ultrasound and a non-stress test were reassuring with normal fetal heart rate with minimal variability and no uterine contractions. Fetal biophysical measurements were normal for gestational age with an amniotic fluid index of 2. A vaginal examination showed a cervix that was long thick and closed, and her Bishop's score was 2.

The patient was evaluated by the obstetric, infectious disease, and anesthesia services and a multidisciplinary plan was made. The patient received initial oxygen therapy with nasal cannula to maintain an oxygen saturation > 95%. A biophysical profile performed 12 h after admission showed a score of 4 and a dose of dexamethasone was administered. An induction of labor with oxytocin was stopped after severe late decelerations were noted. Because of the positive oxytocin challenge test and the potential for rapid maternal respiratory deterioration, the decision was made to proceed with an urgent cesarean delivery (CD) on the day of admission.

After antibiotic prophylaxis with 2 gm ceftriaxone, a successful CD was performed under spinal anesthesia with 10 mg isobaric 0.5% bupivacaine with 20 mcg fentanyl and 100 mcg morphine. All personnel followed WHO guidelines for isolation during the procedure. A vigorous 2.15 kg male with Apgar's 8 and 8 was kept in isolation after delivery and throat swabs for SARS-CoV-2RT were obtained. Postoperatively, the mother was returned to isolation in the recovery area. On the third day following delivery, the neonate's SARS-CoV-2RT test was reported negative and he was released from isolation.

After adequate recovery from anesthesia and assurance of no obstetrical complications, the mother was transferred the first post-delivery day to the University Clinic of Infectious Diseases hospital for further monitoring and treatment. Over the next 4 days, the patient was persistently febrile, with peek temperatures of 39°C, developed increasing shortness of breath despite antimicrobial therapy with meropenem, bronchodilator therapy with aminophylline, intravenous fluid, and anticoagulant therapy with therapeutic enoxaparin. A non-rebreathing mask was placed on the 4th post-delivery day. On the 5th day, she became somnolent, tachypneic (respiratory rate >40), her systolic BP was consistently below 90 mmHg, and her oxygen saturations fell to 80% despite oxygen flow rates > 10 L/m per non-rebreathing mask. An arterial blood gas showed a respiratory alkalosis and moderate hypoxemia. Her laboratory results showed a normal partial thromboplastin and prothrombin times despite a significantly elevated D-Dimers. (**Table 1**) She was endotracheally intubated, transferred to the intensive care unit, sedated, and vasopressor therapy with norepinephrine at 2.6 mcg/min and dobutamine at 500 mcg/min were begun. Her oxygenation saturation improved to > 95% after intubation with a peak inspiratory pressure of 40 cm H_2O, minute ventilation of 7 L/min, an FIO_2 of 100%, and PEEP of 12 cm H_2O;

TABLE 1 | Laboratory results during the patient's hospital stay.

Blood Laboratory test	Day of admission/ delivery	4 Days after delivery	5 Days after delivery	6 Days after delivery
Hemoglobin, gr/dL	11.0	12.1	12.0	9.8
WBC × 10^9/L	7.2	15.0	17.1	19.3
Lymphocytes, %	7	7	6	10
Neutrophils, %	89	89	91	84
Platelets × K/micL	249	231	208	306
Creatinine, md/dL	0.46	0.45	0.34	2.73
BUN, mg/dL	11	31	33	83
Sodium, mEq/L	140	146	142	144
Potassium, mEq/L	3.9	3.4	3.3	5.8
Calcium, mEq/L	1.97	2.08	1.93	1.73
AST, U/L	24	12	18	42
ALT, U/L	55	62	46	251
LDH, U/L	764	1,622	1,464	2,022
D-Dimer, ug/mL			35,712	
CPK, U/L	123	131	242	1,341
CK-MB, U/L				38
Troponin, ng/mL				7.73
PT, seconds			12.8	
PTT, seconds			36.4	
Arterial blood gas				
pH			7.52	
pCO_2, mmHg			25.2	
pO_2, mmHg			57.8	
BE			−0.5	
O_2 saturation, %			91	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPK, creatine phosphokinase; CK-MB, creatine kinase-MB; PT, prothrombin time; PTT, partial thromboplastin time; BE, base excess.

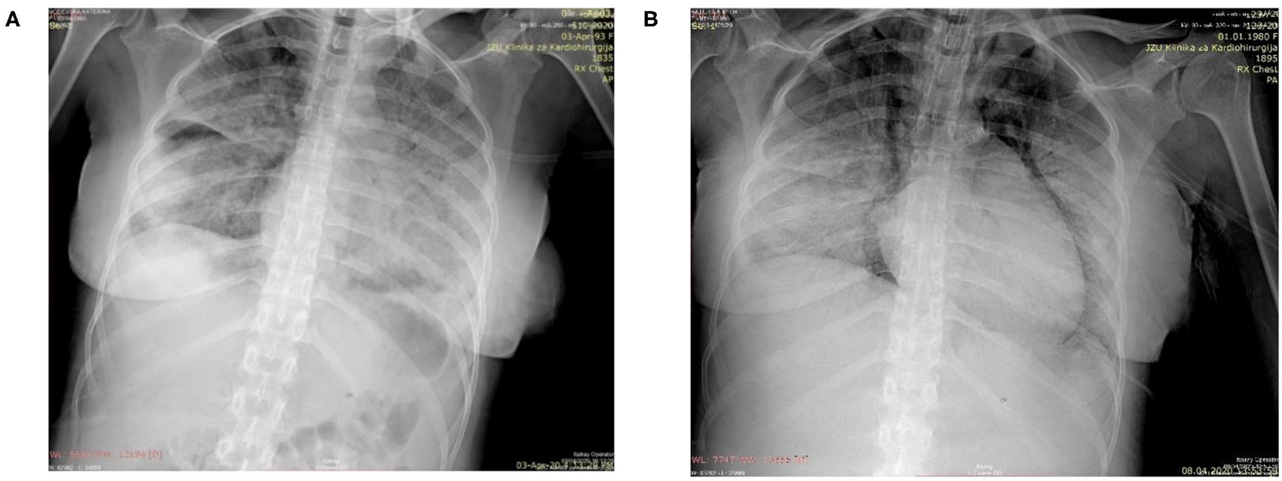

FIGURE 1 | (A) Chest radiograph on day of delivery showing extensive diffuse bilateral opacities suggestive of pneumonia; **(B)** Chest radiograph taken following endotracheal intubation on the 6th post-delivery day showing progression of pnuemonia, subcutaneous emphysema, pneumomediastinum, and prominent right heart contours suggestive of right heart failure.

her hemodynamics improved. However, over the next 24 h she became increasingly hypoxic (oxygen saturations < 80%) despite adjustments in ventilator settings. On the morning of the 6th post-delivery day, she showed laboratory signs of renal insufficiency, liver dysfunction, and significant myocardial damage (**Table 1**). She had a cardio-respiratory arrest later that evening from which she could not be resuscitated. A repeated chest radiograph taken just before her arrest showed progression of respiratory disease complicated by pneumomediastinum and right heart failure (**Figure 1B**).

DISCUSSION

We describe a maternal death following delivery in a pregnant patient suffering from COVID-19. Our patient suffered a cardiopulmonary arrest due to multi-organ system failure with significant signs of heart failure and myocardial damage. Her final radiograph showed evidence of pneumomediastinum, a sign of alveolar sac compromise, which could have abruptly progressed to a tension pneumothorax. Tension pneumothorax occurs in 30–60% of patients who are mechanically ventilated in the setting of multi-organ system failure (9). Spontaneous pneumothorax has been recently described in non-pregnant patients with CVOID-19 who present with respiratory distress (10). Although tension pneumothorax often leads to abrupt hemodynamic failure, our patient's rapid decline in respiratory and cardiac function over the day and a half prior to her arrest was most likely irreversible.

Hantoushzadeh et al. has reported the largest and most detailed case series of maternal deaths (8). Our patient presented with symptoms of dyspnea, fever, cough, and lymphopenia similar to the signs and symptoms reported in their case series and other case reports (2–8). Her course following delivery was also similar with increasing signs of respiratory failure and subsequent cardio-pulmonary failure despite maximal supportive therapy. In our patient, like others, the multi-organ failure that frequently accompanies ARDS was most likely causative, although the relative contributions of respiratory failure, pulmonary thromboembolism, and heart failure cannot be determined.

It is difficult to determine an accurate number of pregnant women who had COVID-19 infection, as many case series and systematic reviews include the same patients (6–8). Reports citing numbers of infections among pregnant patients are inaccurate as many reports come from areas in which undercounting of persons with infection is likely. Data from Centers for Disease Control in the U.S. suggest an overall death rate of 0.4% among persons 20–45, with women ∼2/3 less likely to die than men (11).

The physiological adaptations of pregnancy are thought to predispose parturients to greater risk for pulmonary and cardiac decompensation and a more severe course during pulmonary infection (12). Also, changes in the maternal immune response during pregnancy are thought to increase the risk of pulmonary infection from viruses other than COVID-19 and from bacterial pneumonias (12). However, an overly vigorous immune response may significantly contribute to the syndrome of respiratory and multi-organ failure reported in younger patients. The reduction in interleukin and cytokine release that occurs in normal pregnancy may reduce this response and thus decrease the risk for death in infected pregnant women (13). Although the absence of maternal death in early observational studies of COVID-19 suggests that pregnancy may protect against mortality, previous case series and our case report reinforce that this risk is not zero (1–5, 13–15). In the study by Hantoushzadeh et al., none of the household members of infected women died. In our case, the patient's father in law died from COVID-19. Surveillance studies with long term follow up that account for differences in baseline maternal mortality and adjust for potential co-morbidities that affect risk have not been done.

COVID-19 patients should not be delivered based on infection alone, but for obstetric or fetal indications (15). Timing delivery in the critically patient with COVID-19 may be difficult. Our patient was at risk for respiratory decompensation when admitted, showed signs of fetal non-well-being, and we chose to deliver her by urgent, non-emergent CD at 34 weeks. Many critically ill patients may be successfully cared for periods of time prior to delivery with good outcomes (16) and CD, like all surgical procedures, increases the maternal systemic inflammatory response (17). This increase may add to the overly vigorous innate immune response that is detrimental in patients with COVID-19, although as noted above, the attenuated immune responses that accompany pregnancy may be protective. Risks to the fetus in timing delivery must be carefully considered. Neonatal mortality may be higher in COVID-19 patients than among other critically ill parturients. Six of 11 neonates in the case series by Hantoushzadeh et al. died *in utero* or shortly after birth, despite the descriptions of good fetal surveillance (8).

Stroke and embolic and thrombotic disease of other organs systems is thought to significantly contribute to death from COVID-19 in younger victims, and some authors suggest that pregnant women may be no different (18). It is possible that thromboembolism significantly contributed to our patient demise. Her chest radiograph just before her cardiopulmonary arrest suggested right heart failure which often accompanies pulmonary thromboembolism and had markedly elevated d-Dimers just prior to death; however, significant elevation of d-Dimers often occurs from the disseminated intravascular coagulation associated with ARDS.

Cesarean delivery increases the risk for maternal thromboembolic events when compared to vaginal delivery (19) and the risk for thromboembolism after CD might be accentuated in parturients with COVID-19. If it is a significant contributor, then the routine post CD prophylactic measures described in all previous reports may not prevent it.

Like most of the pregnant women with COVID-19, our patient delivered preterm (2–8). The baby did not test positive for COVID-19 and did not exhibit any symptoms. This is similar to the report by Hantoushzadeh et al. which showed no vertical transmission in the 4 neonates who were tested (8). In those few cases where it has been suspected the neonate may have been infected following delivery (13). The virus has not been detected in amniotic fluid, umbilical cord blood, and is rarely present in the naso-pharyngeal tract of infants whose mothers had COVID-19 (13).

CONCLUSION

We present a case of death due to COVID-19 in a pregnant woman following delivery. Although maternal mortality following delivery has been infrequently reported and early surveys of patient outcomes suggest that the death rate among pregnant women with COVID-19 is different than among non-pregnant women, this conclusion nay be inaccurate. Thromboembolism may contribute to the respiratory failure accompanying COVID-19, but whether this risk is altered by pregnancy is unknown. In timing delivery, the obstetrician must consider the possibility that the inflammatory response associated with CD may increase the risk for multiorgan system failure in parturients with COVID-19 while recognizing that risks to the fetus may be higher in patients with COVID-19 than in other critically ill parturients. Post-delivery supportive care is like that in non-pregnant women and strategies specific for the pregnant women have not been developed. Vertical transmission of COVID-19 has not been conclusively demonstrated.

ETHICS STATEMENT

The Institutional Review Board of the University Hospital of Gynecology and Obstetrics, Skopje, North Macedonia provided permission for publication of this report and images as the deceased patient's family was lost to follow-up.

AUTHOR CONTRIBUTIONS

CB, IV, IM, and NP assisted in the writing of the manuscript and concurs with its content. AS, DK, ND, IA-P, and RK participated in care of the patient and in the writing of the manuscript and concurs with its content. All authors contributed to the article and approved the submitted version.

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OPINION
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Pregnant Women in Low- and Middle-Income Countries Require a Special Focus During the COVID-19 Pandemic

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INTRODUCTION

As the novel coronavirus (SARS-CoV-2) pandemic continues to spread, some predict a disproportionate toll on low- and middle-income countries (LMICs), as it stresses already under-resourced health systems in densely populated regions (1). Two LMICs, Brazil and India, are among the top three countries by number of confirmed COVID-19 cases (2). While the reported prevalence of COVID-19 in sub-Saharan Africa is currently lower than reports from Asia, North America, and Europe, epidemiological modeling suggests that nearly a quarter of a billion people in sub-Saharan Africa may contract SARS-CoV-2 in the first year of the pandemic (3). The UN estimates up to 3 million COVID-19-related deaths in the region (4). Furthermore, the spread of SARS-CoV-2 in LMICs threatens to further increase the burden of adverse birth outcomes among the majority of global pregnancies.

Globally, there are over 213 million pregnancies every year, of which an estimated 190 million (89%) occur in low resource settings where the risk of poor birth outcomes is highest (5). The contributing risk factors for these adverse outcomes are multifactorial: pregnant women in LMICs struggle to access antenatal care (6); an estimated 1 in 10 women in LMICs do not receive adequate nutrition in pregnancy (7); and the majority of pregnant women at risk of, or living with, malaria, HIV, and/or tuberculosis (TB) reside in LMICs (8, 9). High rates of these and other co-morbidities in pregnancy directly translate to adverse birth outcomes: more than 60% of children that are born preterm each year are born in sub-Saharan Africa and south Asia (e.g., India alone accounts for 23.6% of total global preterm births), accounting for over 750,000 deaths within the first month of life (**Figure 1**) (10).

COVID-19 is likely to influence maternal-child health in profound ways, from the physiological impact of the disease itself, to its indirect impacts on health systems, social, economic, and cultural structures, and by exacerbating pre-existing gender and healthcare access inequalities. Research is needed to identify the risks of COVID-19 in pregnancy, and its interplay with highly prevalent comorbidities already concentrated in LMICs including malnutrition, anemia, HIV, TB, and malaria. Identification and mitigation of both infectious and response-related barriers to health access and information for pregnant women during pandemics is essential for protecting the health

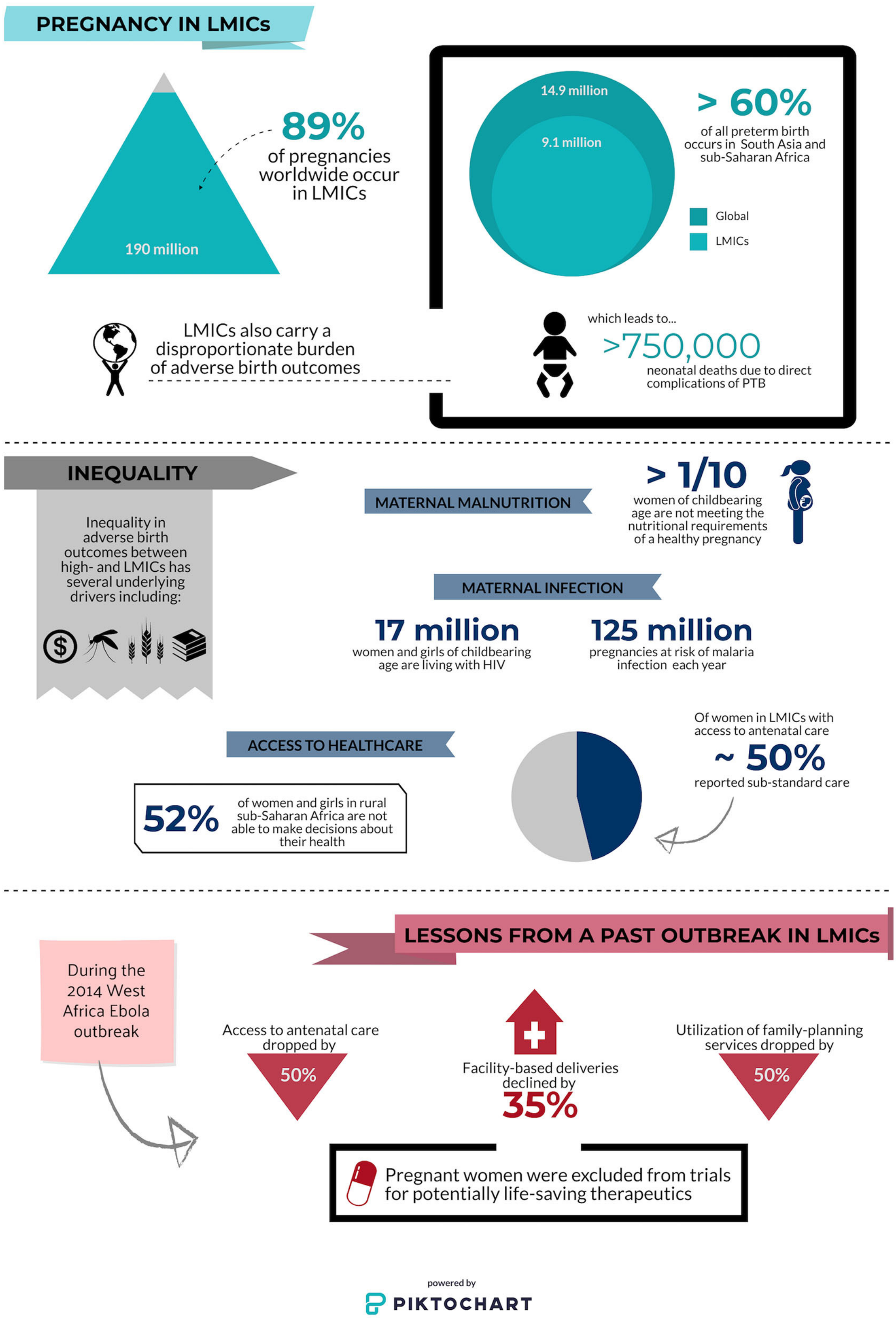

FIGURE 1 | Infographic depicting inequalities in pregnancy outcomes and access to antenatal care at baseline and during a pandemic. Low- and middle-income countries (LMICs); preterm birth (PTB). Data sources (5–7, 9–13).

of women and their children. Despite the current international focus on COVID-19, there remains an urgent need to direct research attention and resources to the impact of emerging infectious disease threats such as COVID-19 on pregnant women in LMICs.

EVIDENCE OF THE IMPACT OF RESPIRATORY INFECTION IN PREGNANCY

Very little information is currently available on the impact of COVID-19 in pregnancy. The first joint report published by the WHO and the Chinese Government mentions pregnancy twice in 40 pages (14). Much of the currently published literature contains conflicting information drawn from case reports and case-series with very small sample sizes. Although several original studies and systematic reviews suggest pregnant women are not at increased risk of severe clinical outcomes and that there is low risk of vertical transmission (15–19), one study reported seven maternal deaths out of nine cases in their multi-site COVID-19 case series (20). Increased rates of preterm birth and cesarean-section have also been reported (19, 21, 22). Due to the timing of the COVID-19 outbreak, most studies have reported on infection during the third trimester and there is little to no evidence of its impact in early pregnancy. Based on outcomes of pregnancies complicated by other severe respiratory infections, we hypothesize that more rigorous, pregnancy-focused research will reveal that pregnant women face an increased risk of poor clinical and birth outcomes during this COVID-19 pandemic.

Pregnant women have a higher risk of viral respiratory infection and are more likely to experience severe clinical symptoms (23). Both pandemic (e.g., H1N1) and seasonal influenza in pregnancy have been linked to severe maternal morbidity and increased risk of fetal death and preterm birth (24, 25). Pneumonia is also associated with increased risk of maternal morbidity, mortality, and poor birth outcomes. Co-existing maternal disease increases both the risk of infection as well as the risk of poor clinical outcomes (26). Therefore, as the COVID-19 pandemic continues, overlap with seasonal influenza and resulting co-infections will likely exacerbate morbidity and mortality in pregnancy. A rapidly growing body of evidence further indicates that infections during pregnancy, including respiratory infections such as influenza, are associated with increased risk of neurocognitive and neuropsychiatric disorders in exposed offspring (27). A review and a meta-analysis of coronavirus-spectrum infections reported increased preterm birth, miscarriage, preeclampsia, cesarean-section, and perinatal death in pregnant women with SARS, MERS, or COVID-19 (28, 29). However, the majority of data on coronavirus spectrum infections has been from Europe and North America. In LMICs, there is very little investigation into the impact of coronavirus infections on pregnancy despite the high prevalence of co-existing maternal conditions or co-infections, and barriers to quality antenatal care.

INCREASED RISK FOR WOMEN IN LOW- AND MIDDLE-INCOME COUNTRIES

During pregnancy, women's attendance at routine antenatal care visits results in high rates of exposure to health care environments. Consequently, women who continue to observe the recommended antenatal guidelines will be at increased risk for exposure to SARS-CoV-2. Furthermore, as health care systems become over-burdened by COVID-19, access and adherence to prenatal and obstetric care, as well as the quality of care, will suffer. Without timely intervention, pandemic-related restrictions on movement, reduced access to care, and economic constraints could lead to the reversal of important gains made in global antenatal care and maternal-child health. The 2014 Ebola outbreak in west-Africa provides a stark warning of the effect an infectious outbreak may have on already weak maternal-child health systems (11, 30). In Liberia, access to antenatal care plummeted by 50% and healthcare facility-based deliveries were reduced by 35% during the Ebola outbreak (11). Similar declines were also reported in Guinea, and by publication in 2017, had still not recovered to pre-outbreak levels (30). Preliminary evidence from both Uganda and Nepal indicates that even without a high COVID-19 burden, pandemic-related restrictions have already begun to impact maternal-child outcomes in LMICs, showing sharp declines in maternal facility deliveries (by 50% in Nepal), and increased maternal and neonatal mortality (31, 32). Although maternal-child outcomes with Ebola virus infection in pregnancy are more severe than existing evidence suggests for SARS-CoV-2 infection, these studies indicate immediate and lasting effects of emergent infectious diseases on vulnerable maternal-child healthcare systems in LMICs, and highlight the need for research and support to address this issue during the current COVID-19 pandemic.

The prevalence of medically complicated pregnancies is high among women living in LMICs. Women in LMICs carry a higher risk of infection with HIV, malaria, and/or tuberculosis compared to populations in high-income countries. Women of reproductive age in these regions are also more likely to have sickle cell disease, cardiac conditions (for example, rheumatic heart disease), and COPD due to indoor air pollution (33), conditions that increase the risk of developing severe COVID-19 (34). Furthermore, pregnant women in LMICs are at increased risk of having undiagnosed and/or sub-optimally managed gestational hypertension, pre-eclampsia, and gestational diabetes (35, 36). Hypertensive disorders and diabetes are both associated with an increased risk of severe COVID-19 in non-pregnant populations (34), but their impact on COVID-19 severity in pregnant women is not known. Furthermore, emerging data indicates the potential for long-lasting unintended consequences of governmental COVID-19 responses and COVID-19 related interruptions to maternal-child health interventions and critical public health programs (e.g., TB, HIV, and malaria diagnosis and treatment programs; nutritional interventions) on maternal morbidity and mortality in LMICs (32, 37, 38). The interplay of decreased health care access, increased prevalence of medical comorbidities, and the impact of SARS-CoV-2 exposure on pregnancy outcomes in LMICs warrants close surveillance and study in order to guide public health policies in the most at-risk regions.

Beyond antenatal care, pregnant and perinatal women will face psychosocial challenges related to stigma and/or social isolation, a lack of information or misinformation concerning neonatal care (e.g., appropriateness of breastfeeding with SARS-CoV-2 infection or suspected infection), and lack of or reluctance to access facility-based neonatal care services (e.g., for routine immunizations). Countries with strict restrictions on movement (e.g., banning public and private transport, curfews) have seen an impact on the ability of pregnant women to seek routine and/or emergency care, as well as increases in food insecurity and sexual and gender-based violence (32, 39). Challenges to providing antenatal and neonatal care during the COVID-19 outbreak will be further compounded if pregnant women and primary caregivers do not have access to up-to-date and accurate public health messaging to understand risks and recommendations.

Access to contraceptives is often limited in LMICs including sub-Saharan Africa and south Asia and the COVID-19 outbreak is likely to both disrupt global supply chains and prevent women from accessing providers of contraception. Many women will be isolated in domestic environments where they may not have input into family planning (**Figure 1**). Lessons from the Ebola crisis of 2014 indicate that widespread school closures will disproportionately affect girls of reproductive age, and lead to increased rates of sexual exploitation, sexual and gender-based violence, and forced marriage (39, 40). Compromising the sexual and reproductive health of women and girls means many are likely to experience pregnancy during the COVID-19 pandemic. Modeling estimates published by the Guttmacher Institute suggest that a 10% reduction in short and long-term contraceptive use could result in more than 15 million unintended pregnancies across 132 LMICs (41). As a result of gender inequality, the impact of a pandemic on sexual and reproductive health often goes unnoticed and unaddressed (12). Efforts to provide the means for pregnant women to safely access healthcare and healthcare providers are critical, as are efforts for widespread dissemination of public health policy and recommendations regarding other critical aspects of pregnancy (e.g., breastfeeding, immunization). Public and private health systems should craft responses to COVID-19 that address barriers to access and sexual and reproductive health outcomes in LMICs, in ways that protect the immediate health of pregnant women and inform future pandemic preparedness measures.

PREGNANT WOMEN DESERVE THE BENEFITS OF DRUG AND VACCINE THERAPY

Pregnant women are almost uniformly excluded from clinical trials. Protecting vulnerable populations from risks associated with experimental therapies is essential and particularly important in LMICs where limited access to high-quality care creates additional vulnerabilities. However, the most at-risk populations also deserve to benefit from therapeutics that may improve outcomes. Many of the drugs being proposed for the treatment or chemoprophylaxis of COVID-19 have evidence-based safety profiles for use in pregnancy including lopinavir/ritonavir, remdesivir, and hydroxychloroquine (42–45). Yet, large government-funded clinical trials for treatment of COVID-19 (e.g., NIH-funded trials [NCT04280705, NCT04332991]) continue to list pregnancy as an exclusion criterion (46). The WHO Solidarity Trial [ISRCTN83971151] originally listed pregnancy in its exclusion criteria but has since removed it. As the WHO seems to have done, the ethics of excluding women from trials where they may benefit from treatments known to be safe in pregnancy needs to be carefully considered. During the 2013–2016 west-Africa Ebola outbreak, where mortality rates for pregnant women and their unborn children approached 100%, women were actively excluded from clinical trials of novel therapeutics (13). Pregnant women could not participate in clinical trials in the face of a life-threatening infection for which pregnancy increased their risk. This highlights the importance of understanding the unique impact of COVID-19 on pregnancy to assess the risk and benefits associated with novel treatments and vaccines.

As novel treatments and vaccines are developed and employed, we must consider why pregnant women continue to be excluded from trials by default, and when it is or is not appropriate to include them. Given the immediacy of the COVID-19 pandemic and the complexity of pharmacokinetics and pharmacodynamics in pregnancy, studies with therapies already known to be safe in pregnancy should be prioritized. To globally maximize benefits and health equity for pregnant and perinatal women, novel treatments should also be accessible to women living in the regions where most pregnancies occur (e.g., LMICs). These treatments should be effective, inexpensive, and easily accessible. Moreover, studies should also examine the impact of co-morbidities on therapeutic outcomes, including co-infection with HIV, malaria, and TB.

CONCLUSIONS

As the global implications of the COVID-19 outbreak in LMICs begin to emerge, it is becoming increasingly clear that vulnerable populations will carry a disproportionate burden. Pregnant women in LMICs can face enormous obstacles to healthy birth outcomes for themselves and their unborn and newborn children and these barriers increase in the face of a global pandemic. As public health systems and the international medical research community focus resources on understanding COVID-19 and identifying therapeutics, the impact of infection in pregnancy and the unique health needs of pregnant women during a pandemic should not be neglected or passed over to be studied retrospectively. Pregnant women, including those in LMICs, deserve an immediate and enhanced focus during the COVID-19 outbreak to protect every woman and every child.

AUTHOR CONTRIBUTIONS

CM and KK: project conception, and oversight. CM, AW, JW, KK, and AC: research, analysis, writing, and editing. All authors: read and approved the final manuscript.

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Are Pandemics Gender Neutral? Women's Health and COVID-19

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In December 2019, coronavirus disease 2019 (COVID-19) emerged as a health crisis in Wuhan, China, and was later declared by the World Health Organization (WHO) as a Public Health Emergency of International Concern. As it spread and its death toll increased, on the 11th of March 2020 it was declared a pandemic at 4,369 deaths worldwide, and cases and deaths have since surged. With gender disparities already known to leave women and their health at the margins of society during outbreaks, it is important to understand how COVID-19 affects women's health. In this article, we discuss how the COVID-19 pandemic can create vulnerabilities for women and their health and further exacerbate long-existing inequalities and social disparities. These include gender-based roles, economic and food security, violence, work pressure, and access to health and healthcare facilities. These issues have significant repercussions on the physical and mental health of women. To focus our lenses on these issues, we draw lessons from three specific examples of past outbreaks: 1918 Flu pandemic, Zika virus disease, and Ebola virus disease. We conclude by stating how public health responses and strategies for COVID-19 can be inclusive to women's health.

Keywords: COVID-19, pandemic, women's health, outbreaks, gender inequality

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INTRODUCTION

At present, the world is in the middle of a coronavirus disease 2019 (COVID-19) outbreak, declared a pandemic on the 11th of March 2020 by the World Health Organization (WHO). The first outbreak was confirmed in Wuhan, China, on the 31st of December 2019, and to date, cases have been reported in at least 188 countries (1). Infected individuals may be asymptomatic or have pre-symptomatic infection, while symptomatic presentation ranges from mild to severe respiratory distress (1, 2). With no existing vaccine therapy, treatment options are limited to broad-spectrum antivirals and management of symptoms. Clinical outcomes are dependent on the patient's immune system, chronic comorbidities, and age, with the elderly holding the highest risk (1). In several countries, measures to control transmission have been implemented at an unprecedented scale. These measures include self-isolation for the infected, quarantine for the exposed, wearing of masks in public places, local and international travel restrictions, and closure of schools and businesses (3). Currently, sex disintegrated data, although incomplete, shows higher numbers of COVID-19 cases in women compared to men, with higher mortality rates in men (4). Understanding the gendered impact of COVID-19 and exploring how it affects women will allow for effective and equitable pandemic responses.

GENDER DISPARITIES AND COVID-19

The differences in how women fare during a pandemic compared to men are largely due to long-existing inequalities and social disparities, which are exacerbated by the pandemic, rather than biology (5). Inequalities created and compounded by outbreaks leave women in a more vulnerable position (6). To put it into perspective, globally, women form 70% of the healthcare and social services workforce (7). This automatically puts them at the frontline during a pandemic response, and thus, they face a high risk of infection. Data compiled by the WHO from over 104 countries (2000–2018) showed that women constituted as the majority of the nursing personnel in the African region (65%), region of the Americas (86%), Eastern Mediterranean region (70%), European region (84%), South-East Asia region, (79%), and Western Pacific region (81%) (7). The female physician population varied in these regions ranging from 28% (Africa Region) to 53% (European region). In the Hubei province of China, more than 90% of the health workforce was reported to be women (8). In a study investigating mental health outcomes of frontline healthcare workers in China, women and nurses were at a higher risk of developing unfavorable mental health outcomes including depression, anxiety, insomnia, and distress (8). Furthermore, personal protective equipment (PPE) shortage for healthcare workers, together with the gendered nature of the healthcare care workforce, puts the women at even higher risk of infection (9). PPE shortage has been reported in several countries since the COVID-19 outbreak. It is important to emphasize that PPE shortages endanger the health of all healthcare workers.

Surviving a pandemic for women means more than just surviving the disease, as there are threats beyond the risk of infection. It is true that during crises, epidemics and pandemics, women tend to take up more caregiver responsibilities than usual, often at the expense of their health (10). Particularly in the COVID-19 crisis, wherein some instances families have to stay at home while self-isolating or during movement restrictions, women can be overworked and overstretched as they take on more domestic care. This increasing burden of care can also take time away from paid work (6). It is therefore clear that to recognize the different patterns of exposure between men and women, understanding societal norms is imperative. The responsibility of taking care of the sick also often falls more on the women at home (11). In some cases, the women at the frontline of pandemic responses have a double-barrel role of being the caregivers both at work and at home, putting women at a higher risk of infection. A gender analysis of reporting media from four countries (Sri Lanka, Malaysia, Vietnam, and Australia) during the COVID-19 pandemic reported intersections between Covid-19 and gendered burdens, particularly in frontline work, unpaid care work, and community activities (visiting the sick, cooking, and cleaning) (12).

During pandemics, women are at a greater risk of more violence and abuse (13). The lockdown and isolation policies implemented in many countries put women at a higher risk of domestic and sexual abuse as they are likely to spend more time with their abusers (11, 13). The need for protection of women against abuse is therefore heightened during the COVID-19 pandemic. Studies looking into the surveillance and evaluation of effective interventions for those at risk of domestic violence during the pandemic are still lacking in literature (13). An increase in teenage pregnancies may also be experienced, due to several factors including sexual violence and negative coping strategies. The need for financial support can also increase exploitative relationships resulting in more teenage pregnancies (11).

Health seeking behavior and access to health care may also affect access to treatment. While in most high-income countries women are more likely to utilize healthcare services than men (11), in some societies women are less likely to seek healthcare services on their own due to social norms or if the healthcare provider is male (5). It has been shown that poor women are less likely to seek healthcare services (5). Furthermore, research on whether women face specific constraints to access healthcare services including the level and type of care during the COVID-19 pandemic needs to be investigated.

The COVID-19 crisis poses a threat to several aspects of women's rights, including reproductive rights, economic rights, and other freedoms. Sexual and reproductive health services remain important even during pandemics. In some countries, however, these become overlooked as funding becomes diverted to pandemic responses. This has dire health (including mental health) consequences for women needing these services. It is projected that due to COVID-19, millions of women and girls may be deprived of family planning services (11). Women's rights and economic gains have been affected by COVID-19. The changes in power relations between men and women during a crisis expose women's vulnerabilities and increases burdens. Generally, during a crisis, women's decision-making power in the home often regresses, as reported in studies done in Zimbabwean and Ethiopia (14). Additionally, in Mali and Niger, women are the first to lose land and income during a crisis (14). This pattern will likely be repeated during the COVID-19 pandemic, leaving a lot of women disenfranchised and rolling back women's rights.

The world food program reported that the number of people who will face a food crisis will likely double because of COVID-19 and warned of a hunger pandemic (15). For women and girls, this could have even worse implications as they already constitute 60% of those facing a food crisis and 76% of the displaced population worldwide (14). Food security for women is therefore at great risk, with more women likely to face a food crisis due to COVID-19. Furthermore, women also face the brunt of food insecurity as in most households the responsibility of feeding the family falls on them (14). Shortages of food in the home means women will more likely sacrifice the food that is available for their children and families by eating less and eating last, resulting in malnutrition. This generally makes more women to be more susceptible to non-communicable diseases and other diseases.

Current data on maternal health has not shown maternal–fetal transmission of COVID-19 (16, 17). This is in contrast to the experience of two other known pathogenic coronaviruses, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), which have been reported to increase maternal morbidity and mortality. Pregnant women have also been reported to not be at a greater risk for contracting COVID-19, compared to non-infected pregnant women (18). However, the immune system is known to experience suppression in normal pregnancy, resulting in increased susceptibility to infection; hence, pregnant women are still a vulnerable patient population (17). Guidelines on the management of pregnant women during the COVID-19 pandemic are continuously being updated. More follow-up and bigger studies on pregnant women and infants with COVID-19 are needed to evaluate their health and safety. Additionally, the inclusion of women in clinical trials for COVID-19 vaccines is imperative.

It is important to reiterate that women's issues stated here did not suddenly appear during this COVID-19 pandemic but have been or will be compounded by it. These issues have a direct and indirect influence on several aspects of women's health, including putting them at a greater risk of COVID-19 infection, worsening already existing diseases, and lastly making them more susceptible to new ailments of physical and mental health. Is COVID-19 gender neutral? No. The gendered burden of COVID-19 is clear and undeniable. Lessons from past outbreaks can shed light on how to better prepare for an inclusive COVID-19 response system.

EXAMPLES FROM THE PAST

Zika Virus Disease

The first human case of the Zika virus (ZKV) disease was reported in 1952 (19). In 2015, an outbreak began in Brazil and spread to parts of North and South America, Southeast Asia, and several Pacific Islands (20). The outbreak took a toll on pregnant women. As they delivered, a pattern of newborns presenting with congenital defects, collectively known as Congenital Zika Syndrome (CZS), such as microcephaly was observed (21). Some women experienced preterm births, stillborn births, and miscarriages (22–24). In Brazil, the epicenter, between 5 and 15% of newborns to infected mothers developed microcephaly and on the basis of the clusters known, microcephaly was declared as a Public Health Emergency of International Concern (25, 26). National governments further advised that women of reproductive age delay pregnancy and avoid unprotected sexual intercourse. Contraception was provided as an alternative despite inadequate health education on where and how the women could access family planning services (27, 28). Subsequently, the WHO's interim guide recommended abstinence and irrationally advised on guarding against mosquito bites as a prevention strategy as the women bear a large responsibility of conducting vector control activities (29). These recommendations infringed on their autonomy and SRH rights and further suggested that women bear the sole responsibility of managing their risk profiles during outbreaks, without supporting resources.

Power dynamics granted women with lesser power in decision-making (30, 31). Abortion is still not accessible in some countries as it is either criminalized or available in restricted circumstances. For example, in African countries such as Angola and Latin American El Salvador (one of the epicenters), abortion is criminalized, while in Brazil it is restricted to anencephaly. Resultantly, multiple El Salvadorean women were sentenced with abortion charges during this outbreak, regardless of whether it was unclear cases of miscarriages or induced abortions (26). Others had unsafe abortions while others faced unprepared for financial, physical, and psychological responsibilities of raising CZS children after pregnancy with limited support (26). These experiences have been implicated in placing women at a higher risk for mental illnesses such as anxiety and depression (32).

Ebola Virus Disease

The 2014–2016 West Africa Ebola virus disease (EVD) outbreak was the most widespread since the virus's discovery in 1976 (33). It highlighted the consequences of neglecting gender-inclusive perspectives during a crisis. Gender is a determinant of health, and gender roles contribute substantially to transmission. They influence where women and men spend most of their time, what infectious agents they are exposed to, and duration and frequency of exposure (5). During this outbreak, risk of transmission was high among those caring for the sick at home (PPR 13.33) and conducting funeral activities (PRR* 4.8) (34). These are two gender roles that sociocultural norms dictate for women In West Africa. No biological sex differences have been implicated to EVD infection vulnerability, while several sociocultural and healthcare factors have been reported to have increased the risk of infection (33).

In low-and-middle-income-countries (LMICs), as in West Africa, health systems are overburdened and resilience against outbreaks is low (35, 36). This is characterized by inaccessible healthcare service, lack of support for a diverse population, and challenges with identifying and isolating health threats while maintaining its core functions. Limited resources are also diverted toward emergency responses (37, 38). In Sierra Leone, preexisting lack of resilience in the health system has been reported to have contributed to reduced utilization of healthcare services, including maternal and newborn health (MNH) services. Pregnant women lacked trust in the low-resilient health system and were resultantly reluctant to access routine healthcare services, concerned about contracting the infection. Structural barriers (e.g., public transport utilization also influenced access to healthcare). Subsequently, this delayed maternal and neonatal health care, indirectly affecting maternal, stillbirth, and neonatal mortalities (39–41). The United Nations Fund for Population Activity (UNFPA) reported that pregnant women in labor were concerned about the competency of their healthcare providers and lack of protection in preventing infection (42). It is since been predicted, through mathematical models, that a 50% reduction in accessing healthcare services potentially exacerbated mortality rates for HIV/AIDS, tuberculosis, and malaria with 2,819 excess deaths in Sierra Leone, 6,269 in Guinea, and 1,535 in Liberia (43). These are infectious diseases that also affect women.

During this outbreak, delayed healthcare was also experienced as a consequence of a broad and vague EVD case definition. There was therefore confusion around its application. In this, unexplained bleeding and spontaneous abortion were used as markers for isolation to Ebola Treatment Centers (ETCs). These markers could not be differentiated from miscarriages. Furthermore, unexplained bleeding is a sign of several obstetric complications. As a result, this was a contributing factor to pregnant women's reluctance in seeking healthcare. They also feared being wrongly isolated to ETCs (39, 41, 44). The overall reluctance in healthcare-seeking behavior among women also meant that sexual assault victims were also compromised with post-rape care.

It is worth noting that women play large roles in agriculture and are affected during restricted trade. Herman reported in 2015 that Sierra Leone's gross domestic product (largely supported by agriculture) dropped from 8.9 to 2.0% due to restricted trade during the EVD outbreak (45). Such repercussions affect women's jobs and limit women's participation in the economy.

1918–1919 Influenza Pandemic

It is just over 100 years since the world's deadliest pandemic, 1918–1919 influenza (flu) with a 50 million estimated death toll (46). In South Africa, about 5% of the total population perished, and right across Africa food security and transport were disrupted (46, 47). The pandemic emerged at a time of underdeveloped medical care globally; hence, incomplete epidemiologic data to date and various challenges were encountered. In America, for instance, the pandemic emerged at a time of war distress, 4 years into World War I (WWI). Public health officials implemented response strategies i.e., isolation and quarantine, to curb transmission (48). This meant more responsibility for women with caregiving roles.

In America, the pandemic distress contributed to a labor shortage (48). The shortage prompted socioeconomic transformation and more women entered the workforce to fill labor gaps. They took up work in the frontlines, while they still had caregiving and childbearing responsibilities at home. This also happened while the women were in movements advocating for their right to vote (46, 49, 50). Their responsibilities and roles heightened, while the risk of infection threatened their health.

WHAT DO WE LEARN FROM THE PAST AND WHAT DOES THIS MEAN FOR COVID-19?

Pandemics exacerbate existing gender inequalities. As seen in the three examples, gender norms, unprepared health systems, inaccessible healthcare services, and power dynamics increase women's vulnerabilities during a crisis. Therefore, pandemics are not gender neutral. In the EVD outbreak, gender roles exposed women to a high risk of infection through caregiving and burial activities. The low-resilient health systems led to women not being able to access healthcare services timely. Unprepared health systems resulted in the neglect of women's SHR services while funds were being diverted toward emergency responses. Subsequently, lack of clear, accurate, and effective communication in responses further compounded these challenges (34, 38, 41). In the ZKV outbreak, power dynamics favored women's exclusion in decision-making, resulting in their autonomy being infringed and SHR rights undermined. Lack of various forms of support for mothers post-pregnancy also became a challenge (26, 28, 30). The frontline healthcare brigade is largely made of women who risk their lives. This was also seen during the 1918–2019 flu outbreak with American women filling labor gaps to curb the pandemic (46, 48). These had additional caregiving and childbearing responsibilities, hence a heightened workload.

Goal 5 of the 2030 Agenda for Sustainable Development Goals (51) aims to achieve gender equality and empowerment women by 2030. COVID-19 public health response strategies should, therefore (52):

- Address gender norms and the need for shared responsibilities at home and in the workplace.
- Prioritize frontline workers' health, including mental health for all women.
- Integrate SRH rights for all women and put in place monitoring strategies.
- Provide accurate and accessible family planning education and all healthcare services.
- Incorporate and keep surveillance and protection systems for gender-based violence victims.
- Be sensitive to the women who are in informal labor because, in LMICs, women also dominate this sector (as mentioned for Sierra Leone during EVD outbreak). There must be clear plans of action to assist these women when there are movement restrictions and there are economic repercussions.
- Appoint women in leadership and management positions for national task teams and global organizations.
- Prioritize and support ongoing scientific research, collaboration, and provide funding for it.

CONCLUSION

In conclusion, outbreaks exacerbate already existing gender inequalities. In the COVID-19 pandemic; women's health needs to be prioritized as women are more vulnerable during this time—as frontline healthcare workers, as primary caregivers at home, as informal sector laborers, and as citizens needing access to healthcare facilities. Sexual and reproductive health rights and access to healthcare should not be neglected during this time. Women and women's perspectives are needed when making decisions for pandemic planning and strategies. Gender informed responses and strategies addressing the gender inequalities that persist during outbreaks must be the norm.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SN and HS conceptualized the idea for the research, performed literature searches, drafted the manuscript, contributed to the critical revision, and intellectual input of the manuscript. All authors contributed to the article and approved the submitted version.

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Postnatal Depression Risk Factors: An Overview of Reviews to Inform COVID-19 Research, Clinical, and Policy Priorities

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The disruption of normal life due to the COVID-19 pandemic is expected to exacerbate extant risk factors for mental health problems. This may be particularly true for women who give birth during the crisis, especially those at risk for postnatal depression. Maternal postnatal depression has been identified as a public health issue with profound impacts on maternal and child well-being. Evidence from previous crises (e.g., earthquakes, terrorist attacks) has shown that crises significantly impact maternal mental health and some perinatal health outcomes. The aims of this paper were therefore to conduct a review to identify the established risk factors for maternal postnatal depression, and generate evidence-based hypotheses about whether the COVID-19 crisis would likely increase or decrease postnatal depression rates based on the identified risk factors. Several databases were searched during May-June 2020 for review papers (i.e., systematic reviews, meta-analyses, qualitative syntheses) using the following keywords: Depression, perinatal, postnatal, postpartum, systematic, review, predictors. Risk factors were extracted in conjunction with indicators for their strength of evidence (i.e., effect sizes, qualitative coding). Risk factors were critically evaluated in relation to their susceptibility to the impacts of the COVID-19 crisis. It was hypothesized that several health policies that were necessary to reduce the spread of COVID-19 (e.g., required restrictions) may be simultaneously impacting a range of these known risk factors and placing a larger number of women at heightened risk for postnatal depression. For instance, factors at a strong risk of being exacerbated include: Perceived low social support; exposure to traumatic events during or prior to pregnancy; significant life events occurring during pregnancy; and high stress associated with care of children. Future research and policy implications are discussed, including how policy makers could attempt to ameliorate the identified risk factors for postnatal depression following the current COVID-19 pandemic.

Keywords: review, COVID-19, postpartum, postnatal, perinatal, depression, systematic, pandemic

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The novel coronavirus (COVID-19) pandemic is an unprecedented global event that has a range of health, economic, and socio-emotional implications. Understandably, governments are first and foremost addressing the physical health crisis, before responding to the economic implications. It is becoming apparent, however, that there is also a need to consider the mental health of vulnerable populations during and following the COVID-19 pandemic (1). Although postnatal depression has been identified as a major public health problem (2) with prevalence rates ranging from 10 to 40% globally (3), the mental health needs of women in the perinatal period have not yet been adequately considered in the context of the COVID-19 crisis. Evidence from previous crises highlights that perinatal health and maternal mental health tends to be negatively impacted in the wake of these crises (4, 5). It is therefore increasingly apparent that health policies necessary to reduce the spread of COVID-19 (e.g., required restrictions; changes to hospital policies; physical distancing; sheltering in-place; restricted travel) may also be simultaneously impacting a range of known risk factors for postnatal depression and thereby placing a larger number of women at heightened risk for postnatal depression.

THE COVID-19 CONTEXT AS IT RELATES TO WOMEN IN THE PERINATAL PERIOD

Early research into the COVID-19 pandemic is beginning to reflect that the socio-emotional impacts are not universal (6). In this next section, an outline of how the COVID-19 crisis may relate to women during the perinatal period is provided to demonstrate impacts on this unique population. It is possible that home isolation and physical distancing may be associated with feelings of loss and loneliness as mothers' social supports are different from what they may have expected. For instance, home isolation and physical distancing measures may mean that new mothers are unable to have family members and friends support them following the birth of their child. This may include those who can no longer travel from overseas, those living across the country, as well as supports who may live physically closer but who are unable to visit due to physical distancing precautions (e.g., older adults). Loneliness may be also experienced, as physical distancing measures have required many postnatal supports to cease operating (e.g., postnatal mothers' groups; libraries; cafes; "mom's and bubs" gym classes); reducing the options for mothers to connect for social and practical support. In addition, some mother-infant dyads may not be able to establish, and maintain breastfeeding due to measures of isolation or separation guidelines. Breastfeeding duration has been associated with less postnatal depression and/or the amelioration of depression symptoms (7), thus some of these women may be at greater risk for postnatal depression.

Uncertainty around health risks (e.g., impact of COVID-19 on pregnancy outcomes) and changes to healthcare systems may also impact well-being during the perinatal period. Common experiences may include: Reduced numbers of support birth partners or no birth partners allowed into the birthing suite (8); reduced stay in hospitals after birth; concerns about management of COVID-19 patients within the same hospital facility; reduced or delayed help-seeking throughout pregnancy due to concerns about contracting COVID-19 when attending appointments; fewer in-person antenatal appointments reducing the frequency of checking mother and infant vital signs; and/or, separations of newborns from COVID-19 positive mothers for 14 days (9). Moreover, the availability of informational affordances for pregnant women and new mothers may also have been negatively affected, for example by canceling face-to-face antenatal/postnatal education classes. Reduced frequency of antenatal medical and sonogram appointments may further reduce opportunities for women to access timely information directly from healthcare professionals to reduce uncertainty and fears about health risks. Fewer antenatal appointments may also reduce opportunities for healthcare professionals to promote knowledge about a range of positive health behaviors for mothers and infants (e.g., positive benefits of breastfeeding, importance of mothers noticing any reduction in movements in the third trimester).

Even while the long-term economic impacts of COVID-19 are not yet known, short-term impacts (e.g., reduced wages; being laid-off; fewer rostered hours; lack of security associated with rostered work) are likely to increase general stress levels. Further, it is currently unclear how the emotional experience of financial hardship may be addressed or ameliorated with the intervention of government support packages. It is clear, however, that the impacts of financial hardship and the associated stress will likely be greatest for women without a spousal partner (10), recent (economic) migrants, asylum seekers undergoing resettlement processing, and refugees (11–13), and, women from traditional and/or conflict-affected backgrounds (14); the majority of whom do not have surplus financial reserves to draw upon during the crisis.

Stress from additional domestic caring duties during the COVID-19 crisis may also impact mothers. Research has shown that a greater number of hours of caring duties typically fall to women (15), and women may be juggling managing older children's educational and emotional needs alongside caring duties for older adults who are self-isolating. With families contained to their homes for extended periods, relationships may also experience strain. The perinatal period has been shown to have a high domestic and family violence risk (16), it is therefore possible that with additional strain comes additional violence risk for some women; particularly those who a history of victimization by their partners or who experience (or have partners that experience) substance-use disorders (17). Less contact with those from outside of the household (including medical and sonographer appointments) means it is possible that those women who experience acute stress from increased threat from, and experience of, domestic and family violence may have difficulty in attaining support (17).

Evidence From Previous Crises

A number of systematic reviews have been conducted examining the effects of previous crises on perinatal health and mental health (4, 5, 18). After reviewing studies examining terrorist attacks (e.g., September 11), environmental and chemical disasters (e.g., nuclear reactor accidents at Chernobyl), and natural disasters (e.g., hurricanes, earthquakes, floods), Harville, Xiong (4) found that severity of exposure to the crisis/disaster was a major risk factor for poor mental health outcomes among pregnant and postpartum women. Further, Harville, Xiong (4) concluded that following crises/disasters, mothers' mental health may more strongly influence child development than any direct effects of crisis/disaster-related prenatal stress. Ren, Chiang (5) examined the mental health of pregnant women following earthquakes and, while they could not determine whether postnatal depression rates were increased, they found that antenatal depression rates were more prevalent in women who had experienced an earthquake during pregnancy than those who had not. Finally, Saulnier and Brolin (18) concluded that maternal stress was a common underlying determinant of children's long-term health when the child was exposed to crises during pregnancy. These reviews on previous crises thus highlight the importance of considering women's mental health in the postnatal period following the COVID-19 pandemic.

Moreover, it is evident that there may be interplay between factors that are indirectly influenced by crises and women's mental health (17). For instance, research has shown that domestic and family violence reports have peaked following previous crises (e.g., the eruption of Mount St. Helens in the U.S.A., 1982; Hurricane Katrina, 2005; "Black Saturday" bushfires in Australia, 2009; Haitian earthquake, 2010) and continued to occur at increased rates for at least a year following crises (17, 19–23). Therefore, it is possible that certain crises may inflate some indirect relationships more than others.

Emerging Evidence From the COVID-19 Pandemic

Early evidence has shown pregnant women are not at a greater risk of catching COVID-19 than the general population (24, 25). However, evidence from other respiratory infections shows that pregnant women may be at risk of greater harm if they get a respiratory infection (24, 26, 27). Particularly during the COVID-19 crisis, it is probable that not all women in the antenatal and postnatal periods will have equal access to this information. The importance of access to official healthcare information has been reiterated by research conducted in China in the early stages of the COVID-19 pandemic (28). Findings indicated that pregnant women who had not accessed antenatal health information from hospitals' official social media accounts self-reported significantly higher stress, anxiety, and depressive symptoms than those who had (28). This study also uncovered that pregnant women in China during the early months of the pandemic were reporting higher rates of general symptoms of psychopathology than earlier cohorts (28). A finding that has been echoed by Davenport, Meyer (29) who conducted a rapid response survey in April-May 2020 capturing data from 900 predominantly North American women in the antenatal and postnatal periods where high levels of self-reported depression and anxiety symptoms were found (29). Thus, early evidence is indicating that higher rates of mothers' mental health symptoms are emerging and are not country-specific.

The Current Study

There are a range of key risk factors that need to be considered when planning how to support and provide interventions to ameliorate the socio-emotional impacts on women and their children during, and following, the COVID-19 global pandemic crisis. Evidence from crises suggests that some risk factors will be more negatively affected than others; thus, we are hypothesizing that there will be an increase in the population prevalence of postnatal depression following the COVID-19 crisis period. In order to identify the range of risk factors most vulnerable to impacts of the COVID-19 crisis, the primary aim of this paper was to review the available summary evidence (i.e., systematic reviews, meta-analyses, qualitative syntheses) to determine a list of established risk factors for postnatal depression. Following this, the secondary aim of this paper was to provide hypotheses about whether the COVID-19 context would likely increase or decrease the identified risk factors for postnatal depression in women. In undertaking this analysis, we hope to equip mental health clinicians, researchers, and relevant policy makers to more effectively address maternal and antenatal mental health concerns following the COVID-19 pandemic. Finally, we hope to contribute to the growing evidence-base for the trade-offs public health settings make with women's mental health in times of crisis.

METHOD

Search Strategy

Identification of articles for this review was guided by the principles as outlined in the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (30). Accordingly, the following electronic databases were searched: SCOPUS, PubMed, EMBASE, PsycINFO, and the Cochrane Library. Each database was searched from its start date through to June 01, 2020 using the following keywords and their conjugates: Depression, perinatal, postnatal, postpartum, review, systematic, predictors. For example, in SCOPUS the search strategy was implemented using the following query: TITLE-ABS-KEY((depressi* AND (perinatal OR postnatal OR postpartum)) AND (systematic OR review) AND (predicto*)) AND (LIMIT-TO (LANGUAGE, "English")). These search terms were developed using an iterative strategy to ensure a high degree sensitivity to target literature. Additional articles were identified by combing the reference lists of relevant articles that met inclusion criteria, in addition to search of gray literature using Google Scholar. Searches were conducted by LK in close consultation with FD; both of which have extensive experience performing literature reviews. Only published peer-reviewed articles available in English were considered for this review.

Article Selection Process

Peer-reviewed publications were identified in the initial stage of the search process with 338 potentially relevant titles, abstracts, and keywords. Each candidate was then evaluated according to the following predetermined exclusionary criteria: (a) The article focussed on factors primarily associated with paternal rather than maternal depression; (b) the article did not use depression and/or depressive symptoms as an explicit variable in analyses; (c) the article did not claim to report on risk factors of maternal depression; (d) analyses used depression and/or depressive symptoms to predict an exogenous factor not of interest; (e) the article was not relevant to the query (i.e. immediate exacerbation linked to the COVID-19 crisis) including those articles reporting on genetic factors, biomarkers, and endocrine factors associated with maternal depression; (f) the article was not a review, meta-analysis, or qualitative synthesis and therefore did not aggregate, or otherwise pool, data from multiple studies. Following the application of these exclusionary criteria, 27 articles were selected for further evaluation. During this process, 13 articles were further excluded according to the following additional exclusionary criteria: (g) The article did not adequately report on their review methodology, in accordance with Downs and Black (31), or, in the case of narrative reviews where these elements may not have been reported (32, 33), that the narrative treatment of reference literature was insufficiently rigorous; (h) The article did not report upon individual risk factors identified for maternal depression in sufficient detail for the purposes of the current review; (i) The article did not evaluate the degree of risk associated with reported risk factors (i.e., effect sizes; clinical risk frameworks). Both FD and LK reviewed article exclusions according to these outlined criteria.

RESULTS

The article selection process yielded 14 articles included for review (for a flowchart of the article selection process see **Figure 1** and for a summary of the included articles see **Table 1**): Eight articles were systematic reviews in which four of these eight explicitly conducted meta-analyses (35, 39–41); six articles used a narrative/synthetic approach to literature review. Nine of the 14 articles studied maternal depression in the general population, however five focussed upon features of maternal depression specific to the local demographic context (36, 40, 42, 43, 45). The most commonly searched databases within the articles, in order from highest frequency, were: PUBMED, Medline, PsycINFO, CINAHL; five articles did not report on the databases used to conduct their review or meta-analyses. The most common reason for the exclusion of articles was (f) accounting for ∼36% of excluded articles; followed by (b) accounting for ∼25%; and, (e) accounting for ∼21%. Strength of evidence was determined by the following effect size thresholds (Cohen's *d*) (46): Strong overall evidence, $d > 0.6$; moderate overall evidence, $0.4 < d < 0.6$; weak overall evidence, $d < 0.4$. In cases where effect sizes were unavailable, under-reported or not reported, an evaluation was made regarding the strength and diversity of domain-specific literature adduced in support of reported risk factors. Data quality overall was moderate to weak, although this can be partially attributed to the wide search window leading to the inclusion of several studies that predate modern statistical reporting standards. Due to this and the diversity of review methods employed across included articles, planned quantitative analyses including meta-analysis and effect size analysis could not be performed. However, a qualitative approach to the abstraction of risk factors of postpartum depression was undertaken with 25 core risk factors being identified (see **Table 2**). As displayed in **Table 3**, each risk factor for postnatal depression was then evaluated for whether risks were likely to be increased or decreased in the COVID-19 context. These hypotheses were determined by the authors based on the literature reviewed on crises, the observations about the context-specific contextual factors for pregnant women during COVID-19, and clinical judgment. FD independently coded each risk factor, and LK subsequently reviewed ratings. Author agreement was established for categorisations for all risk factors.

DISCUSSION

From the 14 articles that were identified in this review (as shown in **Table 1**), it is evident that there are a range of risk factors that have been consistently found to increase the likelihood of women experiencing postnatal depression (as shown in **Table 2**). Although some of these risk factors are unlikely to be increased, others are more likely to be increased during and following the COVID-19 pandemic (see **Table 3**). In particular, it was identified that the following factors are at a strong risk of being exacerbated in the COVID-19 crisis: Presence of depressive symptoms during pregnancy; prior diagnosis of an anxiety disorder including prenatal anxiety; perceived low social support during pregnancy; exposure to traumatic events during or prior to pregnancy (specifically including physical, domestic, and family violence); stress levels (i.e., high generalized allostatic load); significant life events occurring during pregnancy or immediately post-partum (e.g., death of a loved one; loss of employment; relationship breakdown or divorce; relocation including moving house); high stress associated foremost with care of index child but including care of other children; and adverse experiences associated with immigration (e.g., racial/ethnic discrimination; delayed visa status/uncertainty surrounding immigration status; poor access to health services; low language ability for country of settlement). There is also a chance that the following factors may also impact women at this time and therefore need to be monitored in relation to postnatal depression rates: Presence of symptoms of common mental disorders (other than depression and anxiety) during pregnancy; perceived low support from partner; marital dissatisfaction leading to complications (including psycho-emotional but not physical domestic and family violence); low socioeconomic status (i.e., low average income and/or high cost-of-living) particularly in view of the economic shocks leading to reduced employment as a result of the COVID-19 crisis. Given the description of the current COVID-19 climate for pregnant women and the known risk factors that have been identified from previous review papers, it is further hypothesized that overall current population prevalence rates of postnatal depression will increase.

Implications for Research, Practice, and Policy

It is therefore essential that researchers actively examine the identified factors that may increase postnatal depression risk

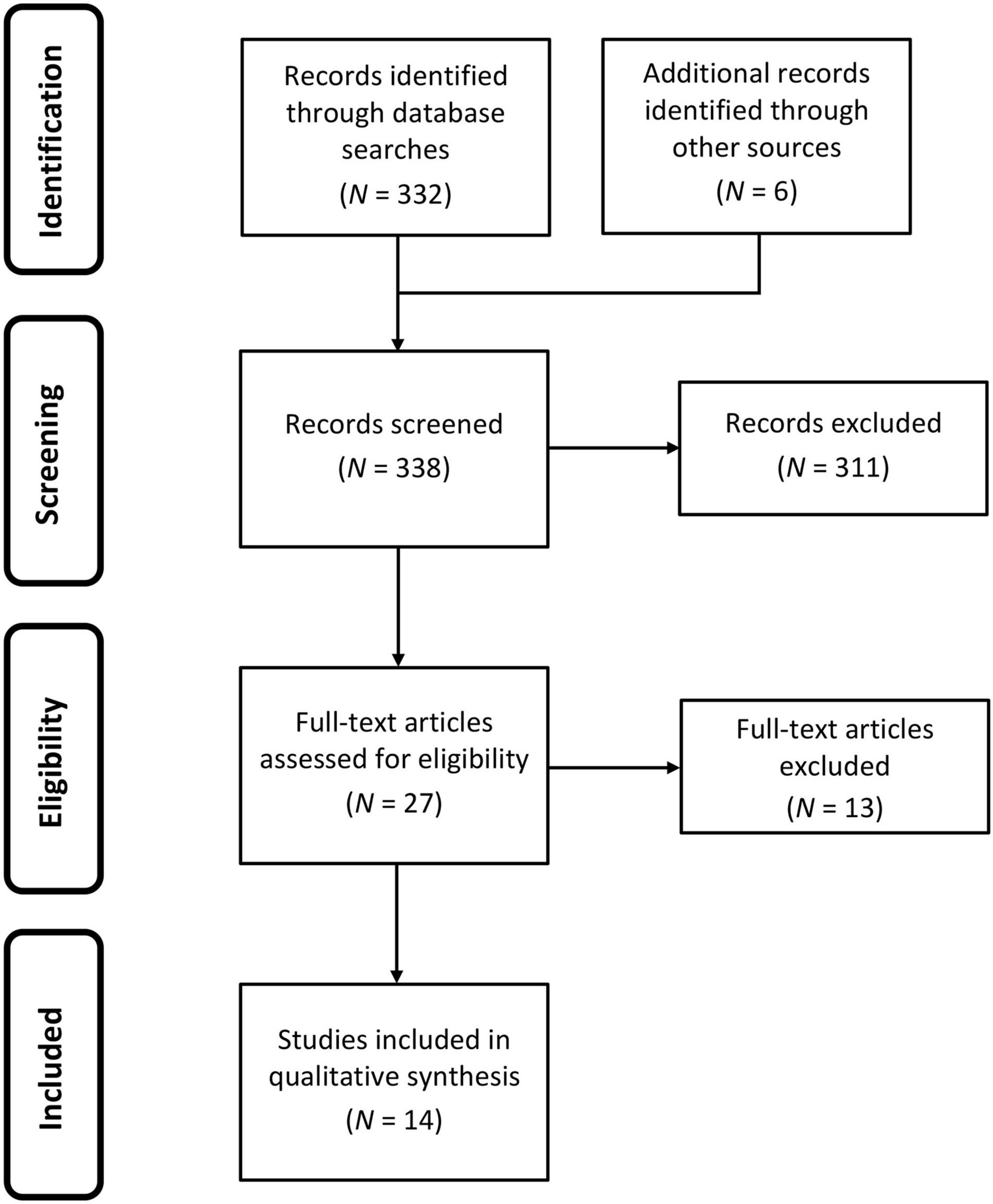

FIGURE 1 | Flowchart reporting the identification and selection of studies for review and qualitative synthesis.

in the context of a pandemic generally, and the COVID-19 pandemic specifically. We urge research funding bodies to work with researchers and mothers with lived experience of postnatal depression to ensure that this research priority is met. Advancing the limited knowledge base regarding maternal postnatal depression risk following crises, particularly

TABLE 1 | Details of the studies included for review.

Article short name	Review type	Databases searched in each article	*N*	Keywords	Demographic focus
Banti et al. (34)	Narrative/synthetic	PUBMED		Pregnancy, perinatal depression, risk factors, clinical presentation, drug treatment	General
Beck (35)	Meta-analysis	CINAHL, MEDLINE, PsycINFO, Eric, Popline, Social Work Abstract, Sociological Abstracts, Dissertation Abstracts, JREF	84	Postpartum depression, postnatal depression, puerperal depression, predictors, risk factors	General
Cutrona (32)	Narrative/synthetic	Nil reported			General
Guintivano et al. (33)	Narrative/synthetic	Nil reported			General
Gulamani et al. (36)	Narrative/synthetic	CINAHL, ScienceDirect, MD Consult		Infants, mother, PPD, postpartum blues, post-natal depression, mental health, postpartum, preterm delivery, preterm infant(s), mother-infant interaction, mother-infant dyad, mother infant bonding, parental stress, early parental stress, culture, ethnicity, society	Pakistan
Koirala and Chuemchit (37)	Systematic	PUBMED, SCOPUS, Web of Science, Google Scholar	38	postpartum, postnatal, depression, violence	General
Lee and Chung (38)	Narrative/synthetic	Nil reported			General
O'Hara and Swain (39)	Meta-analysis	Nil reported			General
Özcan, Boyacioglu (40)	Meta-analysis	PUBMED, Science Direct, MEDLINE, PsycINFO, Ovid, CINAHL, Cochrane	52	Postpartum, puerperal, postnatal, depression, Turkey	Turkey
Robertson et al. (41)	Meta-analysis	Nil reported			General
Schmied et al. (42)	Systematic	SCOPUS, MEDLINE, PsycINFO, Health Source	23	Longitudinal, women, women's health, pregnancy, psychosocial, mental health, physical, infant, perinatal, postnatal	Australia, New Zealand
Takegata et al. (43)	Systematic	CINAHL, MEDLINE, PUBMED, Ovid, SCOPUS, IndMED, ICHUSI	50	Antenatal depression, postpartum depression, India, Japan	India, Japan
Yim et al. (44)	Systematic	PUBMED, PsycINFO	214	Postpartum, postnatal, social, psychosocial, endocrine, partner, immune, inflammatory, cytokine, genetic, stress, demands, events, couple, relationship, partner, marital, marriage, close relationship, interpersonal, social, family, social network, social support, integration	General
Zahidie and Jamali (45)	Narrative/synthetic	PUBMED	12	Depression, risk factors, women, Pakistan	Pakistan

pandemics, could improve future government and clinical decision-making. New cross-sectional and longitudinal cohort studies that attempt to recruit mothers in the perinatal period during the COVID-19 pandemic are therefore urgently needed. Additionally, it may be useful for researchers to consider designs, such as those implemented by Jiang et al. (28), where a previous cohort was used as a comparison group for understanding contextual changes and the impact on maternal and child well-being. Further, research is needed into which mitigation efforts are having a direct effect on population prevalence levels.

Given that postnatal depression is not a new phenomenon, there are effective ways to assess it clinically (e.g., Edinburgh Postnatal Depression Scale; Center for Epidemiologic Studies Depression Scale; Beck Depression Inventory), research and monitor community levels of postnatal depression, examine mechanisms that impact individuals' likely experience of postnatal depression, and intervene (47). For these reasons, healthcare workers (e.g., psychiatrists, midwives, general practitioners, psychologists, social workers, nurses) need to be aware of how known risk factors may be interacting in the context of the COVID-19 pandemic, and consider innovative ways that they can address mental health concerns during and following the COVID-19 pandemic. This is of particular concern as there may be larger numbers of women who could be experiencing postnatal depression due to the exacerbation of risk factors. There is support for the efficacy of telehealth to support caregiver well-being and parenting behavior, as well as internet-delivered psychological interventions for women in the antenatal and postnatal periods in reducing depressive symptoms [for a review and meta-analysis see Loughnan, Joubert (47)]. Yet it is possible that these interventions are not equally efficacious or accessible for all populations, particularly when technology access is not universal and there may be limitations to privacy (e.g., confinement-related crowding in the home). Health care workers also need to be aware of how structural barriers to noticing symptomology may interfere with identification of mothers experiencing postnatal depression at this time. For instance, telehealth options that do not include videos may place greater onus on mothers'

TABLE 2 | Distribution of the abstracted risk factors across the corpus of reviews identified for qualitative synthesis.

Article short name	Risk factors by degree of association per article																								
	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]	[17]	[18]	[19]	[20]	[21]	[22]	[23]	[24]	[25]
Banti et al. (34)	***	***	***		*					**	***	**	*		*	*		*	**						
Beck (35)	**		*	**		*			**	*	*	*					**			**	*	*			
Cutrona (32)	**	*				**	**		***	*	***	**			**						**		*		
Guintivano et al. (33)	***	***			***	*				*	***	***	**		***								***	**	**
Gulamani et al. (36)	*	*	*		*	*					*		**			**	**						*		
Koirala and Chuemchit (37)								**	***			***				**									
Lee and Chung (38)	**		*	*	*		*				*	*				*			*						
O'Hara and Swain (39)				***	**	***	**				***	*	*	*	*				**						
Özcan et al. (40)				**	***	***			**		***	***	*	***	***	*			*			***			*
Robertson et al. (41)	***		***	***							***	**	*		*				**						
Schmied et al. (42)			*	*		*	*		*		*	*	*		*							*			*
Takegata et al. (43)						**	**		**			**			*	***				*		*			
Yim et al. (44)						**	*	**	***		**	*			*	*	**				**				
Zahidie and Jamali (45)						**	**		**	**	**	**	**			***	**			*					**

*Abstracted risk factors indicate degree of association to postnatal depression with asterisks (Weak = *; Moderate = **; Strong = ***).*

[1] Presence of depressive symptoms during pregnancy; [2] Presence of symptoms of common mental disorders other than depression and anxiety during pregnancy; [3] Prior diagnosis of a depressive disorder; [4] Prior diagnosis of an anxiety disorder including prenatal anxiety; [5] Family history of psychiatric illness during or prior to pregnancy including genetic risk factors; [6] Perceived low social support during pregnancy; [7] Perceived low support from partner; [8] History of childhood sexual abuse; [9] Exposure to traumatic events during or prior to pregnancy specifically including physical domestic and family violence; [10] Generalized high allostatic load including the stress hormone cortisol and plasma-derived inflammatory biomarkers; [11] Significant life events occurring during pregnancy or immediately post-partum (e.g., death of a loved one; loss of employment; relationship breakdown or divorce; relocation including moving house); [12] Marital dissatisfaction leading to complications (including psycho-emotional but not physical domestic and family violence); [13] Adverse obstetric factors (e.g., pre-eclampsia; hyperemesis; premature labor including Cesarean section; intrapartum bleeding; pre-term birth); [14] Severe neonatal complications including congenital malformations; [15] Low socioeconomic status (i.e., low average income and/or high cost-of-living); [16] Specific culture-bound factors (e.g., spousal disappointment with sex of fetus/infant; imposition of strict gender roles during and after pregnancy); [17] High stress associated foremost with care of index child but including other young children; [18] Failure to adhere to psychiatric medications including those prescribed to manage depressive symptoms; [19] High maternal neuroticism; [20] Low maternal self-esteem and/or self-acceptance; [21] Difficult infant temperament; [22] Ambivalence associated with parenting including unplanned pregnancy; [23] Historical diagnosis of other common mental disorders; [24] Adverse experiences associated with immigration (e.g., racial/ethnic discrimination, delayed visa status/uncertainty surrounding immigration status, poor access to health services, low language ability for country of settlement); [25] Giving birth at age extremes (i.e., very young or older mothers).

TABLE 3 | Hypotheses for how the COVID-19 crisis may exacerbate known risk factors for postnatal depression.

Established risk factor for postnatal depression (numbers listed in brackets are per Table 2)	Hypotheses: Exacerbated by COVID-19 crisis? *[strongly decreased, weakly decreased, N/A, weakly increased, strongly increased]*	Examples of contextual factors that may be interacting with this risk factor	Disaster-related rationale for hypotheses
[1] Presence of depressive symptoms during pregnancy	Strongly increased	Home isolation; social and physical distancing; some antenatal and postnatal supports have ceased operating; reduced physical activity; cumulative losses; increased media exposure.	Increased rates of depression symptoms experienced in populations following disasters (5), and currently observed in relation to COVID-19 (28, 29). Reduced rates of physical activity reported for those in the perinatal period during COVID-19 pandemic (29).
[2] Presence of symptoms of common mental disorders (other than depression and anxiety) during pregnancy	Weakly increased	Home isolation; social and physical distancing; some antenatal and postnatal supports have ceased operating; reduced physical activity; cumulative losses; increased media exposure.	Increased rates of psychopathology currently observed in relation to COVID-19 (28).
[3] Prior diagnosis of a depressive disorder	N/A for the cohort pregnant and/or giving birth during the COVID-19 pandemic		
[4] Prior diagnosis of an anxiety disorder including prenatal anxiety	Strongly increased	Home isolation; social and physical distancing; some antenatal and postnatal supports have ceased operating; reduced physical activity; cumulative losses; increased media exposure.	Increased rates of anxiety symptoms experienced in populations following disasters (5), and currently observed in relation to COVID-19 (28, 29).
[5] Family history of psychiatric illness, during or prior to pregnancy, including genetic risk factors	N/A for the cohort pregnant and/or giving birth during the COVID-19 pandemic		
[6] Perceived low social support during pregnancy	Strongly increased	Home isolation; social and physical distancing; reduced visitations from social supports; some postnatal supports have ceased operating; reduced time in hospital; reduced number/length of medical appointments.	Social support can alleviate the stress caused by disaster, however it appears to depend on whether support structures are created or destroyed (5). It appears that COVID-19 is likely to reduce the likelihood that social supports can be effectively accessed, thus perceived social support is likely to be lower.
[7] Perceived low support from partner	Weakly increased	Partners may be physically present in the home whilst working from home; possibly increased interpersonal partner conflict from containment in the home for long periods.	Social support can alleviate the stress caused by disaster, however it appears to depend on whether support structures are created or destroyed (5). It appears that COVID-19 may have mixed impacts regarding partner relationships with some partners more able to support when working from home, whereas other families may experience increased interpersonal partner conflict from containment in the home for long periods (17).
[8] History of childhood sexual abuse	N/A for the cohort pregnant and/or giving birth during the COVID-19 pandemic		
[9] Exposure to traumatic events during or prior to pregnancy specifically including physical domestic and family violence	Strongly increased	Home isolation; social and physical distancing; reduced visitations from social supports; changes in hospital policies, for instance, separation of COVID-19 positive mothers from their newborn infants for 14 days in China (9); no birth partners in the labor ward (e.g., in New York in the United States of America).	Domestic and family violence expected to increase during disaster, particularly the COVID-19 crisis (17). Additionally, for some women the impact of changed hospital policies in times of disaster may be perceived to be traumatic.
[10] General stress (i.e., Generalized high allostatic load including the stress hormone cortisol and plasma-derived inflammatory biomarkers)	Strongly increased	Home isolation; social and physical distancing; reduced visitations from social supports; some postnatal supports have ceased operating; reduced time in hospital; reduced number/length of medical appointments; media exposure; financial stress associated with employment uncertainty (e.g., loss of employment hours).	Emerging research from the COVID-19 crisis indicates high levels of stress and associated psychopathology in the general population (6), and high levels of stress have also been recorded within perinatal populations (28).

(Continued)

TABLE 3 | Continued

Established risk factor for postnatal depression (numbers listed in brackets are per Table 2)	Hypotheses: Exacerbated by COVID-19 crisis? *[strongly decreased, weakly decreased, N/A, weakly increased, strongly increased]*	Examples of contextual factors that may be interacting with this risk factor	Disaster-related rationale for hypotheses
[11] Significant life events occurring during pregnancy or immediately post-partum (e.g., death of a loved one; loss of employment; relationship breakdown or divorce; relocation including moving house)	Strongly increased	COVID-19 may in itself be perceived as a significant life event; women may experience death of a loved one due to illness from COVID-19; women may not be able to mourn the death of a loved one in culturally expected ways due to imposed restrictions; loss of employment may be experienced for self or other family members; relationship strain from containment in the home for long periods may result in relationship breakdown or divorce.	No direct evidence identified from previous disasters.
[12] Marital dissatisfaction leading to complications (including psycho-emotional but not physical domestic and family violence)	Weakly increased	Partners may be physically present in the home due to working from home; possibly increased interpersonal partner conflict from containment in the home for long periods; unequal caring and/or home-schooling duties may increase dissatisfaction.	Positive social support from partners can reduce the stress caused by disaster, however not all partners provide positive social support (5). Interpersonal partner conflict and marital dissatisfaction may be amplified within some families (17).
[13] Adverse obstetric factors (e.g., pre-eclampsia; hyperemesis; premature labor including Cesarean section; intrapartum bleeding; pre-term birth)	N/A		
[14] Severe neonatal complications including congenital malformations	N/A		
[15] Low socioeconomic status (i.e., low average income and/or high cost-of-living)	Weakly increased	Loss of employment for self or other family members may change the experience of socio-economic well-being.	Economic factors, such as family income and employment, have been linked to poor maternal mental health after earthquakes (5).
[16] Specific culture-bound factors (e.g., spousal disappointment with sex of fetus/infant; imposition of strict gender roles during and after pregnancy)	N/A		
[17] High stress associated foremost with care of index child but including other young children	Strongly increased	Home isolation with reduced visitations from social supports may increase the perceived stress associated with the index child, and high stress may result from reduced care options (i.e., keeping other children home from care; home schooling; etc.).	No direct evidence identified from previous disasters.
[18] Failure to adhere to psychiatric medications including those prescribed to manage depressive symptoms	N/A		
[19] High maternal neuroticism	N/A		
[20] Low maternal self-esteem and/or self-acceptance	N/A		
[21] Difficult infant temperament	N/A		
[22] Ambivalence associated with parenting, including unplanned pregnancy	N/A		
[23] Historical diagnosis of other common mental disorders	N/A for the cohort pregnant and/or giving birth during the COVID-19 pandemic		
[24] Adverse experiences associated with immigration (e.g., racial/ethnic discrimination, delayed visa status/uncertainty surrounding immigration status, poor access to health services, low language ability for country of settlement)	Weakly increased	Physical distancing; change in economic climate.	Possible increased uncertainty surrounding immigration status with possible longer wait times; access to health services may be impacted; and ability to source help services without face-to-face interaction may be increasingly challenging.
[25] Giving birth at age extremes (i.e., very young or older mothers)	N/A		

self-reporting rather than allowing for additional visual cues to assist clinicians in identifying mothers who may be under-reporting symptoms.

Further, governments and funding bodies need to be aware of the increased need to fund research for monitoring community levels of postnatal depression and the costs involved in upscaling evidence-based interventions to meet increased demand. Research has shown that by investing in women's mental health during the perinatal period there is a reduction in long-term socio-emotional impacts, physical health, and associated societal/economic costs (48). Targeted funding at this critical time may contribute to reductions in the short- and long-term economic, physical health, and socio-emotional impacts for women and their children, feeding into economic recovery on a wider scale. Although there may be some amelioration of risks due to policy and clinical responses, we believe that as a net result there will be an increased number of women needing support for postnatal depression during and following the COVID-19 pandemic. Thus, critical to the success of upscaling evidence-based interventions is having a workforce that is capable and ready to implement them. It is therefore important to consider the training needs and/or digital adaptations that may need priority funding to ensure timely delivery and accessibility of evidence-based interventions to treat postnatal depression during and following the COVID-19 pandemic.

Limitations and Strengths

This review is not without limitations. First, we were unable to use any risk of bias tools to examine study bias. This was due to a combination of factors including the heterogeneity of methods in the identified review papers, changes in reporting standards across the decades, and underreporting of core information in the identified review papers making it difficult to explicitly evaluate risk of bias. Second, it is possible that some risk factors for postnatal depression have not been captured by our review process. These may include risk factors that are important for specific populations, risk factors that may arise specifically in the context of the COVID-19 pandemic, as well as risk factors with a developing evidence-base that have not yet been captured in meta-analyses and peer-reviewed review papers. In addition, qualitative methodologies were employed to critically and clinically evaluate the likelihood that the risk factors identified by our process would be exacerbated by the COVID-19 crisis; as such, it is possible that alternative interpretations may be made. Further, we have attempted to identify those risk factors that may be impacted by a current contextual change, and have therefore excluded a range of early life experiences, genetic factors, and biological vulnerabilities to experience (44). While it may be possible that these risk factors will impact some women's risk of developing postnatal depression in a few decades, they are not likely to immediately impact current population prevalence rates of postnatal depression. Finally, an examination of resilience factors in relation to postnatal depression was beyond the scope of this review yet might be useful to consider alongside postnatal depression risk factors. Future research should consider eliciting resilience factors from previous research, as well as examining resilience factors that are specific to the COVID-19 pandemic.

Nonetheless, this review also has several noteworthy and timely strengths. Although, several studies have shown that stress during pregnancy and postpartum is associated with mental ill-health (4, 5), few researchers have been in the position to prospectively identify the mechanisms that may drive the association between experience of perinatal stress and mental ill-health. In this paper, we have outlined a number of ways that women in the perinatal period may be experiencing increased stress in the context of COVID-19. We have discussed findings from previous crises that indicate that women might be at a higher risk of developing postnatal depression in the wake of crises. Further, this review has highlighted several core risk factors for postnatal depression that are likely to be impacted and/or exacerbated by crisis contexts such as the COVID-19 global pandemic crisis. Thus, we believe that it is likely that there is a heightened chance that women are at risk of developing postnatal depression at this time, and that population rates of postnatal depression may be increased.

CONCLUSION

It is essential for the research community to identify potential mechanisms underlying mental ill-health in crisis contexts so that assessment and testing can be prioritized, and policy makers can urgently address these mechanisms with emergency funding to ameliorate the effects of the COVID-19 pandemic on maternal mental health. In particular, researchers and policy makers should attempt to focus efforts on improving perceived social support, reducing exposure to traumatic events including physical domestic and family violence, reducing the impact of significant life events, and addressing the stress associated with caring for young children during a pandemic; as we hypothesize that these mechanisms may be particularly likely to drive change for women who are at risk of postnatal depression in the wake of the COVID-19 global pandemic crisis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

FD provided the study concept and design. The literature search was conducted by LK in close consultation with FD. FD interpreted the data. FD and LK drafted the manuscript and engaged in critical revision for important intellectual content. All authors contributed to the article and approved the submitted version.

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Sleep Quality, Empathy, and Mood During the Isolation Period of the COVID-19 Pandemic in the Canadian Population: Females and Women Suffered the Most

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Objective: To investigate the sex and gender differences in the impact of the isolation period implemented in response to the COVID-19 pandemic on individuals' sleep quality, empathy, and mood.

Design: Data were collected between March 23 and June 7, 2020 on a sample of volunteers in the Canadian population. Six hundred and thirty-eight volunteers completed an online survey (~30 min).

Main Outcome and Measures: We first examined biological sex, gender, and sexual identity differences (both components of the ampler concept of gender) in sleep, empathy, and mood disturbances. Then, we assessed changes in sleep and mood over the course of the isolation period and tested for significant relationships between sleep variables, mood, and empathy.

Results: We analyzed complete data for 573 participants (112 males and 459 females, 2 undisclosed, mean $\pm$ SD age $= 25.9 \pm 10.5$ years, mean $\pm$ SD education $= 16.2 \pm 2.9$ years). As compared to males, female participants reported lower quality of sleep, lower sleep efficiency, and greater symptoms of insomnia, anxiety, depression, and trauma. In addition, females reported higher scores than males on the IRI empathy scale and all its subcomponents. Similar results were found when stratifying by gender. Sleep and mood disturbances increased over the course of the isolation period in the whole sample. The most significant predictors of poor quality of sleep and insomnia were depression, anxiety, and trauma scores, especially in females; higher empathy trait was associated with higher depression, anxiety, and trauma scores, perhaps indicating a more positive role of fear and anxiety responses to the pandemic crisis.

Significance and Conclusions: Sex and gender differences seem to play a role in the individuals' psychological and behavioral reactions to the COVID-19 pandemic. These differences need to be considered in planning targeted psychological interventions.

Keywords: coronavirus, insomnia, emotions, depression, anxiety

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as Coronavirus disease 2019 (COVID-19), appeared in the province of Wuhan, China, at the end of 2019 and quickly spread across several countries in the word (1). On March 11th 2020, the World Health Organization declared the Coronavirus outbreak a *Pandemic* (2). In absence of pharmaceutical interventions, shelter in place at home and social distancing were globally deemed as the best strategy to stop the spread of the virus (3). On January 27, 2020, the first COVID-19 case was confirmed in Canada. In mid-March, all of Canada's provinces declared states of local emergency and implemented various levels of mandatory isolation with school and daycare closures, restrictions on gatherings, closures of non-essential businesses, restrictions on entry, and mandatory quarantine for travelers. As for August 25, 2020, there have been approximately 125,645 COVID-19 confirmed cases in Canada, with 4,870 active cases and 9,083 deaths.

Although effective in containing the spread of COVID-19, isolation and social distancing caused an interruption in the normal routine of many people in the word (4), with school being closed and parents trying to balance remote working, childcare and house management (5). This has led to changes and disruption of individuals' mental well-being and sleep schedule (6), similar to those observed following previous natural disasters (7–9). To date, only a few studies have examined the changes in sleep quality and mood during the COVID-19 pandemic in both the general population and health care professionals. Casagrande et al. (10) found that 57.1% of responders to an online survey reported poor quality of sleep, 32.1% reported increased symptoms of anxiety, 41.8% increased distress, and 7.6% reported symptoms of post-traumatic stress disorder (PTSD). Sleep disorders and anxiety disorders were more prevalent in women, those unemployed, and those who were worried about being infected with COVID-19 (or knew people who died due to COVID-19). These findings are consistent with other studies conducted in the Italian (11–13), and Chinese populations (14–17), some of the most affected, confirming the significant negative impact of the pandemic on mental health. Although these studies provide a significant contribution to understanding the impact of COVID-19 on the human well-being, the effects of sex and gender in response to the pandemic, as well as the deterioration and progression of the individuals' mental health over the course of the isolation period, remain unknown.

Sex and gender differences, seem to play a role in the individuals' psychological and behavioral reactions to the pandemic (18). While often used interchangeably the two terms indicate very different things. Sex refers to a biological construct primarily associated with physical and physiological features including genes, hormones and anatomical and physiological characteristics (19). Gender refers instead to socially constructed roles, behavior, expressions, and identities (19). To date, there is no standard method to assess gender. However, recent studies have pointed out to the need to assess sexual identity (i.e., straight, gay etc.) and gender identity (man or woman), both part of the ampler definition of gender, separately from biological sex (male and female) (20). Both biological sex and gender have been shown to be associated with pattern of exposure, treatment, and behavioral changes associated with COVID-19. Biological sex seems to be associated with the infection and mortality rates, with higher numbers of men suffering greater health consequences from the virus (21, 22). These sex differences have been thought to be associated with the different immune response in the two sexes, with a different distribution of the ACE 2 receptors where the coronavirus binds, and with potential protective effects of estrogens (22). Gender, on the other hand, has been shown to play a bigger role in pattern of exposures to the virus (gender influences where people are spending time), and in the behavioral reactions to the pandemic (18).

Here, we investigated the effects of sex and gender in response to the isolation period of the pandemic, in the context of different critical elements of the individuals' mental well-being, that are sleep quality, empathy, and individual mental health status of depression, anxiety and post-traumatic stress symptoms. Of particular interest is empathy, defined as the ability to understand another individual's mental state in terms of emotions, feelings and thoughts (23), being an important aspect to consider when examining individuals' reactions to the pandemic. Empathy is in fact a fundamental process underlying the ability of caring for others and, as such, higher empathy for others may translate to higher compliance to public health rules. The concept of empathy can be further separated into cognitive and emotional components (23–27); here we focus solely on the emotional aspect of empathy. Similarly, sleep is well-known to be crucial for well-being and proper neurocognitive performance (28). Several studies have confirmed the negative impact of sleep loss on individuals' mood and emotional processing (29) including empathy (30–33). Based on this evidence, one would expect that the relationship between sleep quality and emotional processing will hold during the COVID-19 pandemic. To date, however, there is no evidence that this is the case.

It is known that sleep, empathy and mental health status may differ between the two sexes. Previous studies have in fact highlighted sex and gender differences in empathy (34), with females usually reporting higher scores as compared to males. Similarly, sleep architecture and quality differs in the two sexes with females having an overall better quality of sleep (35) but higher symptoms of insomnia (36). Males, on the other hand, tend to have more sleep disordered breathing pathologies such as obstructive sleep apnea (37). The negative effects of sleep loss on cognition also seem to be differential in the two sexes due to hormonal effects (38). Finally, mood disorders are more prevalent in females as compared to males and recent studies have tried to explain these differences highlighting how immune mechanisms may differently contribute to stress susceptibility and associated mood disorders (39). However, how these sex differences manifest during the isolation in response to the pandemic is still unclear.

In this study, we investigated if sex and gender are differently associated with sleep, empathy and mental health during the isolation that was implemented to stop the spread of COVID-19, and if the increased number of days spent in isolation heightened individuals sleep disturbances and mental health concerns.

TABLE 1 | Participants' demographics and COVID-19 status.

	M ± SD Whole sample	M ± SD Males	M ± SD Females
Age	25.9 ± 10.5	26.2 ± 9.4	25.9 ± 10.7
Education total	16.2 ± 2.9	16.0 ± 3.2	16.2 ± 2.9
Ethnicity	***N* (%) Whole sample**	***N* (%) Males**	***N* (%) Females**
White	321 (56%)	55 (49.1%)	266 (58%)
Afro-American	2 (0.3%)	–	2 (0.4%)
East-Asian	70 (12.2%)	18 (16.1%)	52 (11.3%)
South-Asian	101 (17.6%)	20 (17.9%)	79 (17.2%)
African	13 (2.3%)	5 (4.5%)	8 (1.7%)
Indigenous	2 (0.3%)	–	2 (0.4%)
Latino	14 (2.4%)	5 (4.5%)	9 (2.0%)
Mixed-race	32 (5.6%)	6 (5.4%)	26 (5.7%)
Other	18 (3.1%)	3 (2.7%)	15 (3.3%)
Neuro/psychiatric condition	***N* (%) Whole sample**	***N* (%) Males**	***N* (%) Females**
NO	439 (76.9)	87 (77.7%)	350 (76.3%)
YES	53 (9.2%)	9 (8.0%)	44 (9.6%)
YES (non-medicated)	53 (9.2%)	9 (8.0%)	44 (9.6%)
Concussion	27 (4.7)	6 (5.4%)	21 (4.6%)
Current situation Days (M ± SD = 42.2 ± 22.1)	***N* (%) Whole sample**	***N* (%) Males**	***N* (%) Females**
Self-isolation	112 (19.5)	26 (23.2%)	85 (18.5%)
Quarantine	48 (8.4%)	11 (9.8%)	36 (7.8%)
Social distancing	406 (70.9)	72 (64.3%)	334 (72.8%)
None	7 (1.2%)	3 (2.7%)	4 (0.9%)
Know someone with COVID (*n* = 336)	***N* (%) Whole sample**	***N* (%) Males**	***N* (%) Females**
NO	247 (73.3%)	38 (33.9%)	209 (45.5%)
Myself	4 (1.2%)	1 (0.9%)	3 (0.7%)
A friend	54 (16%)	7 (6.3%)	47 (10.2%)
A relative	32 (9.5%)	3 (2.7%)	29 (6.3%)
Know someone who died with COVID (*n* = 336)	***N* (%) Whole sample**	***N* (%) Males**	***N* (%) Females**
NO	318 (94.4%)	48 (42.9%)	270 (58.8%)
A friend	11 (3.3%)	–	11 (2.4%)
A relative	8 (2.4%)	1 (0.9%)	7 (1.5%)

M ± SD, Mean ± Standard Deviation; N, number.

Secondarily, we investigated the most significant predictors of sleep quality during the isolation in the whole sample first, and then in subgroups stratified by sex and gender. The findings of this study may provide important insights to be considered when planning personalized psychological interventions to counterbalance the negative effects of the isolation period on sleep and mental health.

METHODS

Participants

We recruited 638 volunteers through the University of Calgary Research Participation System and COVID-19 research page, social media and word of mouth. Collected data were anonymous and participants could voluntary withdraw from the study at any time. The final complete dataset included 573 Canadian volunteers (112 males and 459 females, 2 undisclosed, mean ± SD age = 25.9 ± 10.5 years, mean ± SD education = 16.2 ± 2.9 years). Participants' demographics and isolation status are reported in **Table 1**. Gender breakdown is reported in **Table 2**. The study was reviewed and approved by the local research ethics board (REB20-0650), and participants provided an electronic informed consent before the study began.

Experimental Protocol

Participants were asked to complete an online survey (∼30 min). The survey included a demographic questionnaire inquiring about age, years of formal education, ethnicity, history of neurological/psychiatric illness, medications, biological sex, gender identity, and sexual identity. The following questions were used to inquire about biological sex, gender identity and sexual identity separately: (1) what is your biological sex? Male/female; (2) what is your gender identity? Man, Woman, trans-sexual woman/man, non-binary, other; (3) what is your sexual identity? Straight, gay, bisexual, or other.

Four COVID-related questions inquired about isolation/social distancing status, length of the isolation,

TABLE 2 | Participant's gender breakdown.

		N (%)
Biological sex	Male	112 (19.5%)
	Female	459 (80.1%)
	Undisclosed	2 (0.3%)
Gender ID	Woman	460 (80.6%)
	Man	105 (18.4%)
	Non-binary	5 (0.9%)
	Undisclosed	1 (0.2%)
Sexual ID	Straight	508 (88.7%)
	Gay	16 (2.8%)
	Bisexual	42 (7.3%)
	Other	7 (1.2%)

positivity to COVID-19, or knowledge of individuals infected or who died because of COVID-19.

The demographic questionnaire was followed by 6 questionnaires assessing sleep, mood and empathy. Self-reported sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) (40) and with the Insomnia Severity Index (ISI) (41), a questionnaire that assesses symptoms of insomnia. Both PSQI and ISI are validated questionnaire with Cronbach's alphas of 0.69 (42) and 0.90 (41), respectively. PSQI total score (5)≥ indicative of poor quality of sleep (40) was computed by adding responses to 7 subcomponents: (1) subjective sleep quality, (2) latency, (3) duration, (4) efficiency (hours in bed/hours sleeping), (5) sleep disturbance, (6) sleep medications, and (7) daytime dysfunction. The scores on the duration, latency and efficiency were also analyzed as separate continuous variables. Additionally, we calculated the total score for the ISI with scores ≥9 indicative of clinical insomnia (41).

Participants also completed the State-Trait Anxiety Inventory (43) which has a Cronbach's alpha for the total scores ranging from 0.86 to 0.95 (44), and the Beck Depression Inventory (BDI) (45) with a Cronbach's alpha of 0.81 for non-psychiatric population, and the Davidson Trauma Scale (46) with a Cronbach's alpha of 0.95 (47). The STAI was used to assess participants' current (state) and general (trait) anxiety symptoms, and the BDI was used to evaluate participants' depressive traits (scores >17 indicating borderline depression), while the Davidson Trauma Scale assessed trauma. Finally, the Interpersonal Reactivity Index (IRI) (48) assessed empathy with four different subscales: *Perspective Taking,* the individual's ability to take others' perspective, *Fantasy,* the ability to identify with characters of movies and books, *Empathic Concern,* the feelings of concern and compassion for others, and *Personal Distress,* the negative feeling of distress while observing someone in a negative situation. The IRI Cronbach's alpha ranges from 0.70 to 0.78 (48).

Data Analyses

Data were analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM, Armonk, NY, USA).

We computed descriptive statistics for questionnaires' scores for the whole sample and for males and females separately. Q-Q plots were examined to assess the normal distribution of the data.

First, Kruskal-Wallis non-parametric tests were used to compare participants' questionnaires scores between biological sexes, gender identities, and sexual identities. The choice of non-parametric test was due to the large sample size difference among the subgroups. We then used linear regressions to examine the relationship between number of days spent in isolation and questionnaires' scores separately for males and females. These analyses show the progression of insomnia, depression, and trauma with increasing length of the isolation period. Finally, we ran a series of multiple linear regressions (MLRs) with PSQI total score, sleep duration, sleep latency, sleep efficiency, and ISI total score as dependent variables in separate models, age as forced confounding factor, and scores on the IRI, BDI, STAI (trait and state), and total trauma as independent predictors. We ran the MLRs analyses in the whole sample first, and then stratified by biological sex (20).

All analyses were two-tailed and statistical significance was set at $p < 0.05$. Bonferroni-Holm correction was applied to correct for multiple comparisons and to reduce experiment wise error.

RESULTS

Questionnaires' Descriptive Findings

The Q-Q plots revealed that the data was normally distributed.

Three hundred and eighty-three participants (66.8%) reported poor quality of sleep, and 225 (39.2%) reported clinical insomnia. The average score on the BDI scale was 13.1 representing normal and mild mood swings. Both anxiety state and trait were heightened in the whole sample with average normative scores of 55 and 59, exceeding the cut off for clinically significant anxiety of 40 (43). Scores on the Davidson Trauma Scale were also heightened as compared to the general population with an average total trauma score of 37.9, which according to Davidson classification identifies subthreshold PTSD with impairments (46).

Sex and Gender Differences in Sleep, Mood, and Empathy

Females compared to males reported lower quality of sleep ($p = 0.023$), sleep efficiency ($p = 0.023$), and greater symptoms of insomnia ($p = 0.021$). When correcting for multiple comparisons these differences were not significant anymore. Females also reported significantly higher symptoms of anxiety (both state and trait $p < 0.001$), depression ($p < 0.001$), and greater distress in relation to a traumatic event in both severity ($p < 0.001$) and frequency domains ($p < 0.001$). However, females reported higher scores on the IRI empathy scale ($p < 0.001$) and all its subcomponents (all $p < 0.01$). Please refer to **Table 3** for complete statistics.

In our sample, 459 participants identified as females and 460 as women (99.7% overlap). One hundred and twelve participants identified as males and 105 as men (93.7% overlap). The Kruskal-Wallis non-parametric tests yielded the same statistically

TABLE 3 | Participants' questionnaires data: biological sex differences.

	M ± SD whole sample	N	M ± SD Males	N	M ± SD Females	N	p-value*	Cohen D_z
PSQI total	6.0 ± 2.7	572	5.4 ± 2.7	112	6.1 ± 2.8	458	**0.023**	0.25
PSQI latency (min)	55.9 ± 61.7	562	67.2 ± 75.1	110	53.1 ± 57.8	450	0.212	0.18
PSQI duration (hrs)	7.6 ± 1.4	572	7.6 ± 1.2	112	7.6 ± 1.4	458	0.825	0
PSQI efficiency (%)	88.7 ± 14.1	572	91.3 ± 13.5	112	88.1 ± 14.2	458	**0.021**	0.22
ISI	7.5 ± 4.8	573	6.0 ± 4.5	112	7.8 ± 4.9	459	**<0.001**	0.36
STAI state (raw)	42.9 ± 12.2	544	38.2 ± 12.2	102	44.0 ± 12.0	440	**<0.001**	0.47
STAI trait (raw)	44.1 ± 11.9	541	39.9 ± 12.3	101	45.1 ± 11.6	438	**<0.001**	0.42
BDI	13.1 ± 10.0	573	9.7 ± 9.9	112	14.0 ± 9.9	459	**<0.001**	0.43
Trauma severity	20.0 ± 13.4	552	15.1 ± 13.0	105	21.2 ± 13.2	445	**<0.001**	0.46
Trauma frequency	17.8 ± 13.2	552	12.9 ± 12.9	105	19.0 ± 13.0	445	**<0.001**	0.46
Total trauma	37.9 ± 26.1	552	28.1 ± 25.4	105	40.2 ± 25.7	445	**<0.001**	0.47
IRI total	63.8 ± 15.7	573	54.7 ± 13.4	112	65.9 ± 15.5	459	**<0.001**	0.72
IRI perspective taking	15.8 ± 5.0	573	14.6 ± 5.4	112	16.1 ± 4.8	459	**0.006**	0.27
IRI fantasy	15.3 ± 6.6	573	13.0 ± 6.1	112	15.9 ± 6.6	459	**<0.001**	0.43
IRI empathic concern	20.2 ± 4.9	573	17.3 ± 4.7	112	20.8 ± 4.8	459	**<0.001**	0.75
IRI personal distress	11.0 ± 5.3	573	8.8 ± 4.4	112	11.5 ± 5.4	459	**<0.001**	0.50

M ± SD, Mean ± Standard Deviation; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; STAI, State-Trait Anxiety Inventory; BDI, Beck Depression Inventory (cutoff >17); IRI, Interpersonal Reactivity Index. Bold fonts indicates significant p values.

*Kruskal-Wallis non-parametric test was used to compare males and females due to differences in sample size. Cohen D_z is reported as a measure of effect size.

significant differences as the biological sex comparison. Please refer to Supplemental for complete statistics.

We also observed that straight participants reported the lowest quality of sleep (5.9 ± 2.7 vs. 7.1 ± 2.9 vs. 6.5 ± 2.7, respectively) and gay participants reported the highest insomnia symptoms (7.3 ± 4.8 vs. 9.4 ± 5.5 vs. 8.0 ± 4.4, respectively). The total score on the IRI was highest for bisexual/pansexual participants (63.1 ± 15.2 vs. 62.0 ± 15.0 vs. 71.8 ± 18.9, respectively). The sample size for these subgroups is however small and conclusions cannot be drawn.

Changes in Sleep, Mood, and Empathy Over the Course of the Isolation Period

In male participants, we saw a worsening of trauma severity ($\beta = 0.208$, $p = 0.033$), trauma frequency ($\beta = 0.209$, $p = 0.032$), and trait anxiety ($\beta = 0.220$, $p = 0.027$) with increasing length of the isolation/social distancing period. In females, symptoms of insomnia ($\beta = 0.264$, $p < 0.001$), trauma severity ($\beta = 0.136$, $p = 0.004$) and frequency ($\beta = 0.097$, $p = 0.041$), symptoms of depression ($\beta = 0.102$, $p = 0.029$), and trait anxiety ($\beta = 0.121$, $p = 0.011$) progressed over the course of the isolation period. No changes with increased length of the isolation period were found in the IRI total score and subscales for both males and females (**Figure 1**).

Predictors of Sleep Quality in the Whole sample

Please refer to **Tables 4**, **5** for complete statistics.

In the whole sample, after controlling for age, total PSQI scores were positively associated with depression symptoms, total trauma, and state anxiety ($p = 0.037$). Sleep latency was positively associated with total trauma ($p = 0.013$). Sleep duration was negatively associated with state anxiety and depression symptoms ($p = 0.032$). Sleep efficiency was negatively associated with depression symptoms ($p < 0.001$). Similarly, symptoms of insomnia were also positively associated with depression symptoms, total trauma, and state anxiety ($p = 0.003$).

Predictors of Sleep Quality in the Two Sexes

In males, after controlling for age, total PSQI score, and insomnia symptoms were positively associated with depression symptoms (both $p < 0.001$). Sleep efficiency was instead negatively associated with trait anxiety ($p = 0.005$).

In females, total PSQI scores were positively associated with depression symptoms ($p < 0.001$). Sleep latency was associated with total trauma ($p = 0.007$). Sleep duration was negatively associated with depression symptoms and state anxiety ($p = 0.033$). Sleep efficiency was only negatively associated with depression symptoms ($p < 0.001$). Symptoms of insomnia were associated with total trauma, depression symptoms, and state anxiety ($p = 0.013$).

Exploratory Correlational Analysis

We did not find associations between IRI empathy scores and the sleep variables in the whole sample. IRI scores had small positive correlations with PSQI total score ($r = 0.086$, $p = 0.039$), and symptoms of insomnia ($r = 0.133$, $p = 0.001$) indicating that worse quality of sleep was associated with greater IRI empathy scores. However, when the IRI scores were added to the regression models together with the other predictors they were not significantly associated with the sleep variables. IRI scores were in fact positively associated with trauma severity (r

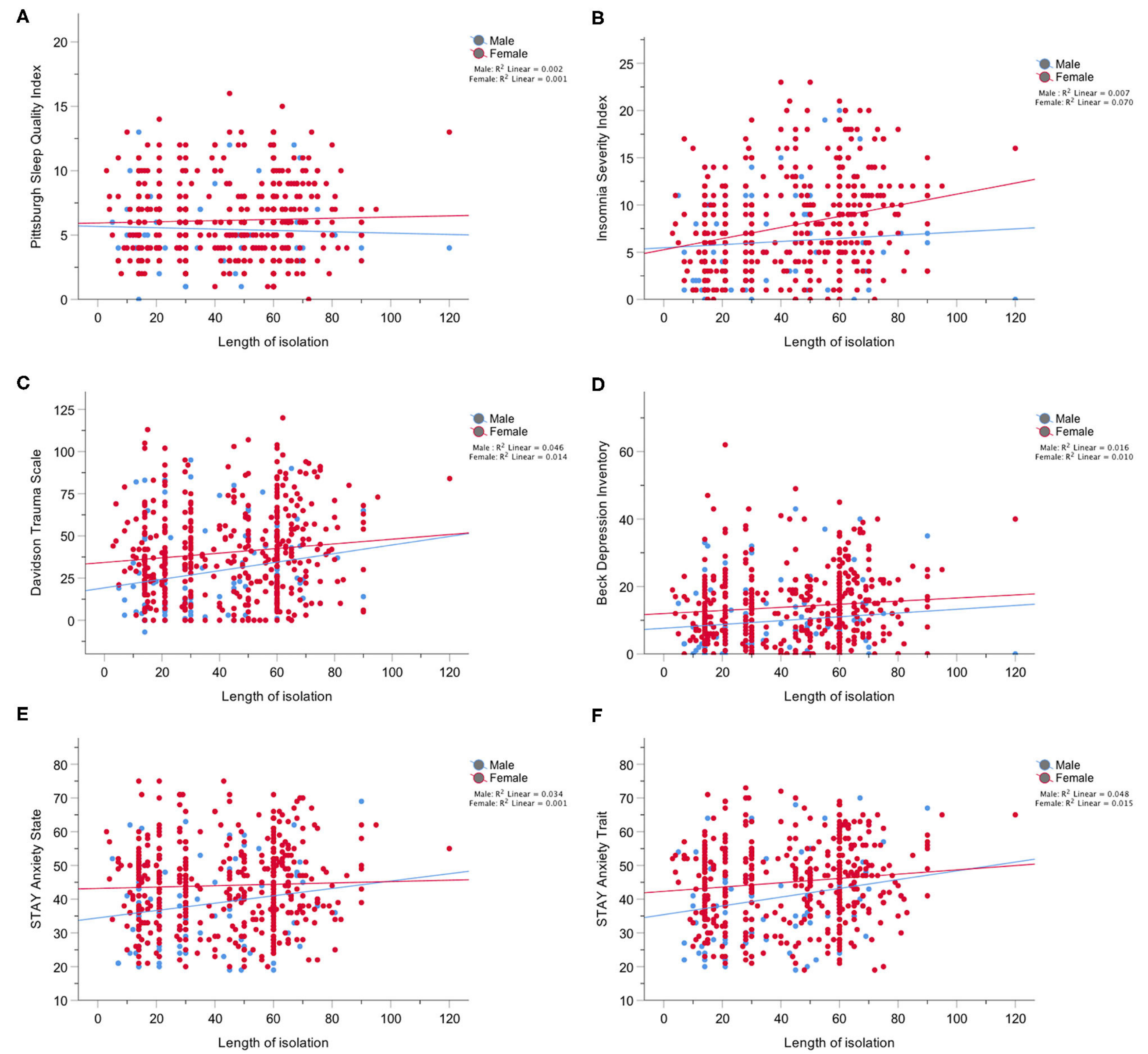

FIGURE 1 | (A) Depicts the lack of changes over the course of the pandemic in the scores on the Pittsburgh Sleep Quality Index in males and females; **(B)** Depicts changes over the course of the pandemic in the scores on the Insomnia Severity Index which were significant only in females; **(C)** Depicts changes over the course of the pandemic in the scores on the Davidson Trauma Scale in both males and females; **(D)** Depicts changes over the course of the pandemic in the scores on the Beck Depression Inventory which were significant only in females; **(E)** Depicts lack of changes over the course of the pandemic in the scores on the STAI Anxiety State scale for both males and females; **(F)** Depicts changes over the course of the pandemic in the scores on the STAI Anxiety Trait scale for both males and females.

$= 0.216$, $p < 0.001$), and frequency ($r = 0.269$, $p < 0.001$), with depression scores ($r = 0.316$, $p < 0.001$) and state ($r = 0.210$, $p < 0.001$) and trait ($r = 0.247$, $p < 0.001$) anxiety. Among all subcomponents (see **Supplementary Material**), only *Personal Distress* was positively associated with sleep duration ($r = 0.087$, $p = 0.038$), sleep latency ($r = 0.085$, $p = 0.044$), total PSQI scores ($r = 0.090$, $p = 0.032$), and insomnia symptoms ($r = 0.166$, $p < 0.001$).

DISCUSSION

We examined sex and gender differences in the effects of the isolation period implemented in Canada to stop the spread of the COVID-19 on sleep, mood, and emotions. We found that compared to males, females reported lower quality of sleep, sleep efficiency, and greater symptoms of insomnia. They also reported significantly higher symptoms of anxiety, depression,

TABLE 4 | Multiple Linear Regressions results in the whole sample.

Whole sample	Age	Depression	Anxiety state	Anxiety trait	Trauma tot	IRI	Total model
PSQI total	$\beta = 0.167$ **$p < 0.001$** VIF = 1.022	$\beta = 0.270$ **$p < 0.001$** VIF = 2.998	$\beta = 0.119$ **$p = 0.037$** VIF = 2.045	$\beta = 0.068$ $p = 0.334$ VIF = 3.859	$\beta = 0.225$ **$p < 0.001$** VIF =2.045	$\beta = -0.001$ $p = 0.968$ VIF = 1.117	$F_{1,532} = 4.367$, **$p = 0.037$**, $r = 0.563$, $r^2 = 0.317$
Latency	$\beta = -0.171$ $p = 0.104$ VIF = 1.000	$\beta = 0.037$ $p = 0.550$ VIF = 1.991	$\beta = -0.022$ $p = 0.694$ VIF = 1.680	$\beta = -0.031$ $p = 0.585$ VIF = 1.728	$\beta = 0.108$ **$p = 0.013$** VIF = 1.000	$\beta = 0.191$ $p = -0.060$ VIF = 1.108	$F_{1,524} = 6.193$, **$p = 0.013$**, $r = 0.130$, $r^2 = 0.017$
Duration	$\beta = -0.292$ **$p < 0.001$** VIF = 1.014	$\beta = -0.135$ **$p = 0.032$** VIF = 2.412	$\beta = -0.148$ **$p = 0.019$** VIF = 2.412	$\beta = 0.034$ $p = 0.669$ VIF = 3.842	$\beta = 0.005$ $p = 0.932$ VIF = 2.045	$\beta = 0.017$ $p = 0.683$ VIF = 1.100	$F_{1,533} = 4.642$, **$p = 0.032$**, $r = 0.371$, $r^2 = 0.138$
Efficiency	$\beta = -0.129$ **$p = 0.002$** VIF = 1.012	$\beta = -0.206$ **$p < 0.001$** VIF = 1.012	$\beta = -0.082$ $p = 0.211$ VIF = 2.412	$\beta = -0.098$ $p = 0.167$ VIF = 2.842	$\beta = 0.036$ $p = 0.542$ VIF = 1.962	$\beta = 0.007$ $p = 0.882$ VIF = 1.099	$F_{1,534} = 23.653$, **$p < 0.001$**, $r = 0.231$, $r^2 = 0.053$
ISI	$\beta = 0.053$ **$p = 0.118$** VIF = 1.022	$\beta = 0.282$ **$p < 0.001$** VIF = 2.995	$\beta = 0.158$ **$p = 0.001$** VIF = 2.507	$\beta = 0.088$ $p = 0.178$ VIF = 3.855	$\beta = 0.275$ **$p < 0.001$** VIF = 2.045	$\beta = 0.022$ $p = 0.538$ VIF = 1.117	$F_{1,533} = 8.991$, **$p = 0.003$**, $r = 0.639$, $r^2 = 0.409$

PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; VIF, variance inflation factor. Bold fonts indicates significant p values.

TABLE 5 | Multiple Linear Regressions results in Males and Females, separately.

Males	Age	Depression	Anxiety state	Anxiety trait	Trauma tot	IRI	
PSQI total	$\beta = 0.026$ $p = 0.751$ VIF = 1.003	$\beta = 0.581$ **$p < 0.001$** VIF = 1.003	$\beta = 0.183$ $p = 0.117$ VIF = 1.989	$\beta = 0.169$ $p = 0.206$ VIF = 2.611	$\beta = 0.047$ $p = 0.730$ VIF = 2.718	$\beta = 0.069$ $p = 0.428$ VIF = 1.098	$F_{1,97} = 49.128$, **$p < 0.001$**, $r = 0.580$, $r^2 = 0.336$
Latency	$\beta = -0.206$ **$p = 0.042$** VIF = 1.000	$\beta = 0.179$ $p = 0.074$ VIF = 1.003	$\beta = 0.119$ $p = 0.237$ VIF = 1.002	$\beta = 0.084$ $p = 0.406$ VIF = 1.017	$\beta = 0.137$ $p = 0.172$ VIF = 1.001	$\beta = 0.047$ $p = 0.649$ VIF = 1.055	$F_{1,96} = 4.243$, **$p = 0.042$**, $r = 0.206$, $r^2 = 0.042$
Duration	$\beta = -0.240$ **$p = 0.016$** VIF =1.000	$\beta = 0.178$ $p = 0.070$ VIF =1.003	$\beta = -0.176$ $p = 0.073$ VIF =1.001	$\beta = -0.158$ $p = 0.110$ VIF = 1.016	$\beta = -0.098$ $p = 0.323$ VIF =1.001	$\beta = -0.061$ $p = 0.545$ VIF = 1.044	$F_{1,98} = 5.998$, **$p = 0.016$**, $r = 0.240$, $r^2 = 0.058$
Efficiency	$\beta = -0.207$ **$p = 0.035$** VIF = 1.016	$\beta = -0.077$ $p = 0.620$ VIF = 2.577	$\beta = -0.074$ $p = 0.714$ VIF = 4.327	$\beta = -0.279$ **$p = 0.005$** VIF =1.016	$\beta = 0.094$ $p = 0.447$ VIF = 1.082	$\beta = -0.057$ $p = 0.573$ VIF =1.082	$F_{1,97} = 8.294$, **$p = 0.005$**, $r = 0.326$, $r^2 = 0.106$
ISI	$\beta = -0.091$ $p = 0.255$ VIF = 1.003	$\beta = 0.609$ **$p < 0.001$** VIF = 1.003	$\beta = 0.148$ $p = 0.190$ VIF = 1.989	$\beta = -0.184$ $p = 0.154$ VIF = 2.611	$\beta = -0.059$ $p = 0.656$ VIF = 2.718	$\beta = -0.060$ $p = 0.476$ VIF = 1.098	$F_{1,97} = 58.327$, **$p < 0.001$**, $r = 0.621$, $r^2 = 0.385$
Females	**Age**	**Depression**	**Anxiety state**	**Anxiety trait**	**Trauma tot**	**IRI**	
PSQI total	$\beta = 0.190$ **$p < 0.001$** VIF = 1.024	$\beta = 0.315$ **$p < 0.001$** VIF =1.832	$\beta = 0.102$ $p = 0.115$ VIF =2.602	$\beta = 0.103$ $p = 0.133$ VIF = 2.925	$\beta = 0.278$ **$p < 0.001$** VIF =1.804	$\beta = -0.010$ $p = 0.807$ VIF =1.096	$F_{1,431} = 26.758$, **$p < 0.001$**, $r = 0.558$, $r^2 = 0.312$
Latency	$\beta = -0.037$ $p = 0.446$ VIF = 1.000	$\beta = 0.019$ $p = 0.777$ VIF = 1.840	$\beta = 0.042$ $p = 0.496$ VIF = 1.648	$\beta = -0.012$ $p = 0.844$ VIF = 1.696	$\beta = 0.130$ **$p < 0.007$** VIF = 1.000	$\beta = -0.034$ $p = 0.496$ VIF = 1.088	$F_{1,424}$ =7.303, **$p = 0.007$**, $r = 0.136$, $r^2 = 0.018$
Duration	$\beta = -0.302$ **$p < 0.001$** VIF = 1.017	$\beta = -0.142$ **$p = 0.020$** VIF = 2.478	$\beta = -0.142$ **$p = 0.044$** VIF = 2.477	$\beta = 0.007$ $p = 0.937$ VIF = 3.529	$\beta = -0.028$ $p = 0.650$ VIF = 1.895	$\beta = 0.012$ $p = 0.791$ VIF = 1.080	$F_{1,431} = 4.581$, **$p = 0.033$**, $r = 0.387$, $r^2 = 0.150$
Efficiency	$\beta = -0.114$ **$p = 0.017$** VIF = 1.016	$\beta = -0.181$ **$p < 0.001$** VIF = 1.016	$\beta = -0.043$ $p = 0.561$ VIF = 2.477	$\beta = -0.055$ $p = 0.489$ VIF = 2.828	$\beta = 0.012$ $p = 0.856$ VIF = 1.804	$\beta = 0.028$ $p = 0.572$ VIF = 1.080	$F_{1,432}$ =15.269, **$p < 0.001$**, $r = 0.205$, $r^2 = 0.042$
ISI	$\beta = 0.078$ **$p = 0.037$** VIF = 1.028	$\beta = 0.256$ **$p < 0.001$** VIF = 2.902	$\beta = 0.147$ **$p = 0.013$** VIF = 2.592	$\beta = 0.087$ $p = 0.208$ VIF =3.560	$\beta = 0.328$ **$p < 0.001$** VIF = 1.895	$\beta = 0.031$ $p = 0.419$ VIF = 1.097	$F_{1,431}$ =6.184, **$p = 0.013$**, $r = 0.649$, $r^2 = 0.421$

PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; VI, variance inflation factor. Bold fonts indicates significant p values.

and greater distress in relation to a traumatic event. In addition, females reported higher scores on the IRI empathy scale and all its subcomponents. Similar results were found when analyzing gender identity differences due to the great overlap between biological sex and gender identity in our sample. Over the course of the isolation period, sleep, and mood worsened, especially in females. Finally, we found that the most significant predictors of poor quality of sleep during the isolation were depression, anxiety and trauma scores. There were no statistically significant associations between IRI empathy scores and sleep variables, nor associations with symptoms of insomnia. A separate correlation analysis showed that higher IRI empathy scores were associated with higher depression anxiety and trauma scores.

To our knowledge, the sex and gender differences in sleep, mood, and emotions during the isolation in response to COVID-19 are novel findings, together with the assessment of the progression of sleep and mental health concerns with increasing days spent in isolation, especially in females. These results complement preliminary data from the recent KKF Coronavirus poll (49) reporting that women worry more about the health of their family compared to men (68 vs. 56%, respectively) and worry more about losing income due to a workplace closure or reduced hours (50 vs. 42%%, respectively). Women, compared to men, also worry more about risk of exposure to Coronavirus (39 vs. 31%, respectively). Women, compared to men reported that worry or stress related to COVID-19 has had a major negative impact on their mental health (16 vs. 11%, respectively). The greater worry and anxiety in women in relation to their role as caregiver clearly reflects differences in gender roles and norms. Unfortunately, in our study we did not collect information on childbearing, role of caregiver in the household, household income, and occupation. Future study should collect this information to better understand gender related differences in responses to the pandemic.

We found that the most significant predictors of sleep quality during the isolation, were depression, anxiety, and trauma in the whole sample, and in females. In male participants, only depression symptoms seemed to play a greater role. Contrary to our previous findings in non-pandemic times (31), here we did not find any significant associations between empathy scores, as measured by the IRI, and sleep variables when simultaneously adding mental health predictors in the models. It is possible that individuals respond to the pandemic with fear and anxiety for their own well-being and that those fight-or-flight responses cause a greater impact on individuals' sleep quality than empathy for others as compared to non-pandemic times. This is confirmed by the positive associations between *Personal Distress* and sleep disturbances. Differently from *Empathic Concern* which is a feeling associated with concerns for others and therefore altruistic, *Personal Distress* is a feeling of distress caused by the suffering of others and motivated by the selfish need of reducing the observer distress. The positive association with poor sleep quality and insomnia therefore indicates that what kept people awake was their own feeling of distress. On the other hand, we found that individuals with higher IRI empathy scores reported higher scores on the anxiety, depression and post-traumatic stress disorder scales. Analogous results were found in a study investigating the overlapping neural network between empathy and anxiety (50). Moreover, another study found that adults who had experienced trauma during childhood reported greater empathy, compassion, and prosocial behavior (51). While heightened anxiety and trauma appear to be a disadvantage for emotional well-being, it is reasonable to think that perhaps individuals who are more anxious about their self and others' well-being will also experience more empathy for others. A phenomenon known as "post-traumatic growth" describes heightened optimistic feelings, prosocial behavior, and trust for the humanity after traumatic events such as terroristic attacks (52–54).

The positive correlation that we found between anxiety and IRI empathy scores may also translate in greater following of the public health rules to protect oneself and individuals at higher risk. In a recent study by Harper et al. (55), the authors found that higher levels of anxiety and fear in response to the pandemic were the only predictors of positive behavior change including adherence to social distancing and greater hand washing practice. Similarly, Oosterhoff et al. (56) reported that the greatest motivators for adolescents in the United States to follow social distancing rules were prosocial motivations including social responsibility and not wanting others to get sick, being in a city/state of lockdown and parental rules. Adolescents that reported following the public health guidelines, reported greater anxiety when the motivation for isolation was fear of getting sick, but also reported feelings of belongingness to the community as a motivation for following public health guidelines. Future studies should directly test how heightened anxiety, empathy, and prosocial behavior are associated with social responsibility behavior during the COVID-19 pandemic. This direct analysis could inform about the importance of media messaging about empathy and caring for vulnerable population as a means to increase social distancing (57).

Our study has some limitations. While we focused specifically on the effects of the isolation on sleep and mental well-being, it is hard to fully distinguish these effects from anxiety or fear reactions to the spread of the virus. A greater number of females completed the survey as compared to males representing a selection bias due to the fact that women are more prone to respond to surveys (58). However, this led to different sample sizes for males and females and the need to use non-parametric statistics to compare the two groups. The study sample was composed of mainly young and well-educated individuals in the Canadian population and therefore the result cannot be generalized to other countries. As mentioned above, we did not collect information on family/household demands or domestic violence, pregnancy and postpartum conditions and other gender related factors that may have allowed a better characterization of the gender differences. Future studies should consider this limitation and collect these data. We did not use a standard questionnaire to evaluate gender but only inquired about biological sex, gender identity and sexual identity through questions in the demographic questionnaire. The use of a standardized questionnaire may have led to different results. Moreover, this study is cross-sectional therefore the causal role of anxiety, depression and trauma on sleep quality cannot be examined. Most importantly, we do not have information about sleep quality, depression anxiety and trauma before the pandemic; is therefore hard to distinguish the effects of the pandemic from individuals' own characteristics. A better characterization of the mental health state before the pandemic would have led to a better insight on the actual changes with the isolation. We only measured subjective sleep quality with questionnaires; the use of objective measures of sleep could result in different associations. Finally, we used the IRI questionnaire to assess empathy, however this is not the best methodology due to the dynamic nature of emotions.

In summary, our study highlights sex and gender differences in sleep, mood, and emotions in response to the isolation period implemented in Canada to stop the spread of COVID-19, with females and women suffering from more of the negative impacts which increased with greater length of the isolation. Moreover, our data provide evidence that the greatest predictors of changes in sleep quality during the isolation period are heightened anxiety, depression, and trauma symptoms, especially in females. Higher anxiety, depression, and trauma were however positively associated with empathy, perhaps indicating a positive role of fear, and anxiety responses to a crisis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Conjoint Faculties Research Ethics Board (REB20-0650). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VG, AU, and GI designed the study. VG and AU dealt with data collection. VG analyzed and interpreted the data and drafted the manuscript. All authors reviewed the manuscript.

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COVID-19 Significantly Affects Maternal Health: A Rapid-Response Investigation from Pakistan

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The coronavirus disease 2019 (COVID-19) is still unfolding. Its several implications are visible, yet more of them we have to observe and witness in future. Dealing with these impacts, this rapid-response article aims to situate the COVID-19 pandemic within Pakistan's overall sociocultural and politico-economic context; next to investigate the impacts of COVID-19 particularly the psychological ones on pregnant women in Pakistan via five case. One case history of Haleema (pseudonym) revealed how the pandemic exerted a substantial amount of mental pressure due to "arranging someone to accompany her to the hospital, finding a blood donor for her, and insecurity of convenience to hospital." In this article, we show that Pakistan's geographical division into urban with an appropriate healthcare system, infrastructure and economic status, and more impoverished rural areas may show different impacts on people in general and the pregnant women in particular. This difference of facilities may contribute to disease transmission in the more deprived areas, that also due to cultural norms and mores such as shaking hands, cheek-kissing, and hugging that spread the virus are being overturned and that pregnant women are particularly vulnerable to psychological effects of the pandemic.

Keywords: COVID-19, pandemic, reproductive health, mental health, low- and lower-middle-income countries, Pakistan, women, women's health

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) is still unfolding. Although we have to observe and witness its several implications in future, its significant marks are already visible currently. It struck us when we learnt about Haleema—a pregnant woman in her last trimester living in a small village of Sindh province of Pakistan—who was struggling to find a female accompaniment to stay with her in the hospital ward for at least one night after the cesarean section and striving for a blood donor during the current 2020 COVID-19 global pandemic. This struggle is not exceptional during extraordinary times, and especially for those who live their lives below or around the poverty line.

Looking back at our sociocultural and biological history shows that infectious diseases have been challenging us for millennia. Historically, they have caused more morbidity and mortality than any other factor, including war (1). During the 1300s, the Black Death killed around one-third of the population of Europe within a few years (2). The Spanish Flu of 1918 killed between 20 and 100 million people (3). During the last two centuries, tuberculosis killed over a billion (4).

In the 20th century, smallpox caused between 300 and 500 million deaths worldwide (5). In 2017, measles caused 110,000 deaths worldwide (6). Globally, from 1980 to 2018, vaccine-preventable diseases (VPDs) have affected around 1.66 million people (7). Until 2020, polio affects children in Afghanistan and Pakistan [Global Polio Eradication Initiative (8)].

Similarly, beginning in late 2019, the 2020 COVID-19 pandemic has spread far and wide. It gradually and rapidly transmitted from person-to-person, country-to-country, and continent-to-continent. At the time of this writing (22nd July 2020), infecting around 14 million people and causing over 610,000 deaths (9), the pandemic has significantly affected every facet of society at local, national, and global levels. The effects are multiple and differentially related to healthcare, physical well-being, mental health, sociocultural patterns, economy, and (geo)politics. Many healthcare systems are overwhelmed, even in high-income countries. Governments have introduced and implemented various measures to slow down the rapid escalation of the virus. Yesterday's "normal" attitudes and behaviors today seem "abnormal." Despite our social nature, we are being recommended staying at home, observing isolation, and self-quarantine, and keeping a physical distance. These measures in some places are voluntary and in others are government-mandated and enforced. The greeting norms of the cordial handshake and, in some countries, hugging, bringing cheeks close, and symbolically kissing have become potentially deadly, resulting in a great deal of cultural confusion and the development of "air hug" and "leg-hugging" as new greeting rituals. Washing hands—sometimes up to 100 times a day—has also become part of "new normal."

Concomitantly, COVID-19 has exerted substantial impacts on "at-risk" groups: older people, healthcare providers, children, the homeless, daily wage laborers, and the economically poor. Direct physical impacts of COVID-19 on pregnant women—that may result in pregnancy-related complications are still unexplored—in low-income countries, where various forms of inequalities and inequities considerably prevail. Yet the pandemic has indirectly had substantial effects on the health, specifically mental well-being, of pregnant women. Indeed, the virus can affect anyone, including the Prime Minister of the United Kingdom. Nonetheless, its effects are disproportionate. Who will contract the virus, and what kind of care they will receive are highly determined by socio-economic and political structures (Ali, 2020, under review)?

Anthropology has devoted substantial attention to the reproductive health (10–12); and the relationship between various forms of inequality and (re)emerging infectious diseases (13–18) to explore sociocultural, economic, and political factors that underpin health emergencies and positively shape the course of health interventions. It has been well documented that outbreaks of infectious diseases primarily affect the resource-deprived and disempowered people severely. The underlying reasons include "Malnutrition, dirty water, crowded living conditions, poor education, lack of sanitation and hygiene, and lack of decent healthcare provisions all increase chances that those who suffer from poverty will also suffer from infectious disease.... Crowded living and working conditions facilitate the spread of disease from person to person. Those who are poorly educated fail to take sufficient disease avoidance measures. Moreover, poor communities often lack adequate resources to improve sanitation" (19).

Yet, what implications an outbreak of infectious disease leaves on reproductive health is still not adequately explored terrain. Women in many countries, especially low-resource countries, suffer from socio-structural disparities and inequities due to a lack of economic resources and often cultural devaluation. These disparities considerably affect their reproductive health during "normal" times (20), then one can assume that the current challenging times can significantly affect pregnant women. Therefore, the aims of this rapid-response article are 2-fold: (1) to situate the COVID-19 pandemic within Pakistan's overall socio-cultural, political, and economic context; and (2) to investigate the impacts—specifically psychological implications—of COVID-19 on pregnant women in Pakistan via five case studies.

MATERIALS AND METHODS

The data for this rapid-response qualitative research come from several sources. First, for obtaining the first-hand and qualitative data on the impacts of the pandemic on pregnant women, we conducted five telephone interviews with pregnant women by using an interview guide. The interviews were conducted during March-April 2020 when the virus was steadily spreading in the country and the government was implementing several stringent measures, such as "lockdown." Following the convenient sampling and sharing the aims and scope of this research among our family, friends, and acquaintances, we found five pregnant women. Afterward, we sent them the research protocols, consent form, and the interview guide. Once they agreed and gave their verbal ethical approval/consent, we called them via mobile phone to collect the required data. Second, we draw on our previous long-term ethnographic fieldworks in Pakistan, mainly in Sindh province—IA (2005–2011 and 2013–2020), (2013–2020), and (2012–2020)—to supply the qualitative data to offer the background information concerning the institutionalized forms of inequalities, and inequities, and perceptions and practices of health and illness. Each of us has conducted his/her research projects for masters and M.Phil. degrees, except Ali, who also has conducted his PhD research in the country, including the province. Third, we have done content and document analysis of the news reports and various surveys, mainly governmental reports, to contextualize the pandemic and situate its significant effects on pregnant women within this broader context. This paper is a part of the larger project approved by National Bioethics Committee of Pakistan (reference No.4-87/NBC-471-COVID-19-09/20/). Moreover, the names of interlocutors have been deliberately anonymized to maintain the necessary confidentiality.

BACKGROUND

Pakistan: The National Context

Among the top ten most populated countries, Pakistan with an approximate total population of 212.82 million is at 150th position out of 189 countries on Human Development Index (HDI) (15, 21). One survey demonstrated that 10% of households did not have water, soap, or other appropriate cleaning agents in place for handwashing, around 70% had an appropriate sanitation facility,[1] and 25% had flush toilets linked to a septic tank (22).[2] Compared with 66% of men, merely 50% of women have formal education, and net (school) attendance ratio (NAR) is 59% at the primary and 38% at the middle/secondary level (15, 22).

Most of Pakistan's population perceives health and illness a divine intervention: health, illness, and recovery are predetermined (13–15, 23). As far as healthcare facilities and providers are concerned, in 2018, Pakistan had 1,280 public sector hospitals, 5,530 Basic Health Units (BHUs), 690 Rural Health Centers (RHCs), and 5,670 dispensaries (15, 21). Around a total of 220,850 registered doctors, 22,600 registered dentists, and 108,500 registered nurses are available in the county that give a current ratio of approximately: one doctor per 970 people, one dentist per 9,420 people, and one hospital bed for 1,610 people (15, 21). In terms of the provision of healthcare, rural populations have inadequate and inappropriate facilities than their counterparts (15). The Infant Mortality Rate (IMR), and the Maternal Mortality Rate (MMR) rates are considered higher than in neighboring countries and globally to be far too high: in 2015, IMR was 62/1,000, and MMR was 170/100,000 (21). Since 2003, around eight outbreaks of HIV have occurred in Pakistan that led the Joint United Nations Programme on HIV and AIDS (UNAIDS) to declare Pakistan the second fastest HIV-growing country across Asia (15). Other communicable diseases include malaria, polio, hepatitis, and measles still prevail here (13–15, 24). Being the two major contributors across the world, approximately the world's 80% of hepatitis affected people live in Pakistan and Egypt (15, 25). Due to neglected tropical diseases (NTDs), Pakistan is in the top 10 countries (26). And, in 2013, around 80 million people suffered from one or more chronic conditions such as cardiovascular diseases, cancers, diabetes, respiratory diseases, and mental disorders (27).

Pakistan has deep and prominent economic disparities, which further intensify based on gender and geographical area (15, 21). For gender-based inequalities and inequities, Pakistan was at 133 on the Gender Inequality Index (GII) in 2017 (15, 21). Recently, female participation in the labor market further decreased (21). In Pakistan, 67% of working women are engaged in the agriculture sector, 16% in the manufacturing sector, and 14.6% in community and personal services (21, 28). The overall unemployment rate of the country in 2017–18 was 5.79%, with high youth employment (21, 28). Around 24.3% of the country's population lives below the poverty line (earning US$2 per day) (15, 21). Moreover, 38% of children are "stunted" (short for their age), 7% were "wasted" (thin for their height), and 3% were overweight hefty for their height (15, 22). Women are also vulnerable to malnutrition, and micronutrient deficiencies resulting in pregnancy-related complications (29, 30). Around half of the women (52%) are overweight or obese (BMI $\geq$ 25.0), 5% of women age 15–49 are short ($<$145 cm), 9% are underweight (BMI $>$ 18.5) (15, 22).

Moreover, cultural norms encourage communal patterns of living, especially in a joint or extended family: Three to four generations live together and share spaces that increase the frequency of physical contact (13, 15, 23). Average household members are around 7 (13, 22). Rural areas also include clusters of houses, locally called *Mohalla* or *Parro,* with one boundary wall, and one cluster may encompass around 100 members (13, 15, 23). Furthermore, cultural norms also encourage handshaking, hugging, and eating with hands—in part due to cultural mores but also to unaffordability of the required cutlery—and these norms regard not engaging in such behaviors as highly inappropriate and unethical (15). Likewise, many people, especially in rural areas, subsist on animals, and the economically marginal often share space with their cattle, including sleeping there at night (13, 15, 23). Not perceiving cattle, including their feces as unhygienic or harmful to health, these people drying dung to use it as a fuel for cooking food.[3]

Rumors and conspiracy theories are widespread in the country, specifically about vaccination programs, including a "Western plot" to sterilize Muslim women, vaccines have potential "side effects" that may kill children (13–15, 24, 34, 35). Although at the beginning of the pandemic suspicions about vaccination did not seemingly spill over into suspicion about COVID-19, currently conspiracy theories about COVID are circulating in Pakistan (14, 15, 24, 35). Some people believe that it is a "Jewish plot" to control the Muslim population, and doctors are working as agents of Jews (Salma et al., under review). One survey reveals that every fifth person in Pakistan believes that coronavirus is a conspiracy of international superpowers (36). In contrast, some people consider it as a "political game" to receive some financial aid (Salma et al., under review). Yet others are spreading rumors about how to deal with the pandemic, such as "brewing a black tea to drink five sips" (14, 24, 34, 35).

Containing Measures: Government's Response During March–May 2020

Pakistan reported its first case on 26th February 2020, and now cases are rapidly increasing. When the cases in several countries are decreasing, there is a swift increase in the infections in Pakistan. By 18th May, the country reported around 41,000 confirmed cases and 900 deaths (9). Drawing an overall picture of COVID-19 in Pakistan is crucial. Briefly described, the government implemented the following measures to deal with this virus. After rise of COVID-19 in China, Pakistan suspended

[1] An "appropriate sanitation facility" includes "any non-shared toilet of the following types: flush/pour flush toilets to piped sewer systems, septic tanks, and pit latrines; ventilated improved pit (VIP) latrines; pit latrines with slabs" (22).

[2] The survey followed stratified two-stage sample design. First, 580 clusters were selected, and in the second stage, which involved systematic sampling, a fixed number of 28 households per cluster was chosen—the total sample size was ∼16,240 households (22).

[3] Annually, zoonoses (diseases transmitted from animals to humans) caused morbidity in billions of people worldwide and mortality in millions, (Organization) and thus were a significant public health concern (31, 32). Also, COVID-19 was a zoonotic disease (33). Nevertheless, these animal-dependent people had no or little choice about their level of proximity with their animals.

flights to China, then to Iran, Qatar and Italy (15, 37). With no test kits available, the country sent specimens to China and the United States of America (USA) owing to the unavailability of test kits in the country, and later imported 1,000 kits from China (15, 37). On March 13, 2020, as the virus infected 30 people, the government closed educational institutions, shut the border with Afghanistan and Iran, opened a quarantine camp at the Pakistan and Iran border, banned congregations of people, including religious gatherings at mosques, churches and temples (38, 39). Although during the mid of March 2020, the country's Prime Minister ruled out the option of lockdown based on the information that 97% of COVID-19 patients recover (40), Sindh province had already implemented a lockdown during March 2020 (37). Thereafter, a countrywide lockdown was enforced after all, and quarantine centers were opened, especially in Sindh province (37). The police and the army were deployed across the country, including Sindh province, to enforce the containing measures, e.g., self-quarantine, physical distancing, shutting markets. If someone breaches these measures, s/he could be booked under Section 188 of the Pakistan Penal Code for violations of the ban: the penalty included 6 months in prison or a fine or both. Besides, people constantly heard via the media that they should stay at home. To help, the government started to distribute food items among daily wage laborers (15, 41).

In contrast, people criticized this distribution not just because of its low quantity but also due to (receivers) being photographed while receiving the food (with selfies) and shared on social media. Many people believed that the actual number of affected people was higher than those reported due to a lack of testing. Currently, the country is substantially in a phase to lift the months-old preventive measures: e.g., easing lockdown, opening shops, resuming domestic and international flights, and starting a domestic transport system. After illustrating the contextual information, now we would like to move to the case histories of pregnant women for demonstrating the impacts of the 2020 COVID-19 pandemic on them.

COVID-19 AND REPRODUCTIVE HEALTH: FIVE CASE HISTORIES REVEAL DISTINCT IMPACT

Case History 1: Severe Impacts of the Pandemic

> I am Haleema, around 25 years old, in my last trimester. I am a house worker living with my husband's joint family consisting of 12 members in a small village in Sindh province. I received merely primary education, and my husband has done 10th grade standards. He works as daily wage labor in nearby mountains to load trucks and earns around US$2 a day.
>
> Nowadays, I am fine, merely feel some dizziness, but have no flu, fever, or cough. Although I am living with my joint family in a *Parro* [more than one house with one boundary wall],[4] I am not meeting someone else or going outside of the house. I go for C-section to deliver a baby, so there is no choice to give birth at home. Last time, I gave birth at a charity hospital. However, we have a family *Dai Aman* (lit. mother midwife—it is used for the traditional birth attendant (TBA)/midwife) who regularly visited me thereafter.
>
> The current disease [COVID-19] has severely affected me, because this is my last trimester, and I already had one miscarriage prior to giving birth to my first son with a C-section. My delivery is complicated. During the last month, when I visited *Mandam* (gynecologist), she gave me a date of mid-April [we conducted this telephonic interview at the end of March]. The month is close. I am already feeling anxiety, dizziness, and a burden on my head. It seems my delivery date is soon.
>
> Nevertheless, neither I can visit a clinic nor invite a *Dai Aman* to visit me for a checkup. Everyone is directing me to stay inside the home due to fear of contracting this disease. They do not permit me to go for a checkup due to the mentioned fears. There is a *Curshew* (curfew). I do not know what will happen. However, if my situation gets intense, then we will go to the hospital where I went the last time to give birth to my first child. It is a charity hospital; therefore, they do not ask about money. It is a neat and clean hospital. My family takes these decisions. When I am pregnant, they, especially my husband and her sister, take diligent care of me, and accompany me to the clinic for a routine checkup.

Due to our quest, we were in constant virtual contact with this family. A few days after the interview, we heard that they went for a checkup because she was feeling constant dizziness. It was quite challenging for them to visit a doctor, but after managing it, his husband brought her on a motorbike to that charity hospital. However, that hospital was situated close to an epicenter of coronavirus in Sindh province: Sukkur district. The distance between their village and the hospital is around 100 kilometers. During this visit, doctors asked them to come on the next day for a cesarean. This dizziness is her labor pain. We called again, and we found a complicated situation regarding a woman to stay with her at hospital, and to find a blood donner. This family called a family meeting to decide on searching for a suitable person. The following are the details with Haleem's husband, mainly his sister:

> The hospital is near the epicenter of the disease. In this charity hospital, there will be many people coming from different areas, including other women, to give birth. Now, who should accompany her? She will need accompaniment because the doctors will keep her for a few days. And males are not allowed to go inside, except the hospital staff. Due to the Purdah system, a young woman or girl cannot accompany her. The older women are in the at-risk group for contracting COVID-19. Every family member is worried. Her husband can accompany her, but he cannot stay inside.
>
> Second, she needs blood. This will be her third cesarean. For the first time, her father donated her blood. During the next delivery, some of their family members found some donors who voluntarily donated blood. This time, her father is old and cannot donate blood. Her husband is weak due to continuous working in the mountains, and has some underlying conditions; hence, he cannot donate the blood. And volunteers are difficult to find due to the ongoing lockdown and fear of contracting the virus. We cannot ask someone and put his [usually male members donate the blood, which is why we are using a masculine pronoun] life at a risk. The time is running short. There is still no blood donor. At

[4]This is our translation.

the hospital, the blood is available, but we cannot buy it due to our economic unaffordability.

The very next day, we called again to family. They had somehow managed to find a 30-year-old woman to accompany her at the hospital, where she gave birth to a son by cesarean. Since they found no blood donor, her husband donated her blood. The hospital kept her for two nights and then discharged her. Her husband stayed outside the hospital and slept on the floor during both the nights. After 3 days in the hospital, they returned to their home.

Case History 2: Preferences and Fears About Hospital

I am Husna, a 28-years old house worker with intermediate education. My husband has also the same educational qualification, who works as a tailor. Our monthly income is around US$100. I have two children and live in a joint family comprising of 10 members. I delivered both babies without any cesarean and did not have any miscarriage history. I do not visit any biomedical hospital for a normal checkup.

Presently, I am in the second trimester, and I do not suffer from any complications, such as flue, cough, and fever. I am not in quarantine as I do not believe that COVID 19 is a disease. It is propaganda. Thus, I am not in favor of quarantine or isolation. I am living at home and going outside as usual like a normal life.

I believe that coronavirus is only rumored by government and media. My deliberation is that "*Jese soch wese sehāt*" (lit. your thoughts significantly affect your health). Thus, if you perceive corona as a disease, it will psychologically affect you. In my opinion, the coronavirus is not a disease; therefore, it cannot affect my health either directly or indirectly. Besides, I want to say to everyone, do not be panic about coronavirus as it is the wrath of Allah. Pregnancy period is the most important part of life, so just enjoy and do not take any stress during pregnancy.

However, the current pandemic has affected our economic position, as my husband is a tailor, and his shop is close. Economically, coronavirus is directly exerting severe effects on our life. We face many difficulties due to the closure of our shop. We belong to an economically low-income family. Despite that, we do not receive any governmental help, such as Funds from *Ihsas* and Benazir Income Support Program (BISP) [both are government supported initiatives to support the economically poor].

My first baby was born at a hospital. Yet I prefer to give birth at home than a hospital for three main reasons. First, I believe that home is better because giving birth at a hospital is too expensive economically, and many people like us could not afford high dues to the hospital for the treatment. For giving birth, we will call a *Dai*—a traditional midwife, who is an old and experienced woman and has been conducting deliveries for a long time. We do not pay money to her, but only give her a new dress and sweets.

Second, during the ongoing pandemic, the government wants to increase the number of infected COVID-19 patients: I am afraid that if I give birth at a hospital, and doctors mention my name in the list of COVID-19 patients.

Third, my husband's mother says me to give birth at home because in the past women, including her, used to do that: That was a preferred mode to deliver a baby.

Although I am in the second trimester, I do not receive any antenatal care. Because my husband's mother does not allow me to go for antenatal checkups at a hospital due to the current pandemic situation. Also, she prefers me to stay away from the hospital. In case, I have abdominal pain, I call the *Dai*, who then suggests some home remedies and does abdominal massage.

I think it is important to make decisions related to pregnancy by yourself because you are the person who is going through pain. However, in my case, my husband's mother decides about everything, including my health. My husband also recommends me to follow the advice of his mother as she is old and experienced who has faced these all situations too.

Case History 3: Worries to Deliver a Baby at a Hospital

My name is Rimsha. I am 27 years old, usually live in Rawalpindi, Punjab, with my husband's joint family, but currently, I am in Karachi with my parents to give birth to my fourth child. I am a home worker and college graduate married to a shopkeeper. Our monthly income would be around US$550. I have three children and previously gave premature birth to a daughter, who died instantly. I am in my last trimester.

Currently, I am healthy with no cough, flu, or fever. By choice, after listening to news about the dangers of coronavirus and lockdown outside, I am staying with my family, not going outside to meet my friends. Back when things were normal, I used to meet my friends every month.

Usually, I go for a routine checkup. I have the authority to make such decisions. With my husband or mother-in-law, I visit a gynecologist. However, this month's visit is delayed because of the corona. COVID-19 has affected me not very much physically, but mentally it is disturbing, and I feel depressed.

I do not give birth to a child at home. It is always a cesarean. Because giving birth to a child at home is not possible, I must go to the hospital. My situation influences my choices.

My family members do not want me to visit a hospital during these days of quarantine. I am worried—how will I deliver a baby during these times of lockdown?

Case History 4: Deep Psychological Pressures of the Pandemic

I am Subal, a 29-years old woman from Rawalpindi, Punjab, in my second trimester. I am a homemaker, have a college degree (12th-grade education), and live in a joint family. My husband, a university graduate, has a government job. Our monthly income is around US$400. I usually visit a clinic for routine antenatal care (ANC). Prior to this pregnancy, I have already delivered a baby via cesarean section and had two miscarriages.

Presently, I am healthy, *Alhamdullillah* (all praises for God), and have no symptoms of coronavirus such as flu, fever, or cough. Despite that, I am observing social isolation and self-quarantine. I stay inside my house and go nowhere outside. I spend the entire time with my family and kids. Observing these measures is by choice as we have been informed very much about the causes and consequences of coronavirus. This pandemic has not affected my health directly, but indirectly. Now I can't go outside for a walk and there is an enormous mental pressure. Everyone is worried. The entire day, the media discusses these issues.

Moreover, because I am a cesarean, it is not possible to give birth at home, but at a hospital that is safe place to give birth. There is a gynecologist where my family brings me to give birth. Hopefully, when I give birth, things will be improved. This virus will be gone.

Presently, we are psychologically very much under pressure. I'm not going for a checkup during this critical situation. Everyone is concerned and does not allow me to visit a hospital. However, when the situation is stable, I will go for a routine checkup—these decisions we all make together: my mother-in-law, my husband and me.

Case History 5: Concerns and Anxiety to Deliver a Baby at a Hospital

My name is Rabia. I'm 33 years old, in my last trimester, and live in a joint family in Rawalpindi city of Punjab province. My husband and I have obtained bachelor's degrees. My husband is a government employee, and our per month income is around US$500. I had three miscarriages. I usually go for a checkup. The decision depends on my mother-in-law, but she respects my opinion and brings me to the hospital.

These days, although I often feel dizziness because this is the last trimester, I have no cough, flu, or fever. I don't go outside of my house. I physical social distancing, but sometimes my child stays close to me. All family members live together. We have revisited our hygienic patterns. The husband has brought anti-septic soaps, so we are regularly washing our hands. We are drinking green tea.

Thus far, COVID-19 has not affected our physical health, but it has exerted effects on our mental health. I will prefer to go to the hospital to give birth because I am cesarean. However, the current pandemic is disturbing us. May God protect us during these testing times!

My parents, husband and his parents are extremely cautious and worried that may Allah keep everything sane and safe. Days of delivery are near, and everything is under lockdown. We are fearful about what will happen in terms of going to a hospital and delivering a baby. There are news stories about healthcare workers being affected by the virus: what if someone is infected, who does my operation? What if we are infected, including my baby? I have no choice to give birth at home, hence, we pray that when I deliver a baby, everything is normal.

DISCUSSION

A few studies have already focused on the implication of COVID-19 on birth practices across the world (12, 42, 43). Yet the literature is scanter in terms of its geographical focus. Hence, this is the first study that has explored the early impacts of the ongoing pandemic on pregnant women in Pakistan and investigated the socio-cultural factors that are likely to facilitate its spread. These four case histories can be seen in the national context, where various forms of inequalities have persisted in since the country's independence in 1947. The case histories reveal prominent forms of inequalities and inequities between wives and husbands related to their education and work, and show a difference between rural and urban areas in terms of availability of healthcare facilities and easy accessibility to these facilities. In rural areas, one might have to travel far to reach a clinic or hospital. This lack of accessibility was further affected by the lack of affordability.

Like other epidemics, COVID-19 is most adversely affecting the economically poor and marginalized. In Haleema's case, because she and her family fall in the low-income category, they struggled to find the "right" woman who was not vulnerable to contract COVID-19 to accompany Haleema and stay with her in the hospital. The most pressing issue was to find a blood donor that during "normal" conditions (in the absence of COVID-19) would have been relatively more easier since many volunteers donate blood.

Through these five case histories, although none of the women contracted the virus, we can see its direct and indirect impacts on their lives and can note that these effects, the psychological, physical and economic, were more profound among the rural and low-resource settings. The three case histories, who were situated in the urban areas, had enough economic resources, were discussing psychological impacts of COVID-19. In contrast, Haleema, located in the rural area and belonging to a low-income family, shared apparent implications of the pandemic. Similarly, Husna's situation is resembling Haleema in terms of geographical location, economic position, and the significant economic impacts of the pandemic.

As we mention it in the title that this is a rapid-response article, who offers not enough evidence but provides ground to conduct further research studies on this important domain. These five case histories beg various questions: how many serious complications, including maternity-related deaths, could be directly attributed to COVID-19? What are the differences in the impacts of COVID-19 on the health of economically poor and rich, rural and urban women? How do Pakistani women's general socio-cultural disempowerment and subservience impact their healthcare and maternity-related choices? How does the situation in Pakistan differ from that in other countries, and how is it the same? The answers to these questions might add to already existing knowledge on outbreaks, epidemics, pandemics, and various forms of inequalities and inequities and their disproportionate effects and challenges, such as for the pregnant women.

STUDY LIMITATIONS

Specific limitations encumber this study analogous to other studies. Geographical, financial, and time constraints restricted choosing sample methodology and size, as only five mothers were interviewed. The sample size is a great limitation of the study; hence, the results cannot be generalized across the country. Despite this limitation, these five case studies explore and provide the useful preliminary indication of the severe impacts of COVID-19 on pregnant women and how various inequalities and inequities related to healthcare and economic conditions, including those between urban and rural areas, play a role in critical and less critical implications. To some extent, this limitation of sample size is counterbalanced by our thorough overview of relevant content analysis regarding politico-economic disparities and by our earlier long-term ethnographic research works focusing on an interplay between sociocultural, economic and political factors that shape distinguishable perceptions and practices of health and illness in Pakistan. Considering the challenges posed by COVID-19 to conduct "traditional" ethnographic research, this rapid study holds great importance to contribute to the existing knowledge regarding maternal health, particularly from a geographical standpoint and provokes further in-depth studies to be conducted in the country.

A WAY OF CONCLUSION

The ongoing COVID-19 pandemic, directly or indirectly, has affected almost everyone across the world, with multiple implications. In this rapid-response article, we have presented the first-hand data to situate this pandemic within Pakistan's overall cultural and socio-economic context and illustrated the longstanding socio-cultural norms, beliefs, and patterns that work to facilitate the spread of the disease. We have also shown the changing patterns and norms, as well as the government efforts, designed to hinder its spread, and demonstrated that the economically poor and disempowered rural population is most vulnerable both to infection and to lack of available treatment. The same is the case with pregnant women. Although any possible pregnancy-related complications due to COVID-19 are yet to be known, we have demonstrated that the pandemic is already exerting adverse social, psychological, emotional and economic effects on such women.

Interview data revealed that all interlocutors found it difficult to access a healthcare facility. The fact that people are saying they "choose" to stay home seems to show that they are claiming agency, even though they are being forced to stay home due to the imposed lockdowns, as we have seen, particularly Haleema suffered in this regard. Four interlocutors reported that the primary effect was on their mental health, due to the stress of worrying about: their births; their enforced inability to attend routine prenatal appointments or to go outside for fresh air and exercise, and contracting the disease. However, one interlocutor stated that the pandemic has only and significantly affected their economic position.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because The interlocutors have reservations about it. Requests to access the datasets should be directed to inayat_qau@yahoo.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The National Bioethics Committee Pakistan. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IA: conception and design, analysis, and drafting manuscript. IA, SS, and SA: data collection, interpretation, and proofreading. All authors contributed to the article and approved the submitted version.

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COVID-19 and Women's Health: A Low- and Middle-Income Country Perspective

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Corona Virus Disease (COVID-19), a contagious disease, is a global pandemic affecting the lives and health of individuals across borders, genders and races. Much of what is known about the effects of natural disasters and disease outbreaks on women's health in particular, is based on studies conducted in high-income countries. The evolving evidence suggests that COVID-19 has a profound negative impact on the perinatal mental health of women. It is also clear that global pandemics such as COVID-19 disproportionately affect the less affluent, including individuals living in low- and middle-income countries. The purpose of this review is to summarize and critically discuss extant knowledge on COVID-19 as it relates to the perinatal health of women in low and middle-income countries, using Pakistan as a case example. We specifically highlight the effects on perinatal mental health, preterm birth, and timing of the COVID-19 exposure. Our review suggests that it is essential to consider the effects of COVID-19 within this cultural context and that findings from high-income countries do not necessarily translate to the situation in low and middle-income countries.

Keywords: COVID-19, pregnancy, anxiety, depression, stress, mental health, preterm birth, low- and middle-income countries

BACKGROUND

Corona Virus Disease (COVID-19), a new ribonucleic acid virus which presents with symptoms of fever tiredness, and dry cough (1), was declared a global pandemic by the World Health Organization (1, 2). Empirical evidence suggests that natural disasters and disease outbreaks elicit a profound negative impact on the perinatal health outcomes in part due to excessive exposure to distressing environmental situations (3–5). With a global pre-pandemic prevalence of 20 percent (6, 7), perinatal mental distress (i.e., anxiety, depression, and stress during pregnancy and postpartum) already imposes a significant threat to women's health (physical and emotional) and perinatal outcomes (8–10). Furthermore, the likelihood of adverse cognitive, behavioral, and emotional outcomes also increases in children born to these mothers (11). Much of this empirical evidence on natural disasters and disease outbreaks is based in high-income countries limiting our understanding of the impact of disease outbreaks on perinatal health outcomes of women residing in low- and middle-income (LMI) countries (3). Moreover, the physiological and cellular-level impacts of COVID-19 on pregnant women have not been studied (12–14). In this concise summary we address the existing knowledge, vastly informed by studies on (a) COVID-19 primarily from China, (b) infectious diseases (disaster and pandemic influenza) predominantly based in high-income countries, and (c) perinatal mental health of women of which only 8–15% of the studies are from LMI countries (compared to 90% from high-income countries) (15). We situate this review within the context of an LMI country like Pakistan.

COVID-19 WITHIN THE CONTEXT OF PAKISTAN

COVID-19 reached Pakistan in February 2020 and a nationwide lockdown was initiated on March 23, 2020 (16). Data from Worldometer info indicates that Pakistan ranks 17 among 213 countries and territories around the word. The number of cases in Pakistan is increasing exponentially with total cases of 103,671 (as of June 7, 2020) among a population of roughly 220 million. The province of Punjab has the highest number of total case. Karachi, which is in the Sindh province has the second highest number of COVID-19 cases in Pakistan (16). Although Sindh is the third largest province, 48 million people with diverse ethnic and religious backgrounds reside there making it the second largest populated province in Pakistan (17). The incidence of COVID-19 in Pakistani perinatal women will vary depending on the number of people per unit area and demographics, and availability of testing and reporting mechanisms (18), which at present is limited in Pakistan.

COVID-19 AND MENTAL HEALTH OF PAKISTANI PREGNANT WOMEN

The pandemic has increased women's anxiety and stress levels, and depressive symptoms (19, 20) and those who are pregnant reported increased worry and fears (i.e., perinatal mental distress) regarding their own, their baby's and their family members' health (21). Albeit limited (4), evidence underlying the impact of pandemic situations on the mental health of pregnant women, suggests an additional burden (22) given the uncertainty regarding disease susceptibility, vertical transmission to unborn baby/newborn, and management of the infected pregnant women (23).

Haider (22) in the article published in The Express Tribune narrated a story of a 27-years old women, 12-weeks pregnant, from the North-East of Karachi who described her level of anxiety as "going through the roof" further adding "Since then, I have not only been fearing for my own life but also for my unborn baby. This feeling of uncertainty is killing me." In a survey undertaken by *The Express Tribune*, 62% of 110 pregnant women across Pakistan, aged 25–30 years, were apprehensive about antenatal visits at hospital or clinics (22). Their primary worry was contracting COVID-19 while in the hospital with secondary fears related to exposure to COVID-19 patients in the hospital (22). Fear and worries were situated in pregnancy as evident from statements such as "How [will I] take care of the baby? Will the hospital be taking mine and the baby's hygiene seriously as they already have so many COVID-19 cases to deal with?" (22) Pregnancy during the pandemic elicited mixed feelings "New additions to the family are a time of celebration and while it still is going to be a celebration, there is still a worry to keep the baby safe—more than ever now" (22).

Accurate health information and engaging in practices to prevent/stop COVID-19 (e.g., washing hands, wearing a mask) lowered stress, anxiety, and depression among women (19). COVID-19 will likely have a disproportionate toll on Pakistani pregnant women's perinatal mental health due to low literacy levels (24), inequities in access to basic needs (e.g., water) and protective equipment given socio-economic determinants of health (25). COVID-19 has altered how women give birth with health care systems instituting varied approaches to care provision during labor and delivery (e.g., no or only one support person). The COVID-19 pandemic limits women's ability to anticipate and form realistic expectations of labor and delivery thereby impacting their readiness mentally and physically, increasing the likelihood of viewing the experience as traumatic (even when their pain is well-managed, or they deliver a healthy baby.

A study examining the psychosocial effect of the Severe Acute Respiratory Syndrome (SARS) outbreak noted worsened mental health and posttraumatic stress disorder among women more so than men (26). Given the vulnerability of Pakistani women, particularly pregnant and postpartum women to post-disaster mental health issues (3), it is imperative to understand women's lived experience to identify strategies to alleviate the negative and unintended consequences of preventive strategies such as social distancing, and self-isolation (27). COVID-19-specific public health strategies such as social distancing and staying home will have social and economic repercussions raising concerns regarding the mental health and social well-being of the general population (28). Across all LMI countries, women and children are the most vulnerable to inequities in socio-economic determinants of health (25) which will be magnified in a pandemic situation. An alarming increase in domestic violence has been reported globally (29). An online mental health counseling service provider in Pakistan indicated an upsurge in domestic violence cases, and psychological health issues amidst lockdown, social isolation and economic crisis (30). COVID-19 pandemic has placed a strain on healthcare systems globally (28), which are primarily focused on the management of outbreak during this time. As a result, antenatal and postnatal care, and mental health services may have been hampered during this time.

Abbreviations: COVID-19, coronavirus disease 2019; LMI, low- and middle-income; DNAm, Deoxyribonucleic methylation.

COVID-19 AND PRETERM BIRTH IN PAKISTAN

In Pakistan 16% of infants are born preterm every year, representing the world's highest rate of preterm birth, a sharp contrast from 8% in a high-income country like Canada (31, 32). The social, cultural, and environmental context of LMI countries like Pakistan produces more extreme and prolonged exposure to stressors (i.e., chronic stress) (33, 34), inducing greater perinatal mental distress (35) and increased risk of preterm birth. The effect of perinatal mental distress on preterm birth however varies by location (high vs. low-income countries) (36), socioeconomic status (36), types of perinatal mental distress, and periods of gestation (37, 38). Pandemic stress or possible COVID-19 infection may exacerbate rates of preterm birth or complicate care as pregnant women's susceptibility to coronavirus, transmission to newborn, and clinical presentation and management when infected remain unknown (23, 39). Risk of preterm birth may be higher amongst Pakistani pregnant women exposed to COVID-19 related stress early in pregnancy.

Both animal and human studies demonstrate that psychological and biological responses to psychosocial distress vary across pregnancy, with the magnitude of responses being more pronounced early in pregnancy (37, 40, 41). Alterations in the stress response may be adaptive to protect the fetus and mother from adverse health consequences (37). The physiological and cellular-level impacts of COVID-19 on pregnant women are unknown; however, previous laboratory studies indicated histopathological and behavioral impacts of prenatal influenza infection in the offspring of mice (12, 13). Consequently, pregnant women who are exposed to the stress of COVID-19 later in pregnancy may have less psychosocial distress, dampened physiological responses, and vulnerability to preterm birth (40, 42–44). The physiological and cellular-level impacts of COVID-19 on pregnant women are, however, unknown (12, 13).

COVID-19 AND EPIGENETICS

Deoxyribonucleic methylation (DNAm) is an epigenetic marker that fluctuates with development and experience, yet, maintains patterns that define the identity of cells and tissues (45). Thus, DNAm lends insights to biological function (e.g., current immune response), as well as how it has adapted to experiences of stress over time, and these properties have made it particularly informative for understanding how stressors "get under the skin" in the way it influences brain development (e.g., regulation of emotion) and behavior (46). For the biological effects of prenatal experiences, especially, DNAm is particularly relevant, as massive epigenetic waves of regulation occur in the prenatal period (46, 47). Exposures, such as COVID-19 related stress, can disrupt critical developmental events *in utero* and exert lasting biological consequences *via* DNAm and other epigenetic alterations. In addition to capturing exposure to prenatal distress (48), DNAm patterns also reflect very early postnatal experiences, and DNAm in genes associated with the stress response (i.e., genes involved in the hypothalamic-pituitary-adrenal axis or HPA) prospectively predict the onset of depression (49, 50). The biological significance of COVID-19-related stress in mothers and links to preterm birth remain unknown.

DISCUSSION

LMI countries, like Pakistan, are characterized by large and densely populated urban regions, fragile health care infrastructure or health systems, resource capacity, water and electricity supplies), economic and social conditions (e.g., multigenerational households in small spaces), and inconsistent availability of COVID-19 testing. These characteristics create a milieu for a very high incidence and prevalence of COVID-19 infection, likely more than the current estimates indicate given data quality, affecting millions of pregnant and childbearing women and their children. Disruptions in routine antenatal care will have a disproportionate toll on maternal and newborn mortality and morbidity (51).

Like past infectious outbreaks, the likely mental health consequences during pregnancy are high, and especially so in already stressed populations as found in LMI countries. The COVID-19 pandemic has led to changes in labor and delivery practices and policies which limits the degree of social support available to women during and following childbirth. Lack of social support can heighten anxiety, delay the progression of labor, and affect the overall psychological well-being of women (52).

Past evidence on MERS-CoV and SARS-CoV also suggests that prenatal mental health of women needs to be prioritized as there is significant knowledge gap to inform practice and policies (4). COVID-19 likely increases risk for preterm birth, linked to stress (23, 39), however impacts may be less in women with advanced gestational age. To limit unintended adverse consequences of COVID-19, and pandemics in general, mental health of pregnant women should be a public health concern with care providers, researcher, and policy decisions makers asking "how are we safeguarding the short- and longer-term mental health of pregnant women and their partners in the age of coronavirus" (4).

Finally, understanding how infectious outbreaks like COVID-19 may impact the fetus' epigenome are unknown and may lead to understanding risk for preterm birth and later child health consequences. The COVID-19 pandemic has arisen at a time where the collection of biological samples for genomics analysis are commonplace due to reduced costs of genome-wide technologies, offering an unprecedented opportunity to explore how the widespread effects of pandemic stress become biologically embedded.

CONCLUSION

This brief review provides some important insights into the differential ways in which COVID-19 influences women in high income vs. low-and-middle-income countries. First, the higher population density in areas such as Karachi makes exposure to

COVID-19 more likely than it is in most high-income countries. Second, educational (low literacy) and economical (access to basic needs, protective equipment) constraints affect how women give birth and how much anxiety and stress they may feel about safely giving birth under the current conditions. Third, for individuals living in LMI countries, the acute stress of a pandemic occurs within an already much more stressful living situation characterized by significant poverty, thus worsening the effects of stress on perinatal health. This exacerbated stress can have detrimental downstream consequences, including preterm birth and later child health consequences. In this regard, epigenetics offers a window of opportunity to understand biological significance of COVID-19-related stress.

AUTHOR CONTRIBUTIONS

SP provided the concept, drafted the manuscript with contributions from KS, SL, IY, SM, and NL. SP and SA revised the manuscript. All authors approved the final version for publication.

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Moving Forward From COVID-19: Bridging Knowledge Gaps in Maternal Health With a New Conceptual Model

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As the world faces the health crisis of a global pandemic—with healthcare protocols in overhaul, and patients and care teams experiencing unprecedented levels of stress and unpredictability—we predict that current knowledge gaps in maternal health will inevitably have a lasting impact on the health of women giving birth now and in the near future. Since we are decades away from closing the knowledge gaps we need filled today, we recommend shifting thinking toward a comprehensive conceptual model that merges knowledge of stress physiology, neurobiology, and pregnancy physiology. The model we present here, the *Maternal Reactive Scope Model*, is an expansion of the Reactive Scope Model built upon the concept of Homeostasis and Allostasis. The model provides a framework to consider pathways and interactions across physiological systems to attribute a physiological basis for considering stress exposure and bridge research gaps on mechanisms to measure or target for treatment. Our intention is to provide an adaptable, heuristic framework for discussion of research considerations and new healthcare models that aim to provide the best care for new mothers during and after the COVID-19 pandemic.

Keywords: maternal health, stress, maternal mental health, COVID-19, pregnancy, pregnancy physiology, allostasis, reactive scope model

INTRODUCTION

The COVID-19 pandemic has exposed pregnant women to an unprecedented level of stress and unpredictability. Due to the limitations on research addressing the links between stress, human pregnancy physiology, and maternal health, those caring for the pregnant population during this crisis are working with an incomplete model of true risk and potential solutions. As discussed in a recent editorial about COVID-19 and maternal mental health, now is not the time to allow knowledge gaps to hold back care strategies aimed at alleviating stress, and, instead, we need to "proactively develop" these strategies "without delay" (1).

In order to predict vulnerabilities, indicate potential preventions, and facilitate discussion for alternative approaches and considerations for care, we recommend a comprehensive conceptual framework that merges knowledge of stress physiology, neurobiology and pregnancy physiology. Our hope is that a conceptual framework will allow for care considerations that look beyond the current knowledge gaps in maternal health and provide an intellectually satisfying merge between considering both the *adaptive* physiological process of pregnancy, labor, and birth and the increased *susceptibility* to pathology requiring diagnosis, prevention, and treatment.

Here we propose such a framework in the form of the *Maternal Reactive Scope Model*. Our goal in presenting this model is *not* to provide a comprehensive overview of all interconnected physiological pathways and potential health outcomes. Instead, we offer this model as an adaptable, heuristic framework for idea-generation and further discussion.

MODELING A BODY IN BALANCE YET PUSHED TO AN EXTREME

Homeostasis is the biological concept that every physiological *up* is met with a physiological *down* to counterbalance and bring the body back to a steady state. A body out of homeostatic balance is prone to disease. Pregnancy and early postpartum represent a unique homeostatic state in a woman's body— in balance yet pushed to an extreme.

The framework we propose here is built upon the Reactive Scope Model (RSM), a model that considers the balance of maintaining homeostasis in the face of adaptive change (2). The RSM is an expansion of Allostasis, a concept demonstrating how the body maintains stability through change (3). Both the RSM and Allostasis models consider the effects of stress and stressors on the body (both psychological and physical). *Allostatic load* is a key concept to describe the adaptive and maladaptive functions of acute stress and chronic stress (4). Both models describe "*wear-and-tear*" or "*weathering*" as the cost of maintaining responses to counteract stress-related changes in homeostasis and demonstrate how accumulation of these costs put the body at greater risk for entering a disease state (discussed further below).

The RSM factors in the role of physiological mediators that change and respond over a set range and time as they respond to predictable and unpredictable stimuli/stressors. Incorporating the physiological changes associated with pregnancy and postpartum and the critical and natural shifts in physiological mediator ranges, we have adapted the RSM into the Maternal Reactive Scope Model (MRSM). Important to the MRSM is that pregnancy, in and of itself, is *not* considered a disease state, but, through the nature of the physiological changes of pregnancy, the maternal body becomes more *vulnerable* to disease during this time (e.g., hypertension, mood disorders, diabetes, autoimmune diseases, etc.).

Similar to our statement that pregnancy itself is not a disease state, we *do not* consider pregnancy itself to be a stressor or a major contributor to allostatic load or *wear-and-tear*. Rather, the MRSM considers how the stress response system stimulates and/or exacerbates pathological outcomes related to pregnancy, birth, and postpartum.

By providing a framework to conceptualize multiple physiological pathways, the MRSM removes the need to focus on a single physiological system or compartmentalize specific physiological contributions to the risks and pathologies associated with pregnancy. The general understanding of human pregnancy physiology continues to have gaps and will likely have gaps well into the future. Until these knowledge gaps fill, a theoretical framework provides a constructive way to attribute a physiological basis for interventions that demonstrate positive outcomes despite lacking an exact physiological mechanism to measure or target for treatment.

THE MATERNAL REACTIVE SCOPE MODEL

Key to the MRSM, the *physiological mediators* of the y-axis represent any aspect of physiology that regulates homeostasis (**Figure 1**). These mediators include insulin, cortisol, cardiovascular factors, among others (see **Table 1**). In the context of the MRSM, these factors change and respond over a set range and across pregnancy, parturition, and postpartum. Four ranges define both adaptive and maladaptive ranges of these mediators: (1) Predictive Homeostasis (2) Reactive Homeostasis, (3) Homeostatic Overload, and (4) Homeostatic Failure (**Figure 1A**).

Predictive Homeostasis is the range of mediators necessary for basic, baseline functionalities that often have a daily circadian rhythm. Mediators will increase yet remain in the Predictive Homeostasis range when responding to predictable challenges (e.g., eating a meal). Reactive Homeostasis includes the range necessary for responding to unpredictable, but *adaptive*, responses (i.e., acute stress response). When mediators exceed the Reactive Homeostasis range, they enter Homeostatic Overload—the mediators themselves become damaging and lead to pathology (labeled *as** in **Figures 1A,D**)—similar to Allostatic Overload in the Allostasis Model. Homeostatic Failure represents the range where mediators are too low to sustain homeostasis.

Put simply, there are specific upper and lower thresholds of "healthy" physiological mediator levels: the lower is the threshold of Homeostatic Failure; the upper is the threshold of Homeostatic Overload. Between the thresholds (the combined range for Predictive and Reactive Homeostasis) is the *normal reactive scope* for an individual - the range required for basic functionality and healthy responses to acute homeostatic perturbations.

During pregnancy, the physiological mechanisms themselves change as the maternal body shifts to prioritize the growth, development, and the birth of the baby [reviewed in (5); represented in **Table 1**]. Such profound physiological changes often occur only during pregnancy. In the MRSM, the natural changes in physiological parameters across pregnancy are reflected in the increasing requirements for maintaining daily function and predictable challenges as reflected in shifting the Predictive Homeostasis range, thus affecting the lower threshold (altering the *maternal reactive scope*). This shift in the lower threshold is considered normal and required for maintaining a healthy pregnancy.

While normal functioning of physiological systems and the body's ability to react to stimuli in the cases of healthy pregnancies are considered *adaptive*, the physiological requirements to both sustain the health of mom, baby, and the maternal/fetal unit and maintain a homeostatic balance

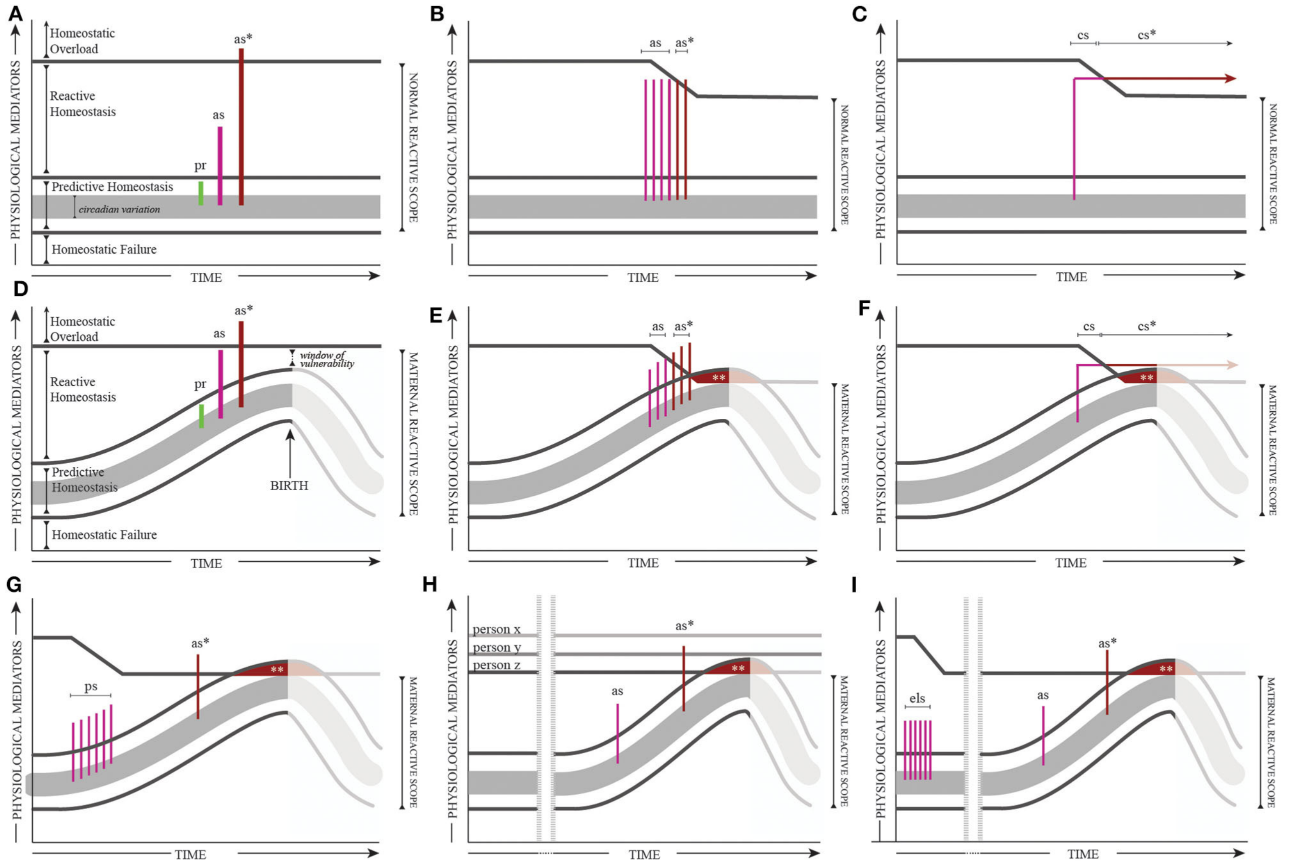

FIGURE 1 | The Reactive Scope Model **(A–C)** and the Maternal Reactive Scope Model **(D–F)** and example modifications of the Maternal Reactive Scope Model **(G–I)**. Acute physiological responses (including responses to stress) represented as "spikes" in the Predictive Homeostasis (pr = predictive response), Reactive Homeostasis (as = adaptive acute stress response), and Homeostatic Overload (as* = maladaptive acute stress response) ranges. The upper threshold between the *reactive scope* and Homeostatic Overload can shift on a short-term or long-term basis in response to stress exposure. Consecutive acute stress responses **(B,E)** and ongoing responses to stress **(C,F)**, lead to "wear-and-tear" that reduces the upper threshold and leads to Homeostatic Overload with additional acute stressors (as*) or continuous chronic stress (cs*). The *maternal reactive scope* **(D–I)** describes the shift in all ranges of Homeostasis to represent the physiological changes required to sustain pregnancy and prepare for labor and delivery. For simplicity, we demonstrate physiological mediators shifting *up* to represent parameters that *increase* across pregnancy through birth, but recognize that this may be mediator specific. In addition, the postpartum period is represented as a drop in mediator levels, however, the exact nature of these shifts are relatively unknown and may be dependent on the individual (e.g., breastfeeding vs. not breastfeeding) and the mediators studied (e.g., cardiovascular vs. endocrine). Prior research has suggested that the dynamics of the stress response may be buffered during pregnancy, reflected in shorter stress "spikes" later in pregnancy. In these versions of the model, the *maternal reactive scope* is progressively compressed as the lower threshold shifts in response to the mediator requirements of a healthy pregnancy; where this compression peaks is considered a "window of vulnerability" given the increased risk of acute or chronic stress resulting in Homeostatic Overload. A reduced upper threshold for the *maternal reactive scope* can also occur due to **(G)** pregnancy-related stress (ps), **(H)** genetic predisposition, or **(I)** early life stress (els). The compressed *maternal reactive scope* due to a reduced upper threshold and natural increases in the lower threshold can also result in responses or functionality in the Predictive Homeostasis range to become pathological (**) and/or previously adaptive acute stress responses (as) crossing into Homeostatic Overload and become maladaptive acute stress response (as*) or chronic stress (cs, cs*). See **Supplemental Material** for further breakdown of stress, pregnancy, and the MRSM.

becomes more *precarious* as the *maternal reactive scope* is naturally compressed (see *window of vulnerability* in **Figure 1D**). Mediator levels that either fail to stay above the lower threshold (inability to maintain Predictive Homeostasis resulting in Homeostatic Failure) or surpass the upper threshold (enter Homeostatic Overload) will likely present as illness, pregnancy complications, and/or developmental issues for the fetus (**Table 1**). As an example, cortisol and the mediators regulating cortisol concentrations, have non-stress related roles, critical to sustaining and supporting a healthy pregnancy and birth (6)—including: preparing the fetus for the outside world (e.g., thermoregulation, glucose metabolism, lung development), labor/delivery, and activation of mammary glands and milk synthesis. As a result, cortisol concentrations rise throughout pregnancy and peak at the end of the third trimester. While the ties between stress/cortisol physiology and Homeostatic Failure deserve further study, one potential example of Homeostatic Overload and this system may be the rates, risks, and role of stress in perinatal depression as cortisol regulation and stress have been tied to mental health disorders [discussed in (7)].

While the lower threshold naturally shifts with pregnancy, the upper threshold can shift on a short-term or long-term

TABLE 1 | Examples of key physiological systems, relative mediators, the reported shift in mediator levels and/or the role they play in Predictive and Reactive Homeostasis during the perinatal period, and potential health complications for mother, baby or the maternal<>fetal unit when mediators are pushed beyond the upper limit (Homeostatic Overload) or fail to meet the lower limit (Homeostatic Failure).

Physiological system	Physiological mediators	Peripartum Predictive/Reactive Homeostasis	Peripartum Homeostatic Overload and/or Homeostatic Failure range
Immune	• Prostaglandin • T-cell activation • Antibody titers • Cytokines	• Pro-inflammatory phases (Support implantation, Parturition) • Anti-inflammatory phase (Maintenance of pregnancy) • Maternal-fetal-placental interactions	• Autoimmune disease • Sensitivity to infectious disease • Preterm birth* • Miscarriage*
Endocrine	• HPA ○ Glucocorticoids (e.g., cortisol) ○ CRH ○ Placental CRH (pCRH) ○ ACTH • Thyroid • Reproductive • Progesterone • Estrogens • Insulin • Oxytocin • Melatonin • Prolactin	• Cortisol increases 30x nonpregnant concentrations • pCRH becomes dominant driver of maternal HPA • Maternal CRH decreases • HPA responsiveness decreases • Progesterone increases nearly 10x nonpregnant concentrations • Estrogens increase nearly 100x nonpregnant concentrations • Insulin secretion increases 200–250% • Insulin sensitivity decreases up to 50%	• Perinatal mental illness* • Maladaptive fetal HPA development • Preterm birth* • Miscarriage • Insulin resistance • Gestational diabetes mellitus • Preeclampsia • High or low birth weight
Cardiovascular (catecholamines)	• Cardiac output • Stroke volume • Heart rate • Blood pressure • Heart rate variability	• Cardiac output increases 30–50% • Stroke volume increases up to 85 mL (20 weeks gestation) • Heart rate increased (up to 90–100 beats/min) • Systemic vascular resistance decreased by 21% (lowest at 20–24 weeks) • Pulmonary vascular resistance decreased by 34%	• Myocardial infarction • Cardiac muscle breakdown • Hypertension • Preeclampsia
Hematologic and coagulation systems	• White blood cells (WBC) • Red blood cells (RBC) • Erythropoietin • Clotting factors • Fibrinogen	• RBC & WBC counts increase • 30% increase in RBC mass • ∼45% increase in plasma volume • Increased erythropoietin production • Hemodilution • Hypercoagulable state	• Anemia • Thromboembolism
Central nervous system	• Neurogenesis • Neurotransmitter concentrations • Cytokines • Neuroendocrine (e.g., Oxytocin) • Neurobehavioral	• Heightened plasticity/malleability of the maternal brain • Increased Oxytocin (maternal bonding)	• Depression • Anxiety • Post-traumatic stress disorder • Attachment disorder

While this is not a comprehensive list, and many links between mediators and complications have been suggested but are not well understood (*), the suggested physiological mechanisms and links are intended to be used for generating further discussion of the Maternal Reactive Scope and its potential application.

basis in response to stress exposure and affect an individual's *maternal reactive scope* range. Maintaining mediators in the Reactive Homeostasis Range (aka - high allostatic load) due to repeated acute stress without recovery (**Figures 1B,E**) or prolonged stress (**Figures 1C,F**) incurs a cost through *wear-and-tear,* resulting in a reduced upper limit. An analogy to demonstrate how *wear-and-tear* affects the body's tolerance for additional physiological pressure is a seesaw balanced with weight on both sides: heavy weights can maintain balance but the seesaw itself experiences more "*wear and tear*," becoming closer to tipping or breaking, than if lighter weights maintain balance [see (2)].

A compressed *maternal reactive scope* makes the body more vulnerable to stressors as mediators typically operating briefly in the Reactive range more readily cross the upper threshold into Homeostatic Overload (**Figure 1E** – *as**). Chronic stress-related shift in upper threshold allows mediators in the Reactive range or Predictive range to cross into Homeostatic Overload (**Figures 1E,F** – *as**, *cs**, **). In pregnancy, chronic stress that exceeds the upper limit and operates in the Homeostatic Overload range may be categorized as "toxic stress," a term used in fetal/maternal health literature, often in context of negative effects on fetal health and development (8). We predict that life stress (e.g., the global pandemic) poses the most risk toward the end of pregnancy into early postpartum, especially for certain individuals as described below (see **Supplemental Material** for further breakdown of stress, pregnancy, and the MRSM).

The consideration of physiological mediators in this model is not intended to pinpoint a simplified metric. Rather, the goal here is to provide a starting point for research and clinical conversation. Designing studies to better measure and monitor such mediators will improve our understanding of the balance and healthy range in the context of pregnancy physiology and maternal health. For clinicians, the MRSM is intended as a high-level view, grounded in evidence from physiological research, to consider the natural aspects of physiological changes during pregnancy alongside the increased susceptibility to pathology and the role that stress and stress reduction plays to alleviate or exacerbate health risks. Considering the application suggestions in the following section alongside **Table 1** may facilitate both hypothesis generation for future research as well as clinical considerations (see **Supplemental Material** for further discussion applying the MRSM to brain plasticity and maternal mental illness).

APPLYING THE MATERNAL REACTIVE SCOPE MODEL

The MRSM provides a framework of pathological susceptibility in the context of normal physiological changes across pregnancy to facilitate assessment and prediction of individual risk levels.

How the upper threshold of the MRSM is set before pregnancy or altered in response to external stimuli during pregnancy affects which women will experience Homeostatic Overload and when. Importantly, the MRSM relies on an individual responsiveness to a stressor (**Figure 1D**) Every "spike" in the Reactive range or Overload range indicates an acute stress response that is modifiable and specific to that individual and circumstance. The stress responses themselves are not *all-or-nothing* and require a psychological input to trigger the physiological output. In the context of life stressors and non-infection related COVID-19 stressors, individual differences in resilience and stress reactivity during this time may account for why certain women are affected more markedly than others.

Other individual and circumstantial differences can result in a range of framework permutations. Differences may include how quickly or robustly an individual's mediators respond to stressors, threshold levels between homeostatic ranges, relative steepness of *maternal reactive scope* changes across pregnancy, etc. The integration of these differences could help create a *maternal reactive scope* profile that is unique for each woman and for each pregnancy.

For the sake of simplicity, this initial discussion is restricted to examples where the *maternal reactive scope* is compressed by decreasing the upper threshold and, therefore, the likelihood of entering Homeostatic Overload.

Stress Exposure During Pregnancy

Often when we think about stress and the impacts during pregnancy, we consider the extreme of traumatic events. In the MRSM, trauma can be reflected as a single stress event stimulating a physiological response that crosses into Homeostatic Overload (spike *as** in **Figure 1D**). Applying this theoretical framework may explain why some women experience negative birth outcomes while others, equally exposed to a traumatic event, appear unaffected. For example, a study compared birth outcomes of women in close proximity to events of the 9/11 terrorist attacks to women who lived five miles away. The researchers found an association between low birth weight, preterm birth and Post-traumatic Stress Disorder (PTSD) diagnosis but no association to proximity (9).

Certain events during pregnancy and birth can also be perceived as *stress* and contribute to increased risk of complications. The *window of vulnerability* predicts that an equivalent stressor might be tolerated early in pregnancy yet cause health problems at the end of pregnancy into postpartum (comparing spike *as* to spike *as** in **Figure 1D**). This prediction may apply to the effects of birth-related stress—in a meta-analysis of maternal stress studies, researchers found that birth-related stress (fear of birth, previous birth trauma) was 2–3x more likely to lead to negative outcomes for baby (low birth weight, preterm birth) than extreme, traumatic events (10).

Even without clear, traumatic stress exposure, the peripartum period is associated with inevitable psychological triggers of the acute stress response—novelty, unpredictability, lack of control. Since a series of small stressors or constant stressors can have a similar effect as a single stressful event and compress the *maternal reactive scope* (see **Figures 1D,E**), it is important to consider *any* stress during pregnancy but especially during the *window of vulnerability*. In a positive context, improved birth outcomes have been attributed to interventions that likely act by decreasing stress - e.g., benefits of mindfulness, labor support, postpartum support (11).

Chronic stress exposure early in pregnancy can lead to a long-lasting decrease in the upper threshold of the *maternal reactive scope* (**Figure 1G**), predicting a decreased resilience later. In other words, the MRSM provides a framework for connecting seemingly unrelated psychological impacts and physiological consequences. For example, a study describing connected rates of gestational diabetes mellitus (GDM) and postpartum depression suggested a link between the mental health outcomes and the psychological stress of the GDM diagnosis/associated lifestyle changes (12). Another study found a link between economic downturns and preterm birth rates (13).

Potential physiological and psychological connections are important to consider in the context of COVID-19 as we will likely see effects of the pandemic on maternal health that extend beyond infected patients and beyond individuals currently delivering or preparing to deliver during the crisis. Furthermore, in the context of controlling the spread of COVID-19, acute stress triggers during the peripartum period are ever more present and heightened and many of the traditional avenues for alleviating or limiting stressors during this time (e.g., doulas for labor support, postpartum support at home) may not be options. The MRSM suggests that prevalence and risk of peripartum-related complications are likely to increase, and care strategies aimed at limiting exposure to stressors or decreasing stress directly should be prioritized.

Genetic Susceptibility to Maternal Complications

For some women, no matter how healthy and stress-free they stay during pregnancy, natural physiological changes of pregnancy will lead to health complications. As an example, genetic susceptibility to perinatal depression likely combines with environmental factors to increase the risk of experiencing a perinatal mental illness (14, 15). Genetic susceptibility is reflected in MRSM as an individual's initial *maternal reactive scope* upper threshold (**Figure 1H**). Some individuals (e.g., person x, **Figure 1H**) have a naturally high *maternal reactive scope* and are thus more resilient. In contrast, for some individuals (e.g., person z, **Figure 1H**), the levels of physiological mediators required to maintain Predictive or Reactive Homeostasis and support pregnancy, naturally cross into Homeostatic Overload at some point in pregnancy and lead to illness and/or complications for mother, baby or the maternal/fetal unit. Other individuals (e.g., person y, **Figure 1H**) may have an intermediate upper threshold such that they will not necessarily experience pregnancy-related health issues but will be less resilient to stress exposure during pregnancy.

Variation in genetic susceptibility may explain why certain individuals are more vulnerable or resilient to stressors during pregnancy. In the context of pandemic-related life stress, genetically susceptible women may experience the effects of stress more acutely or earlier in their pregnancy.

Life Stress Effects on Maternal Health

Continuous or chronic stress exposure prior to gestation can lead to *wear-and-tear* and a reduced threshold to Homeostatic Overload, making women more vulnerable to illness and complications during pregnancy when the *maternal reactive scope* is further compressed.

An example of sustained and chronic stressors prior to pregnancy that may affect pregnancy outcomes is the growing evidence that institutionalized racism underlies the racial disparities in maternal and infant morbidity and mortality (16). The concept of *weathering* in Black Americans, especially Black women, describes a physiological vulnerability to disease that is directly tied to racism-based stress exposure and measure-able as a difference in allostatic load in individuals and populations (17). *Weathering* has been applied to examine the racial disparity in birth outcomes (18) and can be conceptualized with the MRSM as a reduced upper threshold such that women more readily experience ill effects of Homeostatic Overload during/after pregnancy due to chronic stress exposure prior to pregnancy (**Figure 1I**).

In times of pandemic crisis and restructuring of prenatal healthcare, we must consider all sources of stress to better care for the most impacted and at-risk individuals and communities.

CONCLUSIONS

We are living through a global pandemic that has forced us to re-think many of our policies in maternal health while working with and around large knowledge gaps. As discussed in a prior review, uninfected pregnant and postpartum individuals will likely face increased negative health outcomes during and immediately following the COVID-19 pandemic (1). Our hope in presenting a conceptual framework is to bridge current knowledge gaps and start a dialogue of alternative strategies to discuss, describe, and consider the connections between pregnancy physiology, stress, and maternal health. In addition, we anticipate that researchers will add their own permutations to the model to expand it to prediction and application.

Specific stress triggers during pregnancy (related and unrelated to the pandemic) may be hard to directly measure and monitor given the individual nature of the stress response system. The MRSM provides a lens for higher-level consideration of both the cumulative effects of stress exposure and the implications of seemingly "smaller" stressors, especially during more sensitive windows of time. Wide-spread uncertainty, financial instability, racism, and increased demands on the healthcare system are classic stressors insofar as they contain key psychological elements (novelty, unpredictability, lack of control) that could trigger the physiological stress response. In addition, during the global pandemic, many of the traditional avenues for alleviating or limiting stressors may not be options. For healthcare teams adapting and building new models of care, we hope the MRSM highlights the need to discuss and consider stress and stress-buffering in prenatal and postpartum care and the importance of decreasing stress exposure whenever possible.

While individual women will have different *maternal reactive scope* ranges and react differently to individual stressors (i.e., more or less resilient), the added stressors associated with the COVID-19 pandemic could have global maternal health implications, especially in already at-risk individuals and communities.

As we move through and beyond this pandemic, we hope the MRSM will aid the progress in advancing maternal health on a global scale by providing a physiological framework for optimizing research, prioritizing considerations of stress exposure, and inspiring the development and adoption of new strategies for prediction and personalized care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MD and LR contributed to initial conceptualization of the model. JP contributed case study examination. MD drafted the initial manuscript. All authors contributed to exploration and discussion of model application and further definitions and provided critical revision of intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2020.586697/full#supplementary-material

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Female Corporality, Gender Roles, and Their Influence on Women's Mental Health in Times of COVID-19

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INTRODUCTION

The German language distinguishes two distinct words for "the body." *Körper*, which posits the body as an object, and *Leib*, or the experienced reality of embodiment (1). These two forms of acknowledging the body are not as well-expressed in Spanish or English. Ortega y Gasset called the former "extra-body" and the latter "intra-body" (2). The "intra-body" relates to the phenomenological concept of corporality, which refers to the sense of embodiment, and does not represent something anatomical as does the body. Corporality has been studied in philosophy and other disciplines such as psychiatry, feminist psychology (3), and neurosciences (4).

Western society is grounded on a dichotomous view that can be dated back to Plato's metaphysics, closely related to Descartes thinking, where an immaterial spirit is separated from a material substance, which is the body (5, 6). The spirit, reason, and Cartesian logos go invariably behind the subtle and perishable body. As we live in a male-centered and male-identified patriarchal society, the masculine concept is intimately related to reason, to the Cartesian logos, while the body is identified with the feminine (7). From an anthropological perspective, Nature is represented as feminine and subordinated to Culture, which is mainly masculine. Likewise, Reason and Mind are related to masculinity, while Body and Nature are feminine (8).

Patriarchy is based on this anthropological meaning of the body as something identified with femineity (7). Consequently, in Western societies being a man or a woman means a different role of the body in the construction of the own identity, and this creates different interactions with the others (6). Women are acculturated to build their self-image using the eyes of others as the primary view of the physical selves (3, 9), to the point that some authors such as Susie Orbach argue this fact makes women ending up seeing their body as commodities within a consumerist culture (9). Besides anthropological and philosophical theories, psychological research has proven that women, compared to men, focus more on their own bodies' aesthetic features and not on the functional ones (10). Even in childhood, girls are already more conscious about their body weight and appearance than their male counterparts (11).

Several factors have been discussed as potential causes for these differences, in particular gender roles. Femineity contains traits and behaviors related to caregiving, love, and a stereotypical thin body ideal as core factors, all of which constitute a part of the feminine gender role. We live in a gendered society in which there are polarized expectations of the behavior of females and males (12). These gender-stereotyped body image ideals lead to unjustified importance of the body in the social well-being of women, as well as self-objectification and an increased risk of eating disorders to get the thin ideal (13).

INFLUENCE OF THE PANDEMIC ON CORPORALITY

The current pandemic scenario has challenged our own bodies' perception since part of society became aware of their body through the disease process. By experiencing pain, fever, discomfort, and distress, people comprehend how their bodies influence their well-being and identity. In fact, illness can affect self-stem, self-perception, and change body image (14). As women's identity may be more susceptible to being influenced by their physical appearance, the coronavirus pandemic will probably distress women to a greater extent by focusing even more on their vulnerabilities and increasing their body awareness. It has been previously reported that a self-critical attitude against the body and body dissatisfaction are predictors for developing eating disorders (15). Therefore, in these circumstances, an increase in women's incidence of eating disorders could also be expected.

The connection between the body and mental health is bidirectional. Mental distress can interfere with how people perceive their physical sensations, and on the other hand, illness and body dissatisfaction can act as triggers for mental pathology (14, 16–19). The link between body awareness and psychopathology culminates in mental disorders like anxiety and somatic symptom disorders (SSD), in which the cognitive appraisal of somatic symptoms is distorted, and patients catastrophize normal physiological sensations (20). This attitude leads to more anxiety. The COVID-19 pandemic, through increased body awareness, is likely to worsen both anxiety disorders and SSD, as these patients are already distorting their somatic sensations and misinterpreting them as dangerous. As these pathologies have been described to be more prevalent in women, reaching an estimated female-to-male ratio of up to 10:1 in SSD (21), we can presume that women will be affected to a greater extent.

INFLUENCE OF THE PANDEMIC ON GENDER ROLES

Ongoing worldwide pandemic has not only made women more aware of their bodies but also their gender roles. In our culture, female subjectivity is constructed concerning the body, caregiving, and love for the others. Other values, such as sacrifice, effort, affection, and suffering, which are all also associated with the female gender role, are a breeding ground for psychological distress, especially in times of a pandemic. Following the theoretical picture of gender roles, available data show that women contribute to 71% of the global hours of informal care (22), a task that became essential during the mandatory confinement imposed in most countries. As a result, work-life balance has been dramatically affected by closing schools and childcare centers, which significantly burdens working mothers. We can therefore infer that somehow the pandemic has accentuated gender roles by imposing greater responsibility on women. As previous research has shown, gender roles and informal cares are sources of distress and psychosocial exhaust for women (23, 24). An increase in these duties will undoubtedly have long-term implications for mental health that have not yet been objectified by ongoing studies.

CONCLUSIONS

The corporality of women is closely influenced by the female gender role. Gender roles are cultural constructs developed within a male-identified patriarchal culture that identifies femineity with the cult of the body. During the coronavirus pandemic, our androcentric society became aware of its futility, of the human body's fragility through the experience of illness. Women, which were already at a higher risk of developing mental health issues, and increased body awareness may produce more significant psychological distress than men. Parallelly, the accentuation of gender roles by an increased need for caregiving during the confinement can also impact women's mental health, as they are the leading providers of informal care.

Although more research is needed to establish the psychological impact on women, there is enough data to hypothesize that the pandemic will distress women to a greater extent. Therefore, gender-sensitive interventions during the pandemic should be considered, along with psychological interventions that address body awareness. Given this situation, public policies should promote equity in care and strengthen those research programs that include a gender perspective. This is the moment to invest in women's mental health.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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COVID-19 Pandemic: Adaptation in Antenatal Care for Better Pregnancy Outcomes

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INTRODUCTION

Pregnancy is a precious time for an expectant mother, full of excitement and anticipation. Pregnant women need to be aware of various events of pregnancy, including how the fetus will develop and grow in the maternal womb (1). Pregnant women are usually curious about their expected due date of delivery, the recommendations regarding nutrition and exercise, and information related to the safety of the unborn baby. Good pregnancy-related care is paramount for the health of an expectant mother and the normal development of the fetus. Pregnancy is also the time to promote healthy behaviors and good parenting skills. Though pregnancy itself is not a disorder, some undesirable changes may occur during pregnancy due to an altered physiological state, such as nausea, vomiting, edema, varicose veins, heartburn, constipation, backache, tiredness, loss of sleep, hypertension, diabetes, and abnormal bleeding (2–4). Presently, there is not enough information to know whether pregnant women have a higher risk of COVID-19-related illness, although pregnant women are at greater risk of non-COVID-19-associated respiratory infections (5–9). Also, the potential risk of COVID-19 positivity during pregnancy on maternal and fetal health needs carefully designed studies. Preliminary observations, however, suggested premature birth to pregnant women with COVID-19 (10, 11). Some studies also reported infants born to mothers with COVID-19 tested positive for COVID-19, even though the virus was not present in the amniotic fluid or placenta (12). There have been reports of neonates testing positive for COVID-19 30 h after birth, confirming that transmission was not intrauterine. Currently, there is little to no evidence in the literature about the vertical transmission of COVID-19 from mother to fetus. Two studies aimed to detect SARS-CoV-2 in amniotic fluid both reported that no antibody against the virus was detected in women who were pregnant at the time, again suggesting that intrauterine transmission had not occurred (13, 14). COVID-19 presents similar pathogenesis to the SARS virus with a low risk of vertical transmission (13). The close relationship between SARS-CoV-2 and SARS can help predict that the risk of vertical transmission from mother to child is low, and further clinical studies would validate such assumption. Further research will shed light on the impact of the virus on mother and fetus during pregnancy and after delivery.

Regular consultation with a health professional is recommended throughout the pregnancy, known as antenatal care (ANC) visits (1, 15–17). ANC is a critical opportunity for healthcare providers to deliver necessary support and educate pregnant women on unexpected events. As mentioned, effective ANC visits are essential for both maternal and fetal health. The ANC visits help to promote a healthy lifestyle, that include informing patients about sources of good nutrition, detecting and treating any preexisting diseases, counseling, and supporting women who may be encountering domestic violence. The World Health Organization (WHO) provided guidelines for ANC visits, including clinical examination to rule out severe anemia (hemoglobin test), detection of symptomatic sexually transmitted diseases (rapid syphilis test) and their treatment, urine test (multiple dipsticks), blood group and rhesus status, obstetrical examination (like symphysis-fundal height, presentation and position of the fetus, liquor amount, fetal heart rate), vaginal examination (where necessary), monitoring vital signs and parameters (blood pressure, maternal weight/height), and tetanus toxoid vaccination (17). Moreover, during ANC, women are advised to take iron and folic acid supplementation, which is vital for maternal and fetal health. Similarly, it is during ANC visits that pregnant women are educated on emergency danger signs of pregnancy-related complications and given the instructions for delivery and recommendations for lactation and contraception. In developing countries, ANC also increases the chance of using a skilled attendant or community health workers (CHWs) at birth to minimize maternal and fetal health risks (**Figure 1**). Furthermore, pregnant women need to know some diseases that can affect pregnancy outcomes, such as APH, pre-eclampsia, eclampsia, anemia, diabetes, and malaria (in malaria-endemic zones like sub-Saharan African countries). When these diseases are not adequately treated, they can lead to serious complications that impact both maternal and fetal health. Studies have suggested that optimal pregnancy outcomes of a diabetic pregnant woman rely heavily on the quality of diabetes management before and during pregnancy (18–23); such practice goes beyond diabetes, and include all other systemic diseases that might influence normal maternal and fetal evolvement during pregnancy.

It is of utmost importance to the pregnant women to get in touch with the ANC providers if they encounter COVID-19 symptoms or if they are exposed to people with COVID-19; the confirmatory test is recommended for the virus that is causing COVID-19. Pregnant women with COVID-19-positivity should be treated for fever, pain, or coughing; in more severe illness, hospitalization should be recommended. Also, for the pregnant women with COVID-19, the induction of labor or a caesarian section delivery might need additional screening extra precaution before entering the labor and/or delivery unit. Due to concern that newborns might be infected with COVID-19, infants born to COVID-19 positive mothers would need to be temporarily separated (12). Little is known about the vertical transmission in women with COVID-19 to the newborns; studies, however, noted that viral pneumonia in pregnant women is associated with an increased risk of preterm birth, fetal growth restriction (FGR), and perinatal mortality (24). Consequently, women with COVID-19 during pregnancy may present with high fever due to pneumonia, though there is no clear evidence that SARS-CoV-2 undergoes intrauterine or transplacental transmission.

Khan et al. (9) noted in their study that three pregnant women with COVID-19 did not find any vertical transmission. Among

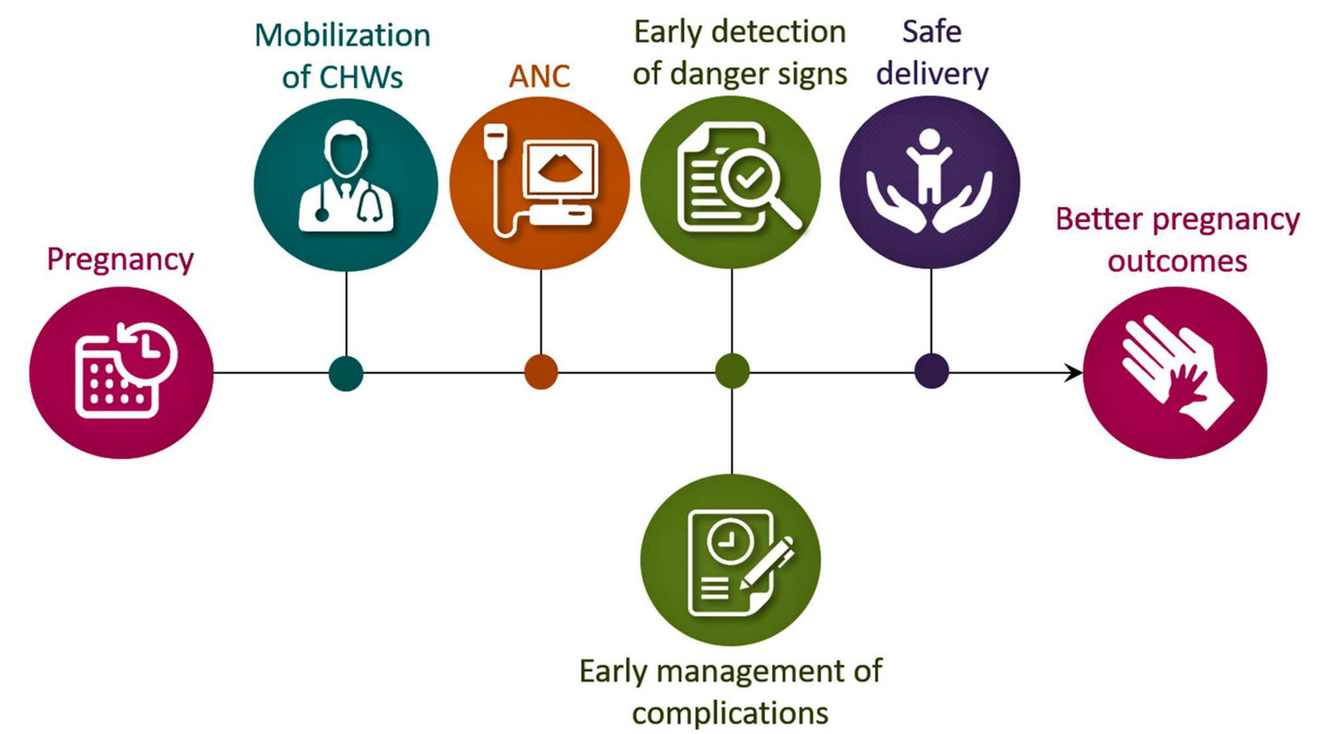

FIGURE 1 | Schematic diagram showing the importance of CHWs and ANC for better pregnancy outcomes, particularly in developing countries. CHWs, community health workers; ANC, antenatal care.

the three studied cases, one was preterm, which was not due to vertical transmission, and perhaps related to pneumonia and psychological stress during pregnancy. No evidence of maternal to the neonatal intrapartum transmission of COVID-19 was noted (9). This study was echoed by other studies that also documented no evidence for intra-uterine vertical transmission of COVID-19 from infected pregnant mothers to their fetuses (25, 26). However, precautions to prevent the spread of infection and early treatment when pregnant women get infected should always be a priority. Although it is unclear whether the virus causing the COVID-19 can be spread through breast milk, an infected mother is likely to transmit the virus, perhaps by respiratory droplets during breast-feeding; pumping out breast milk with proper precautions might be one of the safer options. During breast-feeding the mother should wear a mask and gloves. Coovadia et al. (27) reported that mothers who exclusively breastfed reduced the chances of transmitting HIV to the child compared to mothers who did not exclusively breastfeed (replacement or mixed feeding) (27). Further studies will explain whether a similar phenomenon of protection through breast milk could be achieved for mothers with COVID-19.

According to 2016 WHO reports, an estimated 303,000 women died from pregnancy-related complications and within the first month of life, around 2.7 million newborns died. Among these deaths, 2.6 million were stillborn. Studies show that providing quality health care during pregnancy and childbirth can prevent many of these deaths. Globally, around 64% of women receive ANC services (28, 29). The WHO's new ANC model increases the number of contacts with the healthcare providers throughout the pregnancy from four to eight visits. A higher frequency of contacts with healthcare providers is associated with a reduced likelihood of stillbirths. This is because of the early detection and management of potential pregnancy-related complications. The WHO has proposed a minimum of eight contacts for ANC; such an increased number of contacts can decrease perinatal deaths by up to 8 per 1,000 births when compared to a minimum of four visits (29, 30). Currently, many countries are progressively adopting the new model of eight ANC to improve the health of the pregnant mother and fetus. Nevertheless, confinement measures may hinder women from attending ANC as per schedule, and alternative measures must be considered. During this COVID-19 pandemic, WHO recommended six in-person visits and two virtual visits (3rd and 4th) to reduce the number of times the patient needs to travel and attend hospital/clinics. Using strategies like the involvement of CHWs, utilizing mobile healthcare service, and taking advantage of mass media communication on identifying the danger signs during pregnancy could partly mitigate the challenge (**Figure 2**). Less in-person visits and more online consultations are used in many places to provide ANC during the ongoing COVID-19 pandemic, with encouraging feedback from both care recipients and providers. However, further research using randomized control trials is needed to determine the online ANC delivery system's overall pregnancy outcomes. The cost and benefit analysis of online ANC service is also required to assess the feasibility of continuing online ANC service by the decision-making authorities (31). Of relevance, analysis of mobile health's cost-effectiveness for ANC and facility births showed that mobile health programs were relatively inexpensive and saved lives (for the dollar investment) in Nigeria (32).

PRIORITY ACTION STEPS

In some developing countries like Rwanda, CHWs are trusted frontline health personnel. CHWs are members of the communities where they work and they are usually selected by the communities, answerable to the communities for their activities as well as being supported by the healthcare system (33). In Bangladesh, CHWs are appointed by the government as family welfare assistants, and some are trained as traditional birth attendants for performing safe delivery. The third Global Forum on Human Resources for Health in 2013 concluded that CHWs and other frontlines primary health care workers are the essential workforce to achieve the goals of universal health care and recommended for their integration into the national health systems. Although CHWs are involved in various social works in the community, they are also involved in providing maternal and neonatal healthcare and are trained to follow up women during pregnancy and post-delivery periods. CHWs are trained on identifying danger signs during pregnancy, including APH, eclampsia, hypertension, and malaria, and timely referral to appropriate hospital/clinics so that pregnancy-related complications could be minimized in earlier stages. During this COVID-19 pandemic, these CHWs should be given additional training, not only to report early signs, but also to provide first aid to save the lives due to complicated pregnancies. Who will cater to the training cost and provide protective gear to the CHWs are unsettled issues and need a public-private cost-sharing fusion program. In the case of home deliveries, CHWs should be given the training to manage unexpected post-partum hemorrhage (PPH), and such training should be a priority during the COVID-19 pandemic. Necessary routine testing kits, from pregnancy test to blood sugar test, should be available to these CHWs. Providing adequate training and equipping them with essential materials are important to support pregnant women during COVID-19 pandemic. Also, in the COVID-19 pandemic, providing post-partum care after childbirth should be the continuation of ANC, with virtual support and guidance from the healthcare providers. Additional care should be provided to reduce post-partum depression. Moreover, throughout the pregnancy, adequate nutrition to pregnant women should be ensured for both maternal and fetal health and overall health, in general (34–45).

Mobile health can also be useful during the COVID-19 outbreak. Mobile health is "the use of mobile devices and its associated technology for health interventions" (46, 47). Mobile health can help in the capturing and sharing of texts, videos, audio, and images. A Kenyan study found that mobile health could significantly enhance the treatment of malaria at the remote locations; mobile health was beneficial in the clinical diagnosis as well as management of the disease (46, 48). A report in 2016 of mobile use data found that 40.9 per 100 inhabitants in developing countries are active users of mobile

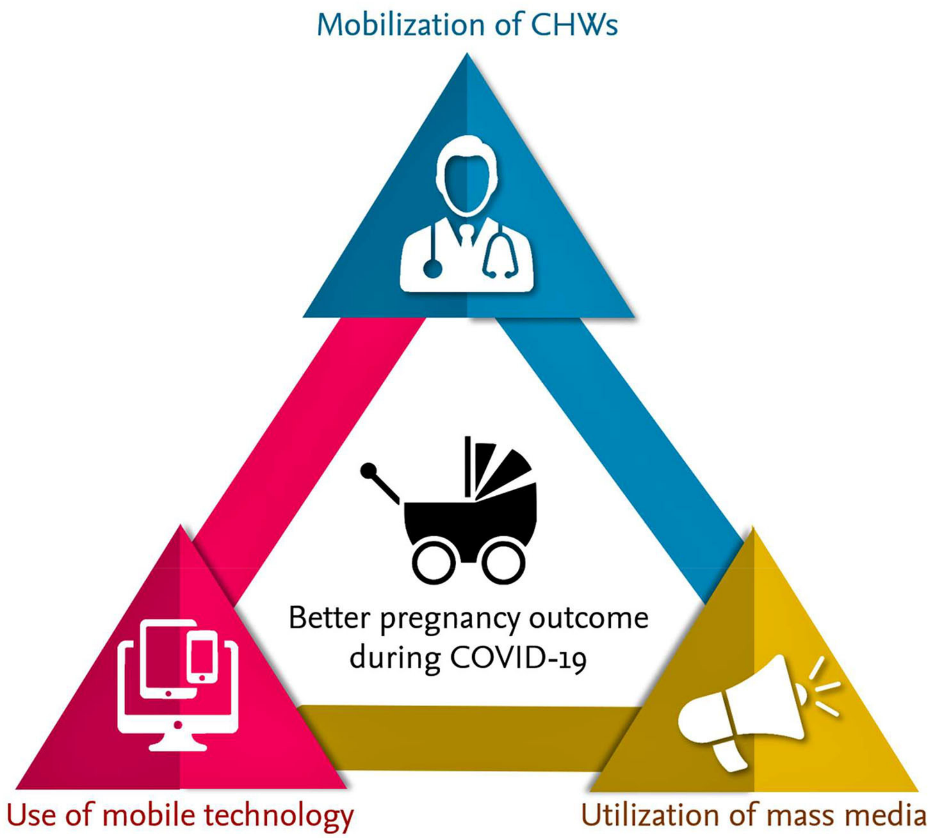

FIGURE 2 | Involvement of CHWs, utilizing mobile healthcare service, and taking advantage of mass media communication on identifying the danger signs during pregnancy could partly mitigate the complications to minimize fatalities.

phones (46, 49); there, government initiatives of capitalizing the use of mobile phones for enhancing ANC during the COVID-19 pandemic are necessary. Such government initiatives are likely to be beneficial for developing countries. For the patient's safety and to ensure the delivery of quality care, a standardized protocol for telemedicine must be established by the health regulatory authorities. Since many people in developing countries have access to mobile phones, healthcare professionals can use this technology to keep contact with the pregnant woman or the family to provide necessary healthcare-related information. Additional studies are needed to ensure that patient safety is not compromised by mobile health's ANC service. Healthcare providers should maintain a low threshold until the availability of further safety data regarding online healthcare services (50). Mass media communication can also serve as an important vehicle to provide essential information to increase pregnancy-related awareness in order to have better pregnancy outcomes during the COVID-19 pandemic. Community awareness of the obstetric danger signs and seeking early medical care is crucial for better pregnancy outcomes including a reduction of maternal fatalities. Of relevance, misconceptions, superstitions, and seeking help from traditional healers could hinder pregnant women's attitude and attendance to the ANC clinics (51–54). Health education initiatives on the danger signs to pregnant women may mitigate those potential dangers.

In the period of confinement due to the COVID-19 pandemic, everyone is required to stay home to minimize the spread of the virus. Pregnant women are also required to follow similar instructions, which might impair them in receiving adequate ANC. Since mass media has a powerful influence on people's thinking and behavior, in the era of COVID-19, mass media could play an important role to increase health awareness to reduce pregnancy-related complications (55–60). The public reliance on the media (radio, television, social networking sites) offers a unique tool to deliver health-related information and to increase health consciousness (57–61). The mass media could, therefore, play a vital role in informing the community about the obstetric danger signs and possible measures, including advising appropriate places for managing those danger signs in the COVID-19 pandemic.

Generally, the studies show the need for mental health support during pregnancy: psychiatric disorders like depression and anxiety with domestic violence affect the mental health and well-beings of the mother and her child (62). Similarly, coincidental adverse life events like the current pandemic of COVID-19 may also aggravate the situation. During COVID-19 health professionals, patients, and the general population are under psychological stress, translating in fear, anxiety, insomnia, and depression (63). A study conducted on pregnant women during this time of COVID-19 concerning health anxiety and behavioral changes reported that around half of the participants were worried about their health; about 83% reported heightened anxiety (62). A shortage of healthcare providers in China with uncoordinated mental health services for dealing with the psychological crisis during the COVID-19 pandemic has been documented (64). Establishing appropriate strategies to address the mental health status of pregnant women should be a priority during this pandemic; mobile technology could be used to provide psychological support to pregnant women to reduce fear, anxiety, and depression. Pregnant women should also be encouraged to report any form of domestic violence to healthcare professionals.

SUMMARY

While other mechanisms of mobilizing people for ANC and management of home delivery cases continue, the governments should also consider active engagement with CHWs, train them with the necessary information, and provide them with the required material for the management of home deliveries. One important unresolved issue is how to keep engaging CHWs and motivate them to adopt added workloads during this pandemic. Further studies will define the types of incentives required for CHWs to provide additional community services (65, 66). The optimal utilization of e-health and e-consultations and virtual ANC consultations may reduce pregnancy-related complications, and therefore improve maternal and neonatal health during the COVID-19 outbreak. However, it is necessary to mention that providing online ANC may be impaired by restricted net access and limited availability of mobile electronic devices to pregnant women to receive online instructions and supervision in developing countries (67). During this pandemic stress, additional support to the mental health of pregnant women should be an essential component of ANC. The involvement of family and friends should be encouraged, with adequate precautions to reduce the risk of COVID-19. Of clinical importance, for high-risk conditions during pregnancy, virtual ANC consultations may not yield the best results. Therefore, creating an individual care plan for high-risk pregnancies instead of a virtual approach may improve feto-maternal outcome. To reduce the risk of COVID-19-related infection, pregnant women should be vigilant, keep social distancing, restrict visitors, and frequently wash hands with soap or use 60% alcohol-based hand sanitizer. Finally, providing necessary training to the healthcare providers in infection management, in addition to ante- and post-natal care, should be a clinical priority to efficiently deal with COVID-19 to minimize fatalities (68). Finally, government initiatives, particularly in developing countries, are needed to support pregnant women who need remote ANC during the COVID-19 pandemic by providing access to mobile devices and network services. Furthermore, government regulations require enforcement to ensure pregnant women's privacy while taking advantage of online ANC services.

AUTHOR CONTRIBUTIONS

PU: design and wrote. GN and SM: wrote. AH and KN: revised and wrote. MR: conceptualized and wrote. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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Occupational Stress, Burnout, and Depression in Women in Healthcare During COVID-19 Pandemic: Rapid Scoping Review

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Objectives: The overall objectives of this rapid scoping review are to (a) identify the common triggers of stress, burnout, and depression faced by women in health care during the COVID-19 pandemic, and (b) explore individual-, organizational-, and systems-level interventions that can support the well-being of women HCWs during a pandemic.

Design: This scoping review is registered on Open Science Framework (OSF) and was guided by the JBI guide to scoping reviews and reported using the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) extension to scoping reviews. A systematic search of literature databases (Medline, EMBASE, CINAHL, PsycInfo and ERIC) was conducted from inception until June 12, 2020. Two reviewers independently assessed full-text articles according to predefined criteria.

Interventions: We included review articles and primary studies that reported on stress, burnout, and depression in HCWs; that primarily focused on women; and that included the percentage or number of women included. All English language studies from any geographical setting where COVID-19 has affected the population were reviewed.

Primary and secondary outcome measures: Studies reporting on mental health outcomes (e.g., stress, burnout, and depression in HCWs), interventions to support mental health well-being were included.

Results: Of the 2,803 papers found, 28 were included. The triggers of stress, burnout and depression are grouped under individual-, organizational-, and systems-level factors. There is a limited amount of evidence on effective interventions that prevents anxiety, stress, burnout and depression during a pandemic.

Conclusions: Our preliminary findings show that women HCWs are at increased risk for stress, burnout, and depression during the COVID-19 pandemic. These negative outcomes are triggered by individual level factors such as lack of social support; family status; organizational factors such as access to personal protective equipment or high workload; and systems-level factors such as prevalence of COVID-19, rapidly changing public health guidelines, and a lack of recognition at work.

Keywords: women, health care, occupational stress, burnout, mental health, pandemic, COVID-19, health work force

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A rapid scoping review was conducted to identify stress, burnout and depression faced by women HCWs during COVID-19.
- To ensure the relevance of our review, representatives from the women HCWs were engaged in defining the review scope, developing review questions, approving the protocol and literature search strategies, and identifying key messages.
- It provides a descriptive synthesis of current evidence on interventions to prevent mental health for women HCWs.
- Most studies used cross-sectional surveys, making it difficult to determine the longitudinal impact.
- There was significant variability in the tools used to measure mental health.

INTRODUCTION

COVID-19 pandemic-related measures, such as prolonged periods of social isolation, unexpected employment disruptions, school closures, financial distress, and changes to routine, are having an unprecedented negative impact on women's mental well-being (UN). Over 80% of the health workers in Canada are women (1). Women in health care already face systemic challenges related to workplace gender biases, discrimination, sexual harassment, and other inequities (2). Studies show that women physicians are more likely than male physicians to experience depression, burnout, and suicidal ideation (3, 4). Additionally, women perform three times more unpaid care work than men as parents and primary caregivers to family members (5).

The COVID-19 pandemic has led to increased psychological trauma and suicide among health care workers (HCWs) (6–10). A poll of HCWs conducted by the Public Health Agency of Canada in April 2020 showed that 47% of respondents expressed the need for psychological support due to COVID-19 related factors; 90% of the respondents were women (11). Similarly, a survey conducted by the British Medical Association in April, 2020 of HCWs showed that 44% of respondents indicated they were experiencing burnout, depression, anxiety, or other mental health conditions due to COVID-19-related factors (12). Unaddressed stress and burnout can lead to depression, suicidal ideation, and substance abuse (4, 13). A healthy workforce is the cornerstone of a well-functioning health care system. Yet, there is a systemic lack of evidence-informed services that provide timely, accessible, and high-quality care for HCWs during public health crises. This is especially relevant for health systems and professional societies who recognize the importance of preventing and mitigating stress, burnout, depression, and suicidal ideation in their workforce during pandemics. In addition, these interventions are essential for the well-being and retention of the health care workforce. This review attempts to answer the following questions: What are the common triggers of occupational stress, burnout, and depression faced by women in health care during the COVID-19 pandemic? What individual-, organizational-, and systems-level interventions can support the well-being of women HCWs during a pandemic?

Overall Objectives

The overall objectives of this review are to (a) identify the common triggers of occupational stress, burnout, and depression faced by women in health care during the COVID-19 pandemic, and (b) explore individual-, organizational-, and systems-level interventions that can support the well-being of women HCWs during a pandemic.

METHODS

Commissioning Agency

The Canadian Institute for Health Research issued a special call to address COVID-19 in Mental Health & Substance Use issues. Given there has not been any previous research in this topic area, and the need to provide decision-makers with timely results, a rapid scoping review was conducted in accordance with the WHO Rapid Review Guide and the JBI 2020 guide to scoping reviews (14, 15) and reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for scoping reviews. Scoping reviews help map the key concepts and underpin a field of research and clarify working definitions (16, 17).

Protocol

This review is registered with the Open Science Framework (https://osf.io/y8fdh/?view_only=1d943ec3ddbd4f5c8f6a9290eca2ece7).

Eligibility Criteria

The following PICOS (population, intervention, comparator, outcome, Study Design) eligibility criteria were developed a priori:

Population

Women HCWs. We define HCWs as "all people engaged in actions whose primary intent is to enhance health," (18). This encompasses a broad array of health workers, including doctors, nurses, pharmacists, midwives, paramedics, physical therapists, technicians, personnel support workers, and community

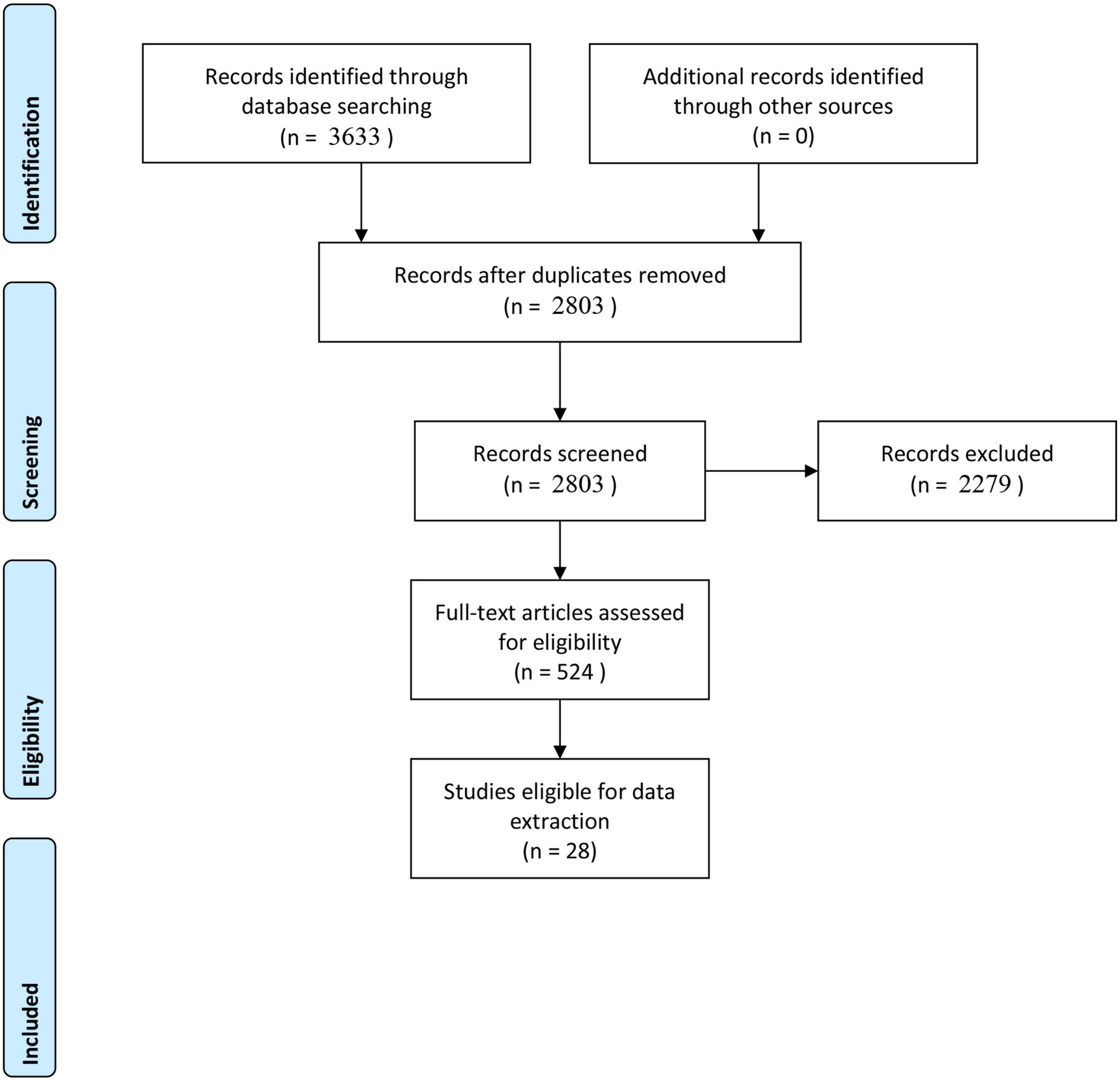

FIGURE 1 | PRISMA 2009 flow diagram.

health workers. We included studies that primarily focused on women.

Interventions

Our inclusion criteria were all studies (primary and review articles) that reported on the causes of stress, burnout, and depression in HCWs and/or reported programs to mitigate stress, burnout, and Depression in HCWs.

Comparators

Not applicable for the purpose of this scoping review.

Outcomes

We looked at following outcomes: stress, burnout, and depression. We define stress as the degree to which one feels overwhelmed and unable to cope as a result of unmanageable pressures (19). We define burnout as the experience of emotional exhaustion, depersonalization, or cynicism, along with feelings of diminished personal efficacy or accomplishment in the context of the work environment (20). We characterize depression according to a series of symptoms, including low mood, changes in appetite and sleep, difficulty concentrating, loss of interest/pleasure and thoughts of suicide that persist for at least 2 weeks (21).

Study Design

We included review articles and primary studies where data were collected and analyzed using quantitative, qualitative, and mixed methods (14). We excluded editorials and opinion pieces unless the authors shared their personal experiences.

Search Methods and Information Sources

We conducted comprehensive search strategies in the following electronic databases: Medline (via OVID), Embase (via Ovid), CINAHL (via EBSCOHost), PsycINFO (via Ovid), and ERIC (via ProQUEST). Search strategies were developed by an academic health sciences librarian (APA), with input from the research team. The search was original built in MEDLINE Ovid, and peer reviewed using the Peer Review of Electronic Search Strategies (PRESS) tool (22), before being translated into other databases using their command language if applicable. The Coronavirus (Covid-19) 2019-nCov expert search from Ovid MEDLINE was used and translated to other databases. Searches were limited to articles published until June 12th, 2020, and by English language. The final search results were exported into Covidence, a review management software, where duplicates were identified and removed.

Screening Process

To minimize selection bias, we piloted 20 articles against *a priori* inclusion and exclusion criteria. Each article title was reviewed by two independent screeners against using Covidence. A third reviewer reviewed conflicts and resolved disagreements through discussion. Two reviewers also independently screened the full text of potentially eligible articles to check whether the articles fulfilled the inclusion criteria.

Data Charting

We used a predefined data extraction form to extract data from the papers included in the review. To ensure the integrity of the assessment, we piloted the data extraction form on three studies. We extracted the following information from the studies: the first author, year of publication, HCWs enrolled in the study, geographic location, study methods, and intervention information that could help answer our objectives. Scoping reviews are conducted to provide an overview of the existing evidence regardless of methodological quality or risk of bias. As a standard, included sources of evidence are not critically appraised for scoping reviews (14, 15). In accordance with this we did not appraise quality or risk of bias of the included articles. Ethical approval was not required for this review.

Data Synthesis

Due to heterogeneity regarding outcome measurement and statistical analysis, data was descriptively synthesized.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study.

RESULTS

Search Results

The search resulted in a total of 3,633 records. After 830 duplicates were removed, 2,803 records remained to be screened. We excluded 2,279 records based on title and abstract screening. We assessed 524 full-text articles. Most of these articles are opinion pieces and commentaries. Twenty eight published studies met our inclusion criteria and were included in this review. **Figure 1** provides a summary of the PRISM flow diagram.

Characteristics of Studies

Our search identified 28 eligible studies; 26 of these studies focused on the prevalence of mental health issues in health care professionals (**Table 1**). Two studies were case studies (**Table 1**). Sixteen of the primary studies were conducted in China, whereas others were conducted in Saudi Arabia, Italy, Singapore, India, and Colombia. These studies primarily focused on doctors, nurses, and generalized groups of allied health professionals. One study focused on dentists, whereas another focused-on pharmacists. The study samples included both male and women health professionals. Only one study focused exclusively on women in health care (23). Anxiety, depression, stress/distress symptoms, post-traumatic stress disorder, and insomnia were commonly assessed mental health issues in these studies.

A variety of assessment tools were used to measure mental health in these studies. Common tools used to measure psychosocial well-being included DASS-21, Impact of Event Scale Revised Questionnaire (IES-R), Connor-Davidson Resilience Scale, Chinese Perceived Stress Scale, Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder (GAD-7) Scale, Questionnaire Star, Psychological Symptom Screening Test (SCL-90-R), Beck Anxiety Inventory and Short Psychiatric Rating Scale, Maslach Burnout Inventory-Medical Personnel, Perceived Stress Scale and Hospital Anxiety/Depression Scale, Post-traumatic Stress Disorder Checklist for DSM-5 and the Pittsburgh Sleep Quality Index, Stress Response Questionnaire, Zung Self-Rating Anxiety Scale SF-12, K6, Insomnia Severity Index, Self-Rating Depression Scale, and Simplified Coping Style Questionnaire.

Common Triggers of Stress, Burnout, and Depression Faced by Women in Health Care During the Coronavirus Pandemic

Common triggers of mental health issues were fears of getting infected with COVID-19 and putting family members at risk (24–26), as well as concerns about professional growth, difficulty meeting living expenses (27), and having family members with suspected and confirmed COVID-19 (23). Individual-, organizational-, and systems-level factors are reported as common triggers of stress, burnout, and depression in women HCWs.

Individual-Level Factors

Women HCWs are more likely than men HCWs to experience psychological stress and burnout (24, 28–36). More specifically, young women HCWs and mid-career women HCWs were more

TABLE 1 | Summary of primary studies.

Author	Study sample	Study type	Female	Doctors	Nurses	Other HCWs	Country
1. Al Sulais	529	Cross-sectional Survey (CSS)	Breakdown N.A	X	–	–	Saudi Arabia
2. Almagharabi	1,036	CSS					Saudi Arabia
3. Cai	534	CSS	367	X			China
4. Chew	906	CSS	Breakdown Not Available (N.A)	X	(N.A.)	(N.A.)	China
5. Chowdhury, S,M		Qualitative					
6. DeStefani	1,500		836	–	–	Dentists	Italy
7. Elbay	442	CSS	251	X	–	–	Turkey
8. Felice	388	CSS	235	X	–	X	Italy
9. Huang	600	CSS	305	X	X	X	China
10. Kang	994	CSS	850	X	X	–	China
11. Karasneh	486	CSS	382	–	–	X	Jordan
12. Khanna	2,355	CSS	1,332	X	–	–	India
13. Lai	1,257	CSS	964	X	X	–	China
14. Li	5,317	CSS	5,317	X	X	X	China
15. Liu	512	CSS	433	N.A.	N.A.	N.A.	China
16. Marton		Qualitative					
17. Pedrozo-Papa	179	CSS	Breakdown N.A	X	X	X	Columbia
18. Romero	1,671	CSS	Breakdown N.A	X	–	–	Spain
19. Song	14,825	CSS	9,536	X	X	–	China
20. Sun	442	CSS	368	X	X	X	China
21. Uzun	103	CSS	91	X	X	X	Turkey
22. Wu	190	CSS	157	–	X	X	China
23. Xiao	958	CSS	644	X	X	X	China
24. Yin	371	CSS	228	X	X	X	China
25. Yuan	939	CSS	582	X	–	X	China
26. Zhang	304	CSS	178	N.A.	N.A.	N.A.	China
27. Zhang	927	CSS	678	X	X	X	China
28. Zhu	165	CSS	137	X	X	–	China

likely to experience emotional and mental health issues due to COVID-19 (23, 29, 37). Similarly, less working experience and self-perception about lack of competency to care for COVID-19 patients was associated with increased prevalence of stress and burnout (29, 37). Women who are single or lacking social support are more at risk of developing symptoms of anxiety, stress and burnout (23, 29, 37–39). Women HCWs with medical or psychiatric comorbidities (23, 39) or increased alcohol use are at higher risk of mental health issues (37). Surprisingly, women HCWs who have more than two children experience higher prevalence of psychosocial well-being (29).

Organizational-Level Factors

Long working hours and increased workload (29, 37, 40); increased number of COVID-19 patients under their care (29, 41); lack of access to personal protective equipment (25, 26, 28, 30, 40, 42–44); lack of infection control guidelines and protocols (26, 29, 42, 45); lack of support and recognition by their peers, supervisors, and hospital leadership (26, 29); and work location (30, 43) are reported as common triggers of mental health issues related to the work environment.

Systems-Level Factors

Increased incidence of COVID-19 cases in the local area (26), changes in public health measures and guidelines (46), information shared in the media (47), and lack of recognition by the government officials and policy makers of HCWs' work conditions (26) are reported to increase stress and mental health issues among HCWs.

Interventions That Can Support the Well-Being of Women HCWs During a Pandemic

Very few studies have discussed potential interventions to support women in health care with COVID-19 related stress, anxiety, and mental health. Women with increased workloads preferred to use psychological support (40). Regular exercise is considered a protective factor for depression and anxiety (23). Time is considered a modifiable factor that improves anxiety level (32). Mental health services such as online resources, psychological assistance hotlines, and group activities for stress reduction are poorly utilized by HCWs (38). Online-push messages of mental health self-help and self-help books are mostly preferred by women HCWs (38). Measures to support HCWs financially (25), provision of rest areas for sleep and recovery (Yin, 29), care for basic physical needs such as food (38), training programs to improve resiliency (33), information on protective measures (38), and access to leisure activities (38) and counselors (38, 41) are considered potential strategies to support HCWs during a pandemic. However, these studies did not measure the impact of these interventions.

DISCUSSION

This review shows that individual characteristics such as sex (women), age (younger women), marital status (single women and women with young children), and career stage (less experience) have been contributing factors to occupational stress, burnout, and depression during COVID-19. The current literature lacks data on how socioeconomic, cultural, and ethnoracial differences influence occupational stress, burnout, and depression in women HCWs.

At the organizational level, lack of training, poor infection control guidelines, work conditions that include changing policies, higher workload, and inadequate access to personal protective equipment are contributing to occupational stress, burnout, and depression in women during COVID-19. The long-term effects of burnout during COVID-19 are unknown. General studies on burnout in HCWs has shown an association between burnout and poor career satisfaction, high absenteeism, career transitions, early retirements, and familial and marital stressors (48, 49).

This review shows there is relatively little empirical research into possible interventions to help support women HCWs during a pandemic. Interventions to reduce occupational stress and burnout among HCWs have primarily focused on providing mental health services such as online resources and psychological assistance hotlines, the effects of which have been mixed. This is consistent with findings from HCW burnout studies unrelated to COVID-19. There is a lack of understanding about the effects of organizational interventions such as workload policies and procedures; organizational support systems, such as employee assistance programs; coaching and resiliency and mindfulness training programs, such as reducing working hours; caseloads; and on-call procedures.

Virtually all empirical studies included in this review are epidemiological studies of occupational stress, burnout, and depression. However, there was a significant variability in the tools used to measure stress, burnout, and depression. Further, the current literature has emerged from limited geographical regions. It is unclear how variations in health care and organizational and cultural contexts will shape the outcomes of similar studies carried out across a broader geographic area. During the search and screening, we specifically focused on including articles focused on female health workers or articles that included both genders. We noticed, often the gender-based analysis was clearly articulated in several publications.

This review covers limited empirical and review studies published on the topic of stress, burnout and health care workers from the start of COVID-19 until June 2020. As a scoping review, we were able to map the emerging concepts that underpin occupation stress and wellness for health care women during the COVID-19 pandemic. We expect to see an increased number of publications concerning COVID-19's impact on health professionals will emerge in the next 6 months. We have registered a rapid review protocol in the International Prospective Register of Systematic Reviews (PROSPERO CRD42020189750) to systematically examine the emerging evidence on occupational stress, burnout, and depression in HCWs during the COVID-19 pandemic.

CONCLUSIONS

Women HCWs are at increased risk for occupational stress, burnout, and depression during the COVID-19 pandemic because of a combination of personal and organizational factors. However, there is a significant gap in the evidence base as to what interventions can help address these issues. We recommend that health-system decision-makers, hospitals, and professional organizations support research that measures the long-term impact of COVID-19 on women in health care and outcome studies that measure the impact of various mental health interventions and resources supporting women in health care. Given the complex nature of these interventions, we urge future researchers to provide the contexts in which the interventions were implemented and the mechanisms that shape successful interventions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AS, SR, AT, and DL conceptualized and designed the review. AS, AA, HP, and DDL reviewed titles, abstracts, and full-text papers for eligibility. AS, HP, and DDL were responsible for extracting data and all data extraction was verified by AS. AS prepared the initial draft manuscript. SR, AT, and DL reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2020.596690/full#supplementary-material

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COVID-19 Effect on Access to Maternal Health Services in Kenya

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Introduction: Maternal mortality continues to be one of the biggest challenges of the health system in Kenya. Informal settlements in Kenya have been known to have higher rates of maternal mortality and also receive maternity services of varied quality. Data assessing progress on key maternal health indicators within informal settlements are also often scarce. The COVID-19 pandemic hit Kenya in March this year and so far, the impact of the pandemic on access to maternal health has not been established. This study aims to add to the body of knowledge by investigating the effects of the COVID-19 pandemic and mitigation strategies on access to health care services in informal settlements.

Methods: Qualitative methods using in-depth interviews were used to assess women's experiences of maternity care during the COVID-19 era and the impact of proposed mitigation strategies such as the lockdown and the curfew. Other aspects of the maternity experience such as women's knowledge of COVID-19, their perceived risk of infection, access to health facilities, perceived quality of care were assessed. Challenges that women facing as a result of the lockdown and curfew with respect to maternal health access and quality were also assessed.

Results: Our findings illustrate that there was a high awareness of the symptoms and preventative measures for COVID-19 amongst women in informal settlements. Our findings also show that women's perception of risk to themselves was high, whereas risk to family and friends, and in their neighborhood was perceived as low. Less than half of women reported reduced access due to fear of contracting Coronavirus, Deprioritization of health services, economic constraints, and psychosocial effects were reported due to the imposed lockdown and curfew. Most respondents perceived improvements in quality of care due to short-waiting times, hygiene measures, and responsive health personnel. However, this was only reported for the outpatient services and not in-patient services.

Conclusion: The most important recommendation was for the Government to provide food followed by financial support and other basic amenities. This has implications for the Government's mitigation measures that are focused on public health measures and lack social safety-net approaches for the most vulnerable communities.

Keywords: COVID-19, informal settlements, Kenya, women, maternity services, access

INTRODUCTION

The Novel Coronavirus disease, commonly referred as COVID-19, was declared a public health emergency of international concern on 30th January 2020 and declared a global pandemic on the 11th March 2020 (1). Previous research has indicated that pandemics, such as Ebola in West Africa, can devastate the provision of maternal health services in low-resilience health systems (2–4). A study modeling the coverage of essential maternal and child health interventions estimated a 8.3–38.6% increase in maternal deaths per month across 118 low- and middle-income countries (LMICs) during the COVID-19 pandemic (5). The COVID-19 pandemic reached Kenya on March 15, 2020. Currently (as per 25th August 2020) the number of cases in Kenya is estimated at 32,577 infections, with 18,895 recoveries and 554 deaths (6). Nairobi City in Kenya is estimated to have the highest the number of COVID infections in the country with at 342 as per July 2020 with ∼30% of new infections in peri-urban settings (7). It is estimated that about 70% of Nairobi's more than 4 million residents reside in urban slums (8–10).

As a preventive response, Kenya imposed strict curfews and lockdown rules to prevent the spread of COVID-19. The Kenyan Government banned international flights, closed schools, and banned large social gatherings; mass prayer gatherings, large weddings and funerals, in order to prevent the accelerated transmission of the virus (11). In addition to this, the Government issued a 30-day lock down as a mitigation measure to COVID-19 transmission. This was accompanied by a curfew that was initially restricted movement between 7.00 p.m. and 4.00 a.m. but was subsequently extended to 9.00 p.m. to 5.00 a.m. These government directives pose a huge dilemma, as they have disrupted access to health services by mothers (12). Despite the fact that expectant mothers have been allowed to leave their houses and go to health facilities to access delivery care during emergencies. They have however had challenges with transportation to health facilities during the curfew. These restrictions may disproportionately affect those living in informal settlements within large cities. Recent evidence has shown that women face access challenges that are both structural, such as transportation to health facilities, and social, such as fear of health care workers (13). These settings also have already existing challenges with regard to the quality of maternal health care services and women report receiving maternal health services of varied quality (13).

Studies that have focused in informal settlements have assessed residents' perceptions of government directives to contain the pandemic and concluded that the Government measures to mitigate COVID-19 need to have communication channels that are targeted at reaching less-educated households (14). Other studies have shown that although COVID-19 mitigation strategies are needed, they are known to have an indirect negative impact on women's well-being, for example many hospitals have put restrictions on visits by partners and relatives during admission at the hospitals for delivery (15). This is despite the fact that women are normally denied companionship during delivery in most hospitals due to privacy concerns (16). The COVID period presents new challenges for women with the lockdowns and curfews instilling fear and necessitating the need for birth companionship. Lockdowns have also result in varied economic consequences such as job loss, food and housing insecurity further aggravating health outcomes (17, 18). It is possible that within informal settlements the impact of the job losses might indirectly affect women's ability to access health care due to economic hardship, subsequently reducing access to health facilities.

A review of the existing literature demonstrates an information gap on the impact of pandemic on maternal well-being especially in a resource-scarce setting where marginalized women often receive poor quality of care (19, 20). A population survey in 60 LMICs suggest a declining trend on utilization of maternal and child health (MCH) services such as delivery, antenatal care (ANC) attendance and child immunization (21). Studies have established that health workers in other sub-Saharan African settings are not well-prepared to provide treatment for COVID patients and insufficiently prepared to meet the demands of the women (22). These limitations may have serious implications for women's health. For example, a recent study modeling the coverage of essential maternal and child health interventions estimated a 8.3–38.6% increase in maternal deaths per month across 118 low- and middle-income countries (LMICs) during the COVID-19 pandemic (5).

This study aimed to assess the extent of the impact of the imposed lockdowns and curfew on access to maternal health services for women living in informal settlements. We also assessed women's knowledge of the signs and symptoms of COVID-19, women's perceived risk of infection to further understand how the virus affects women and their health during the pandemic. These findings provide a critical information for frontline health workers and policy makers who are seeking to quickly develop pandemic responsive programs and strategies that are relevant, person-centered and context friendly. By incorporating women's voices, Ministries of Health and other non-state health care providers can be better able conduct targeted care and minimize the negative consequences of COVID-19.

METHODS

Study Setting

This qualitative study focused on women's experiences with person-centered maternity care amongst women living in the informal settlements in the Embakasi area in Nairobi City, Kenya. The study area has an estimated population of almost one million people, in mostly low-income housing and informal settlements. Residents in Embakasi experience widespread poverty and high unemployment and belong to the lowest wealth quintile in Kenya. The health system consists of both primary public health centers and several private health facilities and mission health facilities. The main referral health facility is a secondary maternity hospital.

Data Collection

Study Design, Recruitment, and Participants

Participants were drawn from an ongoing longitudinal study focused on assesses quality of maternal care services in the Embakasi region of Nairobi, capital of Kenya. For the current study, a subsample of women was selected to completed telephonic interviews (71), which were conducted by four researchers in the months May-June 2020 with women who had received services for childbirth in the past 6 weeks from public, private and missionary hospitals in this region.

The first author is a trained public health specialist and the research assistants were trained on qualitative research methods. The facilities were purposively selected to represent both health centers and secondary maternities. They also represented three types of health facilities present in Kenya: public, private, and mission health facilities. The health facilities in the study were chosen in collaboration with the first author.

Women were recruited during child welfare clinics. The inclusion criteria were women who were aged between 18 and 49 and had delivered their babies within the identified facilities in the past 6 weeks. Verbal informed consent was obtained from all the women after providing information about the study and the potential benefits and risks of their involvement in the study via a phone call. The interviews were conducted by phone to mitigate the risk to participants due to COVID-19. During the phone interviews women were asked whether they had been to the health facility during the COVID-19 pandemic and to share their experiences during this time. A semi-structured interview guide was used (See **Appendix 1**). Interviews were conducted in Kiswahili, a language commonly spoken by women in this setting. The discussions were recorded and transcribed verbatim in Kiswahili. The transcripts were then, translated into English by the sixth author (CM) who is a native speaker of Kiswahili. The transcripts were back translated from Kiswahili to English by the first author also a native speaker of Kiswahili to ensure that the meaning was maintained. A total of 82 women who met the criteria were approached via phone calls. Nine of them were in an area with very poor mobile phone connectivity. Two women were unavailable. Therefore only 71 interviews were conducted. Ethical review approval from Strathmore University IRB, University of Notre Dame IRB and permission to conduct the research from The National Commission on Science Technology and Innovation (NACOSTI).

TABLE 1 | Sociodemographic characteristics of the participants.

Participant characteristics	Percentage $N = 71$
Age (Mean)	28 (5.3)
Parity	
Primiparous	16 (23%)
Multiparous	55 (77%)
Marital Status	
Married	61 (86%)
Single	10 (14%)
Education	
Primary	18 (25%)
Secondary	43 (61%)
College	10 (14%)
Occupation	
Employed	10 (14%)
Unemployed	61 (86%)
Type of health facility	
Mission health facility	29 (41%)
Public health facility	25 (53%)
Private health facility	17 (24%)
Delivery history	
All deliveries in a health facility	61 (86%)
At least one delivery outside health facility	10 (14%)

Data Analysis

We read all the transcripts to gain familiarization with the data. We iteratively coded line-by-line across the entire data set. We then analyzed the data applying emerging codes. We then compared these codes to those in the coding framework that we established a priori from the interview guide. We followed Braun and Clark's (23) thematic analysis to analyze the data. We grouped codes into categories, reviewed the themes for patterns, defined the themes. Four coders compared the themes and discussed the themes. We reviewed transcripts and analyzed the data until we reached data saturation and we could not identify any new themes. An Additional **Appendix 2** to show how open codes were used to generate categories and themes.

RESULTS

The characteristics of the women respondents are contained in **Table 1** below.

The mean age of the women was 28 years. Seventy seven percentage of the women were multiparous with a majority (88%) of the women were married. A vast majority of the women were unemployed (86%). The rest of the characteristics are contained in **Table 1**. We identified four main themes in the data: (1) Awareness and risk perception on COVID-19. In this theme we discuss women's ability to identify at least three symptoms of COVID-19, key prevention measures as well as their perceived risk of infection (2) perceived quality of health services. This theme describes our findings regarding women's perceived changes in the quality of maternal health services during the COVID-19 pandemic. (3) Economic challenges. This theme identifies women's several accounts of economic struggles where they describe their experiences with loss of income generation and this resulting in their in ability to afford transportation to the health facility and (4) mitigation strategies. This theme identifies strategies that women used to try and mitigate the impacts of the COVID-19 pandemic that would allow them to increase access to health facilities.

Awareness and Risk Perception on COVID-19

Most of the respondents with about 60% had a high awareness of the key symptoms and preventative measures employed to reduce the spread of the COVID-19. They were able to mention key symptoms such as high body temperature, persistent cough, and fever. Most women were aware of preventative measures including frequent washing of hands, sanitizing, wearing face masks and maintaining social distance.

> *"...The symptoms include: fever, severe coughing and also an increase in the body temperature. I know it is a dangerous disease whose preventive measures include: frequent washing of hands, sanitizing, wearing face masks and maintaining social distance of one meter away when interacting with other people..." (Respondent #44)*

Perceived Risk of Contracting COVID-19

Respondents were asked about their risk of contracting COVID-19 to self, family and friends and their neighborhood. A majority of the women—∼56% of those women interviewed—perceived a high risk of the virus to their health. They viewed it as serious and anticipated getting infected if they left their residence. They undertook the necessary precautions to prevent infection such as using sanitizer and washing their hands regularly and wearing face masks. They also reported practicing social distancing.

> *"...From my perception I think this Corona issue is serious and that's why I have sanitizer in my house, washing my hands and I ensure I wear a mask whenever I leave the house..." (Respondent #38)*

> *"...According to me it is serious. I don't leave the house to go anywhere, because if I go out, I might meet anyone and contract the disease and infect my baby. So, I just sit in the house and take care of the baby, maybe I send someone to get me something..." (Respondent #40)*

In extreme cases women, were aware that the COVID-19 carried a risk of mortality if precautions were not taken and one was in a crowded setting.

> *"...Coronavirus can cause death if you do not take care of yourself. If you do not take preventative measures when you leave home or are in a crowded place, you can easily get coronavirus..." (Respondent #16)*

On the other hand, a majority of women perceived a low threat of infection to friends and family with 68% mentioned that they perceived their friends and family at a low risk of getting infected by COVID-19. They attributed this to their friends and family being careful and following Government measures to contain the virus.

> *"...If you look at my friends, they are really careful. They are trying their best to follow all the rules put in place so that they do not get sick. Then if you look at my family, they are also careful. I do not think anyone will get it unless...for this person who is always going out. But so far I feel they are all being careful and following the rules..." (Respondent#36)*

They described them as taking precautions such as handwashing, sanitizing and wearing of masks when out in the public. These measures led them to believe that most of their friends and family were at a low risk of infection

> *"...I don't think they might get infected because I have seen the way they take steps and precautions to prevent that. They wash their hands and sanitize regularly and they also take their clothes off whenever they come from out. So, I cannot say they can get the disease because all of them have masks ..." (Respondent #40)*

Almost half of the women perceived a low threat of infection with the virus within their residences. They attribute this low perceived threat to not knowing anyone who had contracted the virus in their neighborhood

> *"... I have heard that this disease is killing a lot of people, but I have not heard about anybody contracting this disease in my area." (Respondent #16)*
> *I don't think it is that serious because so far, I haven't heard of any coronavirus confirmed cases here at our place and the residents are observing all the preventive measures put in place by the government through the Ministry of health. (Respondent #43)*

Perceived Quality of Health Services

The respondents reported varying levels of perceived change in access and quality of services provided as a result of measures put in place due to COVID-19. About half of the women (51%) indicated that they were accessing health services normally and would continue to go to the health facility despite the risk of exposure to the virus.

> *"...I haven't changed the way I access the health care services. I'm just going the way I used to, and also as instructed by the nurse in charge of my baby, although I am fearful and worried of who I might meet at the health facility..." (Respondent# 23)*

Respondents perceived quality of care to have improved due to hygiene, caution, attentiveness, privacy, low patient-load, restricted movements, increased numbers of nurses, and shorter turn-around time for patient attendance.

> *"...I will say that the quality of service delivered has changed for the better because the Health workers are more vigilant when attending to the patients unlike before when they weren't that*

much cautious such as observing good hygiene all the time..." (Respondent #41) "...I will also say that the social distancing rule put in place whereby each patient is attended to one by one has made the patients to be more free to the doctors and tell them what they are really undergoing through because in the past, patients could be congested in one room and make the other patient fear to speak up what he or she is going through..." (Respondent #44)

The change in the health facility culture was perceived to be contributing to improved quality of care. There was an observed change in how COVID-19 preventative measures were enforced by the security at the entrance of the health facility as well as by health workers such as doctors and nurses.

"...I will say that the quality of service has changed for the better because even the watch man and every health worker is observing all the hygienic measures put in place thus the patients feel safer ... they wear masks, protective clothes which they were not using before" (Respondent #45)

"...Yes there has been a change in the quality of service e delivered because the health workers are more cautious when handling patients and also the patients are attended to one by one unlike before where three patients could congest in one room....and the way they handle patients is totally different because they handle shifts to prevent overcrowding" (Respondent #46)

Although most facilities were strict in enforcing the COVID-19 mitigation measures, some respondents reported that experiences at the health facilities they attended as not taking seriously the mitigation measures against COVID-19

"...they just kept telling us to have our masks on, but it was not that serious. They were not taking this Corona thing seriously. But in facility X you always had to have your mask on. For me I did not see anything different in the facility Y...." (Respondent #36)

Perceptions of time taken at the facility were mixed. Women described health services that were delivered efficiently at times, and slower health services at other times. Less time was attributed to fewer patients as well as hastened health services.

"...when I left my home for the hospital, the services were quicker than before because during this COVID-19 period there were fewer patients at the health facility.... the duration taken in the facility was very little and the nurses were fast in their services..." (Respondent #19)

Although most respondents seemed pleased with the change in the quality of services, some mentioned changes to routine prenatal services. One woman who had taken her baby for immunization witnessed other women who had taken their babies for growth monitoring been turned away by the health care workers. She overheard them been informed that it was unnecessary during the COVID-19 times.

"... I visited the hospital when I took my baby for immunization; at the hospital I observed mothers whose babies were to be weighed were turned back by the nurses who said it is not necessary at this time of COVID-19 they were avoiding crowds..." (Respondent #15)

Other women also described been turned back because of the large number of people being served

"...It is because sometimes you can't come there at the hospital because you will not even be served. You see people are many so you go and you are told to go and come back some other day..." (Respondent #41)

On the other hand, COVID-19 transmission mitigation strategies such as mandatory temperature checks and sanitization at every station were perceived to increase time spent at the facility. The respondents attributed the long waiting time due to health personnel constantly changing their protective gears.

".... Before we just used to enter, they write something for you, you go somewhere else but now you see you must be tested first then you go sanitize before you now go inside the hospital..." (Respondent #24)

Although COVID-19 mitigation strategies had led to perceived improvements in quality at the outpatient department, the inpatient services seemed to have remained the same. There were also incidences of slower services and overcrowding public maternity hospital wards.

"...That one was tough, because there were many people. When I went to the ward, if any one of us in there would have been having corona, all of us would have contracted it. One bed three people, there's no space to turn, that was a challenge, because those giving birth were many, those undergoing CS were many. There was nowhere to rest, you are just told to go to room three. where you ask for some space on a bed to put your baby, then you can sit on the bench after undergoing the CS. It was quite a challenge...." (Respondent #40)

Fear of Infection With COVID-19

While nearly half reported that they were able to access the health facilities, slightly less than half (40%) were hesitant to visit health facilities due to fear, they indicated that their main reason for not going into a health facility was fear. They described uncertainty regarding meeting people with COVID-19 at the health facility and risking exposure to the virus.

"...I'm going less times compared to non-COVID-19 times. First of all it is because of fear, I'm worried that maybe if I go to the Hospital more often I may get exposed to the people who are infected with coronavirus and unluckily I get infected with the disease too..I am also afraid of exposing my child to the Corona virus when I frequently visit the hospital..." (Respondent #43)

They further expressed fear of contracting COVID- 19 from health care workers who were regularly being exposed and risked infecting them.

"... I will be afraid because I don't know if the nurse or the doctor, I find at the facility has the disease. So, I will be afraid..." (Respondent #2)

This fear of the health facility resulted into some women foregoing scheduled visits to the health facility

"...It has reduced. I go a few times now. I cannot say it is because of money for me. It is just because I fear to get this disease. It is not easy for me to go to hospital because I fear. I would just stay in the house and wait to feel better. I would just take medicine until I feel better... " (Respondent #36)

Some respondents also feared to be deemed to be COVID positive if captured by the temperature screening processes that could find their temperature to be high.

"...You know right now, you do not even want to go to hospital, even when the baby is sick you become scared. You see how they say when you have corona your temperature is high; they might say that you have corona ... " (Respondent #36)

Some of the mitigation measures put in place for COVID-19 were reported to instill fear among community members and the employers of casual laborers which could easily resort to stigma. This stigma resulted into unemployment for some people.

"...Keeping distance has also made people fear each other......employers are afraid that you might infect them with COVID-19." (Respondent #33)

Economic and Food Security Challenges

Some women identified economic reasons for not accessing health services. They said that they were unemployed and loss their sources of income and lacked money for transportation to health facilities. They therefore prioritized essential provisions such as purchasing food over going to the health facility.

".... As a result of COVID 19. I don't have a job, so the little that we get we prioritize for food then health will come after." (Respondent #43)

For those who had some money to purchase food items, they found them to be very expensive because the supply was low.

".... you will go to the shop especially to the groceries and they tell you this curfew and lockdown has affected the supply chain and food stuffs are overpriced... " (Respondent #6)

Reports of food insecurity were also reported as a result of loss of income.

"...So, there is low income.... sometimes we don't consume the way we used to, we have to minimize the expenditure on the house, food, getting food and something to eat is a challenge ... " (Respondent #6)

The lockdown together with the curfew that was initially put at 7.00 p.m. affected businesses with most of them closing as early as 5.00 p.m. This resulted in a significant loss of gainful income.

"...Things have become difficult... because going for stuff to come and sell is an issue. I have been staying in the house, I have spent all the money, it is over. If it is time to close work, I have told you I just sell vegetables so these hours of leaving have become stressful. You must close early before 7.00 p.m. Things have become difficult now... " (Respondent #22)

These difficult economic situations resulted in challenges with psychosocial well-being.

"...Stress, stress is there because of these lockdowns because business is not there and there is no money and you see I now have 4 children... " (Respondent #5)
"...Am stressed with the children, I am the one is blamed by my husband if anything goes wrong in the house, I am also stressed when my baby doesn't get enough milk to breastfeed, all this is happening because of the lockdown and curfew... "

Children being at home was mentioned as a challenge.

"... the challenge that I face is that all my children are back at home and none of them is in school... " (Respondent #62)

The Government initiated curfews to reinforce social distancing not only constrained access to health care services but also led women to attend health facilities unaccompanied. Reports of support companions being denied entry at the health facilities when women sought delivery services.

"...when my labor started, I went to the hospital x with my cousin and neighbor but could not be allowed in. Unfortunately, this was way past curfew hours (7 pm). However, they couldn't go back to the home and had to stay at the hospital. I had to pretend that I couldn't walk so that the watchman could allow them to help me walk back to the hospital building. After I went inside the maternity they were not allowed inside." (Respondent #40)

Coping With the Challenges Brought About COVID-19

Following the challenges described above, several coping strategies were reported by the respondents. Most of the strategies came from non-governmental organizations and the local administration to cope with loss of livelihood. Non-governmental organizations commenced food distribution to the affected families. In one of the settlements, respondents reported receiving food rations twice a week.

"...There were people getting aid at the centre A. They were receiving assorted food items. So, for someone like me with a child and I have a very big demand, I queue and then get some food stuff. They come twice a week... " (Respondent #66)

Other non-governmental organizations distributed items such as soap and money

"...one day we were given a bar of soap with an organization called H"... "I have received a little support in terms of funds and am so thankful for that." (Respondent # 035)

Some respondents however mentioned favoritism in food distribution, citing a lack of transparency and clear criteria.

"...Have not seen anything or maybe it's given and am not aware because I hear from people food is distributed at night to those who are known to the people concerned... " (Respondent # 62)

However, the support received from the local administration fell below community members' expectations. They expected economic support, but the support they received was often advisory and related to COVID-19 containment measures. The area administration and landlords were reported to have teamed up to enforce curfew measures.

> *"...The Member of County Assembly (MCA), and the Chief, even the landlords have also helped when it came to warning and enforcing the restrictions. He used to call and warn people about letting strangers in and encouraging people to report anyone who does it…they should give food to people like us who can't go to work because I wash clothes for people but now, they can't allow us in the house. Food is very expensive at the moment people are taking advantage by adding the prices of items. Because you know food is the reason you will go get infected with these diseases because you are going look for food." (Respondent #24)*

Recommendations by Women to the Government

Our respondents were mostly concerned about food, basic supplies, rent. and financial assistance. They made no recommendations regarding their access to health services. The most important recommendation was for the Government to provide food with one third of the women recommending this. They suggested that the Government should support families economically by providing food items so that people don't have to go look for work and thus endanger their families.

> *"… providing essential needs such as food...talking to the landlords at least yeah the rent issue is also a problem for so many of us… If they can get someone to help us with pads because there are no pads." (Respondent # 6)*

In addition, some saw the role of the Government as going beyond food items to encompass provision of hand sanitizers and masks; as well as ensuring that families were not evicted from their houses due to lack of rent.

> *"...The government should buy for people mask and sanitizer, there is no money paying for house rent is a problem the government should talk to the owners of the house to make them understand what people are going through, those people who work their time is limited because of curfew…" (Respondent # 65)*

DISCUSSION

Our study sought to explore the maternity experiences women residing in informal settlements during the COVID-19 pandemic. Specifically, we assessed women's knowledge of COVID-19, their perceived risk of infection, access to health facilities, perceived quality of care and challenges experienced as a result of the COVID-19 pandemic mitigation measures. Overall, the findings revealed important effects of the pandemic on maternity care and access, suggesting some improvements in quality of care as well as some continued challenges with access and quality that were further exacerbated by the pandemic. In addition to their reflections on maternity care, specifically, women also commonly reported more general concerns and economic stressors about the effects of the pandemic that have important implications for how multisystemic supports might be put into place to support perinatal women.

The findings revealed that women continued to access health facilities and would continue to do so despite the perceived risks of infection by COVID-19. Less than half of women reported reduced access due to fear of contracting the coronavirus, deprioritization of health services, economic constraints, psychosocial effects due to the imposed lockdown and curfews. Some of the reduced access was due to new hospital policies that restricted women's entry to the health facility. These changes resulted in hospital policies that dictated for certain routine services such as growth monitoring were unimportant during this time due to the risk of contracting COVID-19. Other restrictions included prohibition of friends and family accompanying women to the health facility at a time when they were needed most by the women. Jolivet et al. (24) emphasizes that respectful care and human rights need to be upheld even at times of a pandemic such as the COVID-19. They call for the use of ethical guidelines in access to proven practices during maternity care.

Most of the respondents perceived improvements in quality of care due to short-waiting times, hygiene measures and responsive health personnel. However, this was only reported for the outpatient services as some in-patient services remained overcrowded. While the Government measures to contain COVID-19 were lauded and appreciated by all, there were several effects; some were unintended. This includes fear of exposure to the virus, economic constraints and effects on psychosocial well-being. While nearly half reported that they were able to access the health facilities, slightly less than half (40%) were hesitant to visit health facilities due to fear, stigma, and reported lack of proper COVID-19 preventive measures at the facilities. This is in line with findings of a study in West Africa conducted during the Ebola outbreak that illustrated that the outbreak disrupted services and fear of seeking treatment (2). There were reports of overcrowding especially in the inpatient department and most mothers were scared due to lack of physical distancing which is one of the measures for preventing COVID-19 infections

Women's positive response to the increased attention and privacy their received during care highlight that the COVID pandemic mitigation measures at health facilities might have led to better experiences of patient centered maternity care and dignified care particularly during outpatient care. Studies focused on women experiences during facility-based delivery highlight High quality patient centered maternity care as represented by dignified care including privacy (25).

Our findings also illustrate that awareness of the symptoms and preventative measures for COVID-19 was high. These findings are consistent with a study by the Population Council to assess COVID-19 knowledge attitude and practices in informal settlement in Nairobi showed that knowledge on COVID-19 symptoms was high and respondents could name several preventative methods (14). Our findings however differ from other studies conducted by White Ribbon Alliance (WRA) in selected counties in Kenya between April and May 2020 to determine the impact of COVID-19 on reproductive, maternal, and newborn health services. Whereas our study reported high levels of knowledge on COVID-19, this study found out that many citizens who live in slums in other parts of Kenya, did not know about the curfew. This was attributed to women lacking phones or radios, and the fact that information takes time to disseminate particularly in rural areas. This might also possibly be due to the changing demographics that indicate that women in informal settings are increasingly younger and possess secondary education (26). Our study was also conducted 2 months later which could possibly explain the learning curve. Findings show that women's perception of risk to themselves was high, but that perception of risk to family and friends, and in their neighborhood was low.

A majority of the participants had lost their jobs and their source of livelihoods and were struggling with access to income. Consequently, there were reports of lack of food, lack of rent and stress. To cope with these challenges, some women reported receiving support from the non-governmental organizations as well as government local administration. However, they reported that government support was focused on enforcing COVID-19 preventative measures while women's priority was food and rent. Our findings conform with other studies that have been conducted during the COVID-pandemic that indicate that effects of the lockdown have been primarily economic (14). In the case of women's access to maternity services, the primary access difficulty may therefore be women's in ability to pay for costs associated with accessing health care, despite its ongoing availability and women's overall willingness to use it. Evidence from the Ebola virus outbreak in 2013–2016 in Western Africa shows the negative indirect effects that such crises can have on sexual and reproductive health (2).

A major cross cutting issue from our study was stress related to the loss of livelihoods and severe economic constraints. Women reported being stressed due to unemployment, food security, rent, and sudden school closures. This economic hardship led to some women reducing their access to health care by prioritizing their finances to basic provisions as opposed to using it for transportation costs to the health facility thus reducing access to health services overall. We recommend that state and non-state actors should focus efforts on the impacts of income loss and food security, with special attention to women. This can be achieved by ensuring that those most at need of assistance are the ones receiving it by considering that assistance is getting into the hands of women given their increased experience of social and economic impacts.

A major limitation of the study was that the first lock-down which had restrictions on movement after 7 p.m. and before 4.00 a.m. greatly limited travel. The only plausible means to communicate effectively with the women was via mobile phones. The penetration of mobile phones is reasonably high within the urban slums of Nairobi. However, this might have limited the population we interviewed to women who are slightly economically stronger because of the ability to afford and use a mobile phone.

CONCLUSION

It is likely that despite the best efforts of health professionals, that an upward surge in the numbers of COVID-19 related deaths in women of reproductive age, including pregnant and post-natal women, will take place. It is crucial, however, to continue every effort as a vital contribution to safe childbirth and high-quality maternal care, and to continue to work toward the achievement of sustainable development goals. Although the Kenyan Ministry of Health (MOH) launched a COVID-19 Taskforce to steer the country's prevention, containment and mitigation measures, there is need to include additional measures to prevent the devastating health, social and economic impact of a COVID-19 outbreak particularly among women living in informal settlements.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Strathmore University IRB Ethics Committe. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JO-A, LM-G, and RD conceptualized the study. JO-A, TC, CM, and MN analysed the data. JO-A, TC, and MN wrote the manuscript. JO, DG, and LM-G provided critical feedback to the manuscript. All authors read and approved the manuscript prior to publication.

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SUPPLEMENTARY MATERIAL

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Women's Mental Health in the Time of Covid-19 Pandemic

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Even if the fatality rate has been twice higher for men than for women, the Covid-19 pandemic has affected women more than men, both as frontline workers and at home. The aim of our article was to analyze the differences observed in mental health and violence between men and women in the COVID outbreak. For this purpose, we have used all papers available in PubMed between January and July 2020 as well as data from non-governmental associations. We have thus successively analyzed the situation of pregnancy during the pandemic; the specific psychological and psychiatric risks faced by women both as patients and as workers in the health sector, the increased risk of violence against women at home and at workplace and, finally the risk run by children within their families. In conclusion, research on the subject of mental health issues during the Covid-19 pandemic is still scarce, especially in women. We hope that this pandemic will help to recognize the major role of women at home and at the workplace.

Keywords: domestic violence, gender, women, mental health, Covid-19, pregnancy, pandemic

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INTRODUCTION

The Covid-19 outbreak is the most severe pandemic since the H1N1 influenza (Spanish flu) pandemic that occurred in 1918.

In Western Europe, men represented a slight majority of coronavirus cases (52–58%) but around 70% of coronavirus deaths. In contrast, in South Korea, men represented less cases of coronavirus cases (40%) but still a slight majority of coronavirus deaths (around 52%). The largest proportion of deaths (male-to-female ratio) in confirmed cases was observed in Myanmar, Thailand, Albania and Wales (ratios > 2) (September 2020) (https://globalhealth5050.org/the-sex-gender-and-covid-19-project/). The highest death ratio reported in men may be partly explained by pre-existing cardio-vascular or metabolic diseases, as well as a higher prevalence of at-risk behaviors such as alcohol abuse or tobacco smoking. Interestingly, according to Johnson et al. (1), women seem more likely to follow hand hygiene practices, which may decrease the infectious risk. In addition, sex chromosomes, sex hormones may contribute to the differences observed between males and females in the immune responses (2).

Yet, Covid-19 pandemic has affected women more profoundly than men in several areas, both at workplace (especially in the health and social sector), and at home with an increased workload due to lockdown and quarantine measures. Worldwide, 70 percent of the health workforce is made up of women who are often frontline health workers (nurses, midwives and community health workers). Similarly, most of health facility service-staff (cleaners, laundry, catering) is made up of women (3). In the US, women hold 78 percent of all hospital jobs, 70 percent of pharmacy jobs and 51 percent of grocery store roles (4). Consequently, women are more likely to be exposed to the virus (5). In Italy and Spain, 66 and 72% of health workers infected were female as compared with 34 and 28% of males respectively (3).

Many countries have reported an increase in domestic violence cases after the viral outbreak (6). Asking for more support with domestic burden can trigger domestic violence against women. In countries where lockdown is observed, home is unfortunately not always a safe space. The exacerbation of gender-based violence may not receive the attention needed in the context of the pandemic. Past experience from the Ebola and Zika epidemics have already shown that these crises have increased existing inequalities including those based on gender and economic status (UN issue-brief-covid-19-and-ending-violence-against-women-and-girls-en).

A lack of adequate domestic and emotional support can have consequences on women's mental health. The risk of anxiety, depression and post-traumatic stress disorder (PTSD) is also much higher in women (7, 8).

According to Mrs Phumzile Mlambo-Ngcuka, Executive director of United Nations (UN) Women: Covid-19 pandemic is not just a health issue, it is a profound shock to our societies exposing the deficiencies of public and private arrangements that currently function only if women play multiple and underpaid roles. This is a moment for governments to recognize both the enormity of the contribution women make and the precarity of so many (3).

The aim of this review was to analyze the differences observed in mental health and violence between men and women in the COVID outbreak. For this purpose we have used all papers available in PubMed between January and July 2020, using the following keywords: women, gender, pregnancy, domestic violence, mental health, pandemic and COVID-19; as well as data from non-governmental associations. The search was restricted to manuscripts written in English language and published in peer-reviewed journals. We have thus successively analyzed the situation of pregnancy during the pandemic; the specific psychological and psychiatric risks faced by women both as patients and as workers in the health sector, the increased risk of violence against women at home and at workplace and, finally the risk run by children within their families.

THE SPECIFIC SITUATION OF PREGNANCY DURING THE PANDEMIC

Infectious Risk

Several papers have reported a high rate of maternal and neonatal complications in COVID-19 positive pregnant women [(9, 10); for review see (11)]. According to a retrospective study conducted in the US by Lokken et al. (12), of 46 pregnant women SARS-CoV-2 positive nearly 15% developed severe Covid-19, which occurred primarily in overweight women with comorbid somatic disorders. However, the increased risk of having more severe COVID-19 disease during pregnancy, was not observed by Chen et al. (13).

COVID-19 was associated with a high rate of miscarriage, preterm birth, pre-eclampsia, cesarean (for unknow reasons), and perinatal death (14). However, Baud et al. (15) did not confirm the higher risk of miscarriage. A relatively high proportion of pregnant women (13.0%) were admitted to the intensive care unit, but no deaths were reported [(11): review of 13 Chinese studies]. In contrast, a study conducted on 116 Chinese pregnant women reported that no increased risk of spontaneous abortion and preterm birth was observed (16). Most of these studies were case reports or observational studies which may have contributed to these discrepancies. All these uncertainties are likely to increase the level of psychological stress and may contribute to an increased risk of pregnancy terminations.

As regard to the risk of neonatal infection, the proportion of infected neonates was low (6%) and two neonates died in Capobianco's review (11). In all cases, respiratory symptoms were observed. Interestingly, Vivanti et al. (17) described the first documented case of congenital COVID-19 infection associated with neurological symptoms following neonatal viremia. Transplacental transmission was associated with inflammation in the cerebral spinal fluid in the neonate and magnetic resonance imaging showed bilateral lesions of the white matter.

Although transmission of SARS- CoV-2 through breast milk was considered unlikely (18), some positive women may choose not to breastfeed to avoid direct contact with the newborn and reduce the risk of neonatal infection (19). Indeed, close contact of mother and infant after birth can increase the risk of transmission of the virus to the baby through droplets or micro-droplets. Sighaldeh et al. (20) recommended separating the baby from the mother with confirmed (or even suspected) COVID-19 infection for at least 2 weeks. In addition, infected mothers should be taught about the symptoms of baby's infection in case it happens, and the principles of hygiene to protect the baby and prevent transmission.

Psychological Risk

The pandemic can be particularly distressing during specific situations such as pregnancy. In a Canadian study, two cohorts of pregnant volunteer women were compared (21). The first one was recruited before the COVID-19 pandemic ($n = 496$); the second one ($n = 1,258$) online during the pandemic in April 2020. This study was only focused on distress and psychiatric symptoms. Women from the COVID-19 cohort as compared with pre-COVID-19 women showed higher levels of depressive and anxiety symptoms (OR = 1.94). Moreover, in the COVID-19 cohort, women with previous psychiatric diagnosis or low income were at higher risk to report elevated distress and psychiatric symptoms.

Potential Risk for the Children

Moreover, we do not know yet the after-effects of maternal exposure to COVID-19 infection and the risk of future mental disorders in offspring since the virus may have toxic effects on fetal brain. Vivanti et al. (17) reported the first case of a neonate with white matter injury due to a COVID-19 infection after transplacental transmission. At 2 months after birth, the neonate's hypertonia was improved and white matter lesions were reduced. However, early brain lesions may increase the risk of further mental disorders (22).

WOMEN MAY BE AT HIGHER RISK OF PSYCHIATRIC SYMPTOMS DURING THE PANDEMIC

In order to investigate the prevalence of psychiatric disorders during the COVID-19 pandemic peak, several large surveys were conducted online in the general population. Liu et al. (23) found a prevalence of post-traumatic stress symptoms of 7% in Wuhan (China) 1 month after the COVID-19 outbreak (in 285 residents). In sub-symptom analysis of PCL-5 (PTSD Checklist for DSM-5), women suffer more re-experiencing, negative alterations in cognition or mood and hyper-arousal as compared to men. In the same way, Li and Wang (24) found that 29.2% of the 15,530 respondents in the UK scored 4 or more on general psychiatric disorders measured by the 12-item General Health Questionnaire (GHQ-12) and 35.86% of the respondents sometimes or often feel lonely. Women and young people had higher risks of psychiatric disorders and loneliness. Being employed and living with a partner were protective factors. Moreover, participants who have or had COVID-19-related symptoms were more likely to have psychiatric disorders. Liu et al. (25) have also reported high levels of depression (43.3%, PHQ-8 scores $\geq$ 10), anxiety scores (45.4%, GAD-7 scores $\geq$ 10), and PTSD symptoms (31.8%, PCL-C scores $\geq$ 45) in 898 Americans (18–30 years) during the pandemic. In this latter study, no differences were observed between men and women.

HEALTH CARE WORKERS (ESPECIALLY WOMEN) WERE AT HIGHER RISK OF MENTAL HEALTH SYMPTOMS

The WHO postulated that many health care providers could develop PTSD, depression, anxiety and burnout during and after the pandemic peak (5). Lai et al. (26) have conducted a cross-sectional study in 1257 Chinese health care workers treating patients with COVID-19 (76.7% of all participants were women, and 60.8% were nurses). They found a high prevalence of mental health symptoms. In total, 50.4, 44.6, 34.0, and 71.5% of participants reported symptoms of depression, anxiety, insomnia, and more than 70% reported psychological distress, respectively. Female gender and having an intermediate occupation were associated with experiencing more severe depression, anxiety, and distress. Working as a frontline health worker (41.5% of the participants) and in Wuhan (the epicenter of the crisis) were also risk factors for worse mental health outcomes. In fact, the chance of being infected was much higher in this latter group, which added a fear of transmission to their families. In contrast, Chew et al. (27) reported that in 906 healthcare workers (64.3% were female) from Singapour and India, only 5.3% had moderate to severe depression, 8.7% had moderate to severe anxiety, 2.2% moderate to severe stress, and 3.8% moderate to severe levels of psychological distress. The most common symptom observed was headache (32.3%). A significant association between the prevalence of physical symptoms and psychological outcomes was reported but no association was observed with gender. As a comparison, 10% of 549 health care workers reported high levels of PTSD symptoms at some time during the 3 years following the severe acute respiratory syndrome (SARS) epidemic in 2003 (28). Being single and with low income were risk factors for PTSD. In another study conducted during the previous SARS pandemic in Hong Kong, 25% of health care workers required psychological follow up (29). Gender was not taken into account in these analyses.

Furthermore, the conflict professionalism as well as personal fear for one's health contributed to burnouts as well as physical and mental symptoms in health workers (30). Increased workload, isolation, and discrimination were also common in caregivers and could result in physical exhaustion, fear, emotional disturbance, and sleep disorders (31). In addition, in the time of pandemic, few adequate services may screen physicians and nurses in contact with infected patients for anxiety, depression and suicidality and provide counseling.

PSYCHIATRIC SYMPTOMS IN COVID 19 POSITIVE PATIENTS

Guo et al. (32) reported that COVID-19 positive patients had higher levels of depression, anxiety, and post-traumatic stress symptoms as compared with normal controls. Women reported significantly more "Perceived Helplessness" as compared to men and controls. There was a correlation between depression and CRP levels among patients indicating that the immune-inflammatory response may be involved. Many patients complain also of intense fatigue and apathy in the weeks or months following infection, which have already been observed with previous SRAS infections or influenza. These symptoms highlight the link between depression, viral infections and inflammatory mechanisms (33). Further exploration of the mental health outcome of COVID-19 positive patients using an gendered lens would be of high interest.

Similarly, studies exploring the psychological consequences of the 2002–2004 SARS outbreak in China reported that anxiety and depression as well as PTSD occurred after the epidemic. At 30 months post-SARS, 25 percent of the patients had PTSD, and 15.6 percent depressive disorders (34). Mak et al. (35) and Lam et al. (36) reported more that 40% of SARS survivors had post traumatic stress symptoms (PTSS). Single subjects, those working in high-risk workplaces, or having close relatives with SARS were two to three times more likely to develop high levels of PTSS than those not exposed to the virus (37).

DOMESTIC VIOLENCE

Intimate partner violence (IPV) includes physical or sexual violence, emotional abuse and stalking. It is the major cause of homicide death for women (38). Victims of IPV are at increased risk of multiple mental disorders as well as somatic diseases (cardiovascular disease, chronic pain, sleep disturbances, gastrointestinal problems, sexually transmitted infections, traumatic brain injury) (39). Exposure of children to family violence may also increase the risk of perpetrating violence in their adult relationships (40). Several risk factors have been identified: low income, social isolation, loss of bearings, narrowness of premises, loss of loved ones, fear of dying, difficulties in accessing medical and social services, inability to flee, increased consumption of addictive substances, etc. (41–44). All these risk factors usually associated with intra-family violence are increased during epidemics. In addition, male aggression with or without alcohol often appears as a mode of reaction to a crisis (45). In these situations of dramatic crises, male aggression has long been more easily excused, especially when the anger was only temporary and had been the subject of sincere regret. Male violence may even have seemed legitimate for some people, as at it can be normal for a man to behave aggressively in situations of crisis and personal suffering, women then are being accused of having over-reacted or their requests for help in the face of violence have sometimes been simply ignored (46). For women at high risk of abuse, home may not be a safe place. Without private place, many women will find difficult to make a call or to seek help online. Similarly, in all crisis situations, whether wars, natural disasters or serious epidemics, whatever the country concerned, intra-family violence increases. In the aftermath of Hurricane Katrina, which occurred in 2009 in the United States, the prevalence of domestic violence had quadrupled; the physical violence suffered by women had almost doubled (4.2 to 8.3%) but remained unchanged for men (47). In the weekend following the 2010 New Zealand earthquake, police reported a 50 percent increase in calls for family violence (48). Pregnant women are also not immune to physical violence since after the Fukushima disaster, physical violence against pregnant women was four times greater in this region compared to other Japanese provinces at the same time, which was approximately 1.5 percent (49). In the same way, data from Hubei province in China, particularly affected by the coronavirus epidemic, showed a tripling of reports of intrafamilial violence in February 2020 during confinement compared with February 2019 (50). In the UK, a project tracking violence against women reported that deaths from domestic abuse between 23 March and 12 April had more than doubled (16 deaths) compared with the average rate in the previous 10 years (51). There are many reports of increased violence against women worldwide, with increases of 25 to 30% in countries with reporting systems (6, 52). These figures may reflect only the worst cases. More complex forms of violence may also develop when perpetrators may further restrict access to services and psychosocial support. Exposure to COVID-19 can be used as a threat. Abusers can also exploit the inability of women to call for help or escape; women may even be put out on the street without any shelter (43).

The disruption of protective networks may further exacerbate IPV and its consequences. The reduced functioning of the justice services and the fear of contamination in prisons make it more difficult to manage the perpetrators. Police and health services, which are the first line responders are overwhelmed and less available. Support services are affected by lockdown or, in some cases, reallocation of resources. Domestic violence shelters may be full, closed or repurposed. Yet, domestic violence shelters must remain open during the lockdown. UN Women Policy Brief (3) has reported some examples of how the government can help during the pandemic: in China, the hashtag #AntiDomesticViolenceDuringEpidemic has links to online resources; free calls to helplines were implemented in Antigua and Barbuda; in Spain, an instant messaging service with a geolocation function offers an online chat room with immediate psychological support; in the Canary Islands, Spain, and France, women can alert pharmacies about a domestic violence situation with a code message "Mask-19" that warns the police; in the UK police has enlisted postal workers and delivery drivers who can look out for signs of abuse. A popular app called "Bright Sky" provides support and information, but can be disguised when the partners check the phones. In France, 20,000 hotel room nights were available to women needing shelter to escape from abusive situations; in Colombia, the government has guaranteed continued access to services, including legal advice, psychosocial advice, police and justice services, including hearings. Similarly, virtual justice system were established in different countries.

According to diverse media sources and women rights experts, different forms of online violence, such as stalking, bullying, sexual harassment, and sex trolling, have also increased during the pandemic (53).

Finally, reports of both physical and verbal attacks on healthcare workers have increased in China, Italy, France, and Singapore (54). Given the higher vulnerability of female frontline workers and the increased risk of violence against them, specific measures must be put in place to protect them.

VIOLENCE AGAINST CHILDREN: TYPE AND RISK FACTORS

The number of calls to 119 for child victims of violence also increased by 20% with an increase in urgent calls by 60% compared to March 2019 in France. With regard to violence against children, low-income is the most often reported risk factor of violence against children; sexual violence being more likely against girls than boys (55). Other risk factors are past history of exposure to violence in parents, parental substance abuse, child labor (56). The closure of schools increased the risk of violence against children. Additional constraints faced by families as a result of the Covid-19 crisis such as job loss or falling income, social isolation, excessive confinement in often cramped premises, fear related to the pandemic situation, enhanced the risk of domestic violence, whether inflicted between partners or on children by adults who care for them (57, 58).

Simultaneously, the Covid-19 crisis increased the risk of child sexual exploitation on the internet. Europol recently reported that law enforcement auxiliaries are reporting more online activity by people looking for content from child abuse. The French government, in partnership with care services, victim assistance services and the justice system, has taken a certain number of measures to maintain assistance to victims during this period of confinement. Psychiatrists, like all doctors and health personnel, are on the front line in detecting violence against children (for example: https://www.stopblues.fr/fr/node/449).

CONCLUSION

Research focused on the subject of mental health issues during the COVID-19 pandemic is still scarce, especially in women. Yet, Covid-19 pandemic has affected women much more profoundly than men, both as frontline workers and at home. Financial crisis is gradually developing and as a consequence mental health issues are likely to grow exponentially. According to the United Nations (3), women aged 24 to 34 are already 25% more likely than men to face extreme poverty.

Nevertheless, we should consider this pandemic as an opportunity to build better, stronger, more resilient societies that could bring relief as well as hope to all women on earth. For example, during the First World War and the concomitant flu pandemic, for the first time in the history of the United States, black nurses had the opportunity to serve the US army. In fact, this drama has been turned into an opportunity to improve gender equality (59). We hope that this pandemic will also help to recognize the major role of women at home and at the workplace. To achieve this goal, the UN recommended allocating additional resources to protect women, putting women at the center of policy changes and collecting more sex-disaggregated data to analyze the impact of pandemics on women (60). Moreover, the 17 Sustainable Development Goals (SDGs) proposed by the UN offer a unique opportunity to achieve gender equality (Goal number 5), which is a key element of all SDGs and simultaneously improve health and well-being for all before 2030 (61).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Assessing Mental Health of Women Living in Karachi During the Covid-19 Pandemic

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Introduction: Women are more susceptible to mental health disorders and have been reported to experience higher levels of depression and anxiety during previous large-scale disease outbreaks. Stressful events like the COVID-19 pandemic can add extra burdens to women's already multifaceted lives. Keeping the gender implications of COVID-19 in mind can assist health care workers to offer more effective management. In our study, we aimed to assess the impact of COVID-19 on the mental health of women in Karachi, Pakistan and investigate the possible risk factors.

Methods: An online questionnaire was distributed to women on social media platforms in the month of June 2020. The questionnaire had two self-assessment scales, Patient Health Questionnaire (PHQ-9) scale which measures the symptoms of depression and General Anxiety Disorder (GAD-7) scale which measures anxiety.

Results: Three hundred and ninety three individuals completed the questionnaire with the mean age calculated to be 27.6 ± 11.7 years. Age, education, marital status, number of children, financial issues, employment status, smoking, comorbidities and mental illnesses were significantly associated with participants' mean anxiety and depression scores. The depression scores were generally higher compared to anxiety scores in each category. As the age increased, their scores decreased, with women aged 18–30 having a significantly higher mean depression and anxiety scores compared to women who were above 50. Severe anxiety was identified in 21.9% women and severe depression was noted in 17.8% women. A frightening number of 148 (37.7%) was found of women who had self-destructive thoughts at one time or another. Out of these women, surprisingly 97 (65.5%) individuals were not previously diagnosed with any mental illnesses.

Discussion: This study supports the existing literature regarding the disturbed psychological state of women close to the peak of the covid-19 pandemic. We noted increased percentage of depressive women as compared to studies conducted before the covid-19 era. This raises concern especially with our thought provoking finding of self-harm or suicidal thoughts among women. Most of our female population is also seen to be anxious. This study highlights the importance for help and support groups of mental health to effectively reach women during this period of social isolation.

Keywords: COVID-19, mental health, women, depression, anxiety, pandemic, Pakistan

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INTRODUCTION

The outbreak of pneumonia like cases of a novel etiology that was first observed in Wuhan, China, in December 2019 (1), swiftly spread across the globe and led to the pandemic now known as the coronavirus disease 2019 (COVID-19) (2). SARS-CoV-2, a member of severe acute respiratory syndrome-related coronavirus species, the virus that causes COVID-19, is predominantly transmitted by person-to-person contact via respiratory droplets (3).

In an attempt to curb its spread, countries all over the world have taken strict public health measures (4). Large-scale spread of COVID-19 has caused mass panic and anxiety (5), which are further amplified by introduction of lockdowns, travel restrictions and suspension of educational institutions (6). In Pakistan, the first case of COVID-19 was reported from Karachi on February 26, 2020 (7). As of August 13, 2020, there have been around 287,000 confirmed cases and more than 6,100 deaths in Pakistan. The province of Sindh has recorded the highest percentage of cases, with its capital city Karachi forming more than 30% of all cases in the country (8).

Historically, extensive outbreaks of infectious diseases have been linked to a variety of profound psychological effects among people (9, 10). In a study conducted in 2010 about public's response to influenza A H1N1 outbreak, it was found that 9.6 to 32.9% of people were "very worried" about contracting swine flu (9). Another study in Hong Kong concluded that 10 to 18% of participants appeared to have symptoms of depression, anxiety and post-traumatic stress disorder during the Severe Acute Respiratory Syndrome (SARS) epidemic (10). Factors that may affect the intensity of psychological impact among people include gender, age, income stability, place and mode of residence, presence of underlying chronic conditions, previous or existing psychiatric illness and presence of a relative diagnosed with or deceased due to the disease (11, 12).

Among these factors, it is notable that women are more prone to disorders of anxiety and depression (13) and have been reported to experience higher levels of anxiety during previous pandemics (14). Women also showed an anxiety risk that was 3.01 times higher than males in a study performed to assess the general publics' psychological health during the current COVID-19 pandemic in China (15). Disease outbreaks are known to multiply women's burdens with pre-existing stresses at work and home being enhanced as schools shut down and family members get infected (16–18). With Pakistan having a predominantly patriarchal society system, women are expected to experience higher degrees of unpaid care work, economic burden and domestic abuse in current periods of social isolation (19, 20).

Several studies were conducted to evaluate the mental health of high-risk groups like adolescents, students and health care workers during the COVID-19 pandemic in Pakistan (21–24). However, to the best of our knowledge after an extensive literature search, no studies were found to assess the psychological impact of this pandemic solely on women. Therefore, this study aims to determine the levels of depression and anxiety related to COVID-19 among adult women in Karachi, Pakistan and to identify potentially associated factors, to assist health care workers to provide a more effective and specific response to the affected women.

MATERIALS AND METHODS

This is a cross-sectional study designed to identify the effects of Covid-19 pandemic on the mental health of women in Karachi, Pakistan by an online questionnaire which was kept anonymous. A convenient sampling technique which engaged the general female population was used. Taking the anticipated frequency to be 50%, at a confidence interval of 95%, a sample size of minimum 384 was calculated. The inclusion criteria consist of all women living in Karachi who are above the age of 18, had access to internet and understood English, the language in which the questionnaire was composed. Females below the age of 18 were excluded from the analysis.

The quantitative data was collected on a validated online questionnaire which consists of informed consent, demographic data, Patient Health Questionnaire (PHQ-9) scale and General Anxiety Disorder (GAD-7) scale. The online questionnaire was distributed to women on different social media platforms through a google form link in the month of June 2020. The demographic data consists of general characteristics age, marital status, level of education, employment status, co-morbidities etc.

Previous studies on mental health during COVID-19 pandemic have widely used these two scales (25, 26), one of which was conducted on female health care workers in China (25). The PHQ-9 scale is used to measure symptoms of depression and has the total score range from 0–27 where 0–4 is minimal, 5–9 is mild, 10–14 is moderate, 15–19 is moderately severe and 20–27 is severe depression (27). The GAD-7 scale is used to measure anxiety and has the total score range from 0 to 21 where 0–4 is no anxiety, 5–9 is mild, 10–14 is moderate and 15–21 is severe anxiety (28).

Descriptive statistical analysis was carried out on a data set with IBM SPSS 23.0. All information gathered via google forms was recoded into variables. Missing values were coded as −1 so as not to affect results. Normality of data was tested using Shapiro-Wilk test. Both descriptive and inferential statistics involving Mann-Whitney U test and Kruskal Wallis H test were used to present results. For each test, a P-value < 0.05 was considered statistically significant.

RESULTS

Out of 404 individuals who accepted to participate in the study, 393 completed the questionnaire, giving a response rate of 97%. The qualitative characteristics of the participants are summarized in **Table 1**. Of the 393 participants, 79.2% were aged 18–30, 11.8% were aged 30–50 and 9% were aged above 50. The mean age was calculated to be 27.6 years with a standard deviation of 11.7. One hundred and seven (27%) women were married, and of those women, 86 had children, with 51 women having 3–5 children. 66.8% women were undergraduates; 25.1% were post-graduates; 7.8% had received higher secondary education and 0.3% had received secondary education. More than half the participants

(56.6%) reported to be students. 23.4% i.e., 92 women were employed, of whom 84 were working during the pandemic with 45 women working from home and 39 going to the workplace. The vast majority of participants (98.2%) were living with their families. Women living alone or with roommates were grouped together as the number was very small (7). 22.4% individuals suffered from comorbidities; 18.6% were previously diagnosed with mental illnesses; and 6.1% reported to be smoking. A relatively low proportion of women (15%) reported to exercise regularly for four times a week, while a high proportion of women (42.7%) did not exercise at all. Forty five percent women had relatives and friends diagnosed with COVID-19, while 6.1% women had relatives and friends who had died of COVID-19.

The mean depression and anxiety scores related to participants' demographics are described in **Table 2**. The depression scores were generally higher compared to anxiety scores in each category. As the age increased, their scores decreased, with women aged 18–30 having a significantly higher mean depression score than women who were above 50 (P = 0.000). Single women had twice the depression score as married women, and the relation was seen to be statistically significant (P = 0.000). Similarly, there was a significant relation with women who had children and specifically 3–5 number of children with their depression scores being less compared to their counterparts ($P = 0.000$ and $P = 0.018$ respectively). The mean depression scores were similar with different levels of education, however, the relation between the two factors is statistically significant (P = 0.000). Students had a significantly higher depression score than employed and unemployed women ($P = 0.000$). Women who reported to be working from home had a higher depression score than those going to the workplace with the difference being statistically significant ($P = 0.013$). Individuals with chronic diseases had a significant association with their mean depression score ($P = 0.014$). Participants who faced financial problems during the pandemic and participants who reported to be smoking had significantly higher depression scores (P = 0.000 and $P = 0.000$, respectively). No significant difference in mean depression scores was observed among women who were working during the pandemic, women who lived with their families, women who exercised, and women who had a COVID+ patient among friends and relatives.

Table 2 demonstrates that there is a statistically significant inverse relationship between age and mean anxiety scores with women aged 18–30 scoring thrice as high as women aged 50 above ($P = 0.000$). There is a significant relation between marital status and anxiety score with single women scoring higher than married women ($P = 0.000$). Women who did not have children had significantly twice as high anxiety scores as women who did have children ($P = 0.000$). While women who had 3–5 number of children had significantly lower scores than women who had 0–2 number of children ($P = 0.005$). Mean anxiety scores across different levels of education were similar but the relation was noted to be statistically significant ($P = 000$). Students had significantly higher mean anxiety scores compared to employed and unemployed women ($P = 0.000$). Among working women, the ones who were working during the pandemic had significantly higher anxiety scores than their

TABLE 1 | Sociodemographic factors of participants.

Characteristics	*N* (%)
Age (years)	27.6 ± 11.7
18–30	309 (79.2)
30–50	46 (11.8)
>50	35 (9.0)
Marital status	
Single	281 (72.4)
Married	107 (27.6)
Have children	
Yes	86 (22.2)
No	302 (77.8)
Number of children	
0–2	34 (40)
3–5	51 (60)
Level of education	
Secondary	1 (0.3)
Higher Secondary	30 (7.8)
Undergraduate	259 (66.8)
Post-graduate	97 (25.1)
Work status	
Student	219 (56.6)
Employed	92 (23.4)
Unemployed	76 (19.3)
Working during the pandemic	
Yes	84 (93.3)
No	6 (6.7)
Workplace	
Work from home	45 (53.6)
Going to workplace	39 (46.4)
Living status	
Living alone/roommates	7 (1.8)
Living with family	386 (98.2)
Comorbidities	
Yes	88 (22.4)
No	304 (77.6)
Diagnosed with any mental illness	
Yes	73 (18.6)
No	320 (81.4)
Smoking	
Yes	24 (6.1)
No	368 (93.6)
Exercise	
No	168 (42.7)
1–2 times a week	106 (27.0)
3–4 times a week	60 (15.3)
>4 times a week	59 (15.0)
Currently faced any financial issues	
Yes	96 (24.4)
No	297 (75.6)
Acquaintances diagnosed with COVID	
Relatives/friends diagnosed with COVID	177 (45)
Relatives/friends died from COVID	24 (6.1)
Both	20 (5.1)
Neither	172 (43.8)

TABLE 2 | Association of sociodemographic factors with mean depression and anxiety scores.

Characteristics	Depression M ± SD	Anxiety M ± SD
Age		
18–30	12.9 ± 6.9	10.7 ± 5.9
30–50	5.7 ± 4.7	6.1 ± 5.1
>50	2.4 ± 2.8	3.2 ± 3.6
P-value	0.000*	0.000*
Marital status		
Single	13.2 ± 6.9	10.8 ± 5.9
Married	6.0 ± 5.8	6.1± 5.3
P-value	0.000*	0.000*
Have children		
Yes	4.7 ± 4.7	5.2 ± 4.6
No	13.1 ± 7.0	10.8 ± 6.0
P-value	0.000*	0.000*
No of children		
0–2	5.7 ± 4.4	6.7 ± 4.8
5-Mar	4.1 ± 4.5	4.1 ± 4.0
P-value	0.018*	0.005*
Level of education		
Secondary	20 ± 20	20 ± 20
Higher Secondary	13.3 ± 7.8	10.7 ± 6.3
Undergraduate	12.5 ± 7.1	10.5 ± 5.9
Postgraduate	6.9 ± 6.5	6.5 ± 5.7
P-value	0.000*	0.000*
Work status		
Student	12.9 ± 6.9	10.6 ± 6.1
Employed	7.8 ± 6.6	7.3 ± 5.8
Unemployed	10.3 ± 8.1	9.3 ± 6.2
P-value	0.000*	0.000*
Working during the pandemic		
Yes	8.1 ± 6.7	7.7 ± 5.8
No	3.3 ± 3.8	3.0 ± 3.5
P-value	0.063	0.043*
Workplace		
Work from home	9.7 ± 7.0	8.8 ± 5.8
Going to workplace	6.2 ± 5.9	6.5 ± 5.8
P-value	0.013*	0.054
Living status		
Living alone/roommates	6.2 ± 5.2	4.8 ± 3.4
Living with family	11.2 ± 7.4	9.4 ± 6.2
P-value	0.125	0.189
Comorbidities		
Yes	12.3 ± 8.5	10.9 ± 6.6
No	10.8 ± 7.1	8.9 ± 6.0
P-value	0.014*	0.103
Diagnosed with any mental illness		
Yes	16.2 ± 6.6	13.6 ± 5.3
No	9.9 ± 7.1	8.4 ± 6.0
P-value	0.000*	0.000*
Smoking		
Yes	16.8 ± 7.4	12.7 ± 6.0
No	10.7 ± 7.2	9.2 ± 6.2
P-value	0.000*	0.006*
Exercise		
No	11.4 ± 7.2	9.5 ± 6.4
1–2 times a week	11.5 ± 7.7	9.5 ± 6.1
3–4 times a week	11.5 ± 6.8	9.2 ± 5.6
>4 times a week	9.4 ± 7.9	8.9 ± 6.8
P-value	0.171	0.848
Currently faced any financial issues		
Yes	13.8 ± 7.6	11.6 ± 5.8
No	10.2 ± 7.1	8.6 ± 6.2
P-value	0.000*	0.000*
Acquaintances diagnosed with COVID		
Relatives/friends diagnosed with COVID	11.2 ± 7.2	9.4 ± 6.2
Relatives/friends died from COVID	11.6 ± 8.1	10.7 ± 5.8
Both	11.0 ± 8.0	7.7 ± 5.8
Neither	11.0 ± 7.5	9.4 ± 6.4
P-value	0.977	0.44

(Continued)

TABLE 2 | Continued

**P-value < 0.05 is significant.*

counterparts ($P = 0.043$). A significant association was seen in individuals who reported to be smoking and their anxiety score ($P = 0.006$). Women who faced financial issues and women who had been diagnosed with mental illnesses had a significant relation with their anxiety scores ($P = 0.000$ and $P = 0.000$, respectively). There was no significant association of mean anxiety scores among women who worked from home, women who lived with their families, women with comorbidities, women who exercised, and those with a COVID+ patient among friends and relatives.

Figure 1 summarizes the depression scores of the participants. Although 18% participants were previously diagnosed with mental illnesses and 81% were not, all participants had notable anxiety and depression symptoms. All women showed degrees of depression with 23.2% suffering from minimum, 23.4% from mild, 21.1% from moderate, 14.5% from moderately severe and 17.8% from severe depression.

Participants' anxiety levels are portrayed in **Figure 2**. There was roughly equal distribution of participants in all categories with 31% having no anxiety while 27% had mild, 20% had moderate and 21.9% had severe anxiety.

Table 3 depicts participants with thoughts of self-harm. The question 9 of PHQ-9 scale asked participants whether they had thoughts that they would be better off dead or hurting themselves. Women who picked the option of several days, more than half the days and nearly every single day were grouped together as "yes." An alarming number of 148 (37.7%) was found of women who had self-destructive thoughts at one time or another. Out

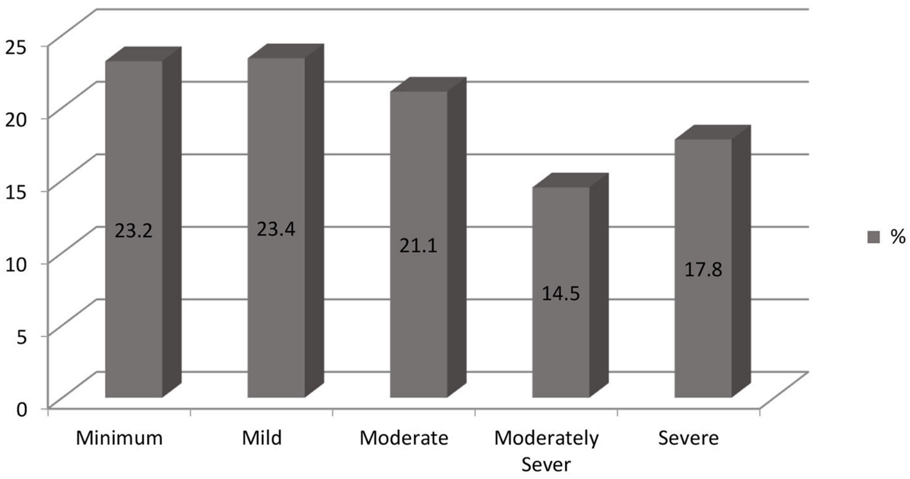

FIGURE 1 | Distribution of participants PHQ-9 scale scores.

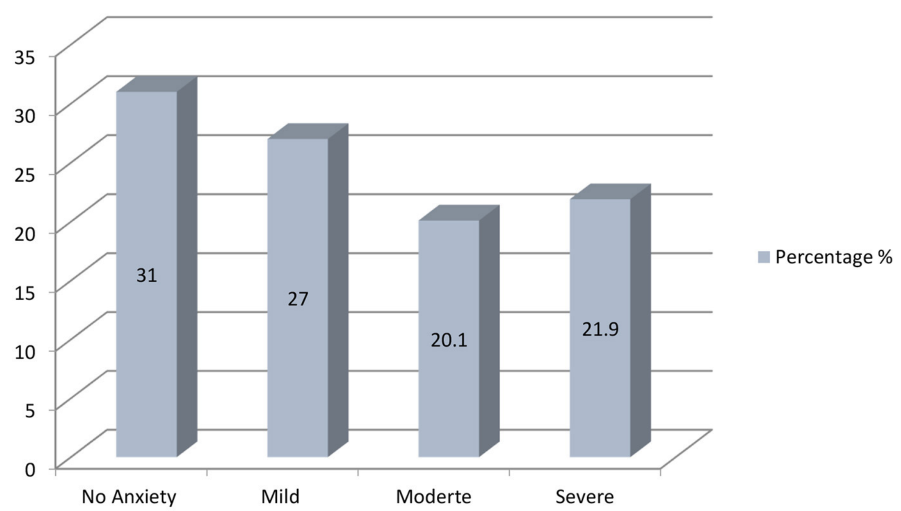

FIGURE 2 | Distribution of participants GAD-7 scores.

of these women, surprisingly 97 i.e., 65.5% individuals were not previously diagnosed with any mental illnesses.

DISCUSSION

This study acknowledges COVID related increase in depression and anxiety levels among adult women living in the cosmopolitan city, Karachi. It has been evidenced through research that women are prone to developing mental health problems (29–32). This study was conducted close to the dates the pandemic was estimated to reach its peak in Pakistan (33), hence it was hypothesized that there might be alarming levels of depressive and generalized anxiety disorders among the chosen sample. It was also later observed that the country witnessed its highest number of cases during our data collection period, in the month of June (34).

In a study assessing psychological distress, inclusive of depression and anxiety, Qiu et al. (35) report higher scores among the young adult group. This finding is supported by our research where higher scores for depression and anxiety are seen among women aged 18 to 30 as well. This pattern can be explained with findings of Cheng et al. (36) that young people have access to overwhelming information through social media which may be increasing their psychological burden. Association of age is found to be significant with depression in our study, which is supported by a study conducted in USA (37). However, it is mostly seen to be in contrast with other studies (11, 15, 26, 31). Similarly, age and anxiety are found to be significantly related in our study which is consistent with findings reported by a nationwide survey

TABLE 3 | Participants with thoughts of self-harm.

Parameter	Total	Previously diagnosed with mental illness	
	***N* (%)**	**Yes**	**No**
Thoughts of self-harm			
Yes	148 (37.7)	51 (34.5)	97 (65.5)
No	245 (62.3)	22 (9.0)	223 (91.0)

conducted in Italy (31). Nevertheless, it is in contrast with a few other studies too (11, 15). These variances might be due to the differences in the context and sample population.

An unanticipated finding in our study shows that women with no children have significantly higher levels of depression and anxiety both whereas women with children only report mild levels of depression and anxiety. This is in accordance with findings reported by a study in Italy where childlessness was associated with depression (31). This could be due to lack of loneliness and a sense of fulfillment associated with having children in south-Asian communities in particular.

It is expected that students, in any outbreak of an infectious disease, might suffer from various psychological burdens as it may be a direct impediment to their ongoing education, with number of corona virus patients rising, all educational institutes were shut down nationwide. A study in China states students to be dealing with high levels of depression and anxiety (29). Odriozola-González et al. (38) in their study conducted in a university report significantly higher levels of depression and anxiety among students when compared to university employees.These findings are supported by our study, where students seem to have suffered a higher degree of mental impact when compared to employed or unemployed people.

Depression and occupation or being an employee are seen to be significantly associated in a few studies while no such association is seen between these variables and anxiety (15, 31). In total contrast to these findings, our study shows working during the pandemic to be significantly associated with anxiety and not depression. In a study in Turkey no significant relationship is seen between working during the pandemic and anxiety or depression (11). Such differences however can be expected in different geographical regions.

Our study shows people having comorbidities with a significantly higher mean score for depression, while no significant association is seen with mean anxiety scores which is in accordance with the study conducted in Turkey (11). A study in Italy however shows both anxiety and depression to be significantly associated with history of medical problems (31). These findings could be accredited to COVID-19's worse progression with various chronic illnesses (39).

Smoking, in our study, has been shown to be significantly associated with higher mean values for depression and anxiety both, which could be attributed to the adverse progression and severe outcomes associated with the sars-cov-2, if contracted (40).

It was anticipated that having people affected with the contagious virus in an individual's close vicinity might have had a direct mental impact on the individual. However, to our surprise our study found no significant relationship existed between having friends, relatives or acquaintances with covid-19 and depression or anxiety scores. The finding is in contrast with some existing literature (15, 26). A research conducted in turkey also reports significantly higher means scores for depression and anxiety for the same variable (11). The disparity could be attributed to contextual differences.

A study discussing the psychological burden in women during the Severe Acute Respiratory Syndrome (SARS) epidemic in Hong Kong showed 28.6% women to have mild depression or higher, which is a higher number than noted before the pandemic (41). Similarly, to assess the occurrence of depression before and during the pandemic, we compare our results with studies conducted among women living in Karachi before the spread of this contagious virus. These studies state overall depression among women to be a little <40% (42, 43). Another study reports prevalence of depression and anxiety among women living in Karachi to be 30% (44). Gadit and Mugford (45) also report frequency of depression in Karachi to be 35.7%, however, the percentage is inclusive of both genders. On the other hand, our study shows over 53.4% of women with major depression, calculated taking a PHQ-9 score of 10 and above. This was based on the findings of Kroenke et al. (27) who reported a PHQ-9 score $\geq$10 to have a sensitivity of 88% and a specificity of 88% for major depression. The increased percentage of depressive women seen in this study as compared to studies conducted before the covid-19 era, reaffirms our assumption that the pandemic may have had a direct psychological effect on women. The study on the SARS epidemic shows a statistically significant relationship between all age groups and depression (41). Our study supports this existing literature. These similar findings reflect a pattern which is expected in any outbreak of an infectious disease; however, it must be noted that our study is inclusive of younger age groups as well.

Huang and Zhao (46) in their study reported 34.1% of females to have anxiety symptoms using the GAD-7, taking score 9 or higher as presence of anxiety, whereas our study, using the same scale, shows 42% women to have moderate anxiety levels or higher i.e., score 10 and above. The percentages both the studies show seem close. The minimal difference noted might be explained with differences in understanding of the same scale. Khan et al. (47) in their study conducted prior to the COVID-19 pandemic have reported, taking the GAD-7 score 5 and above to show some degree of anxiety, 45.5% of anxious women. Using the same score as a threshold in an attempt to draw a comparison, we find our study reports 69% of women to have anxiety, which is a much higher number than noted before the pandemic. It can be concluded from the available data that the pandemic may have had a direct effect on the anxiety levels found in our population. It must be noted that the relationship between COVID-19 and depression, or anxiety could not be founded conclusively in our study; however, it can be strongly inferred as a possible cause. A key adverse effect of the pandemic has been said to be loneliness and increased social isolation (48) which have been linked with anxiety and depression strongly in other studies (49, 50), therefore this is an issue which warrants immediate attention.

A thought provoking finding in our study is the vast number of people considering self-harm or suicide. As shown in **Table 3**, while 62.3% of the people never thought of hurting themselves or being dead, 37.7% of the studied population had thoughts relating to self-harm, ranging from several days to nearly every day which calls for immediate action to help. A study in UK shows 17.9% of women having similar thoughts, however the percentage is much smaller than ours (51). In a paper discussing suicides in Pakistan, we found that there have been sixteen suicidality related cases since January 2020 which were all associated with the COVID-19 pandemic, of which two of the stated cases were women reportedly killing themselves because of suspected infection and economic distress (52). This also brings our attention toward our results where 24.4% of the women studied faced financial issues, which is a smaller percentage compared to 40% of women reportedly affected during the SARS epidemic (41) however, still holds importance.

Our limitations include use of a small sample size. More precise results can be obtained with a similar survey conducted on a larger scale. Due to convenience sampling technique, there was an oversampling of a certain group i.e., students and to avoid that, the next research may divide the population in groups and various sets. Given that this study is a cross-sectional survey, it at best serves as a snapshot of the situation. It cannot be made sure through our study that the psychological impact was due to the pandemic specifically, as life events or any personal factors were not adjusted for. To interpret whether COVID affected the prevalence of depression and anxiety, we have compared our results with studies conducted in our population prior to the pandemic, however it must be noted that some comparisons were drawn between different assessment tools for the same disorders. The study included self-assessment questionnaires and no professional diagnosis was made for any of the mentioned ailments above. The study does not conclusively establish a relationship between COVID and depression, or anxiety since cofounders were not accounted for. Ethics approval from a Human Research Ethics Committee was not obtained due to implementation of a strict lockdown. However, the questionnaire circulated online comprised of validated scales and had an elaborate consent form included. Anonymity of the collected data was maintained to ensure that any information cannot be traced back to the participant. All participants voluntarily consented to take part in our study and there was no in-person or physical human recruitment.

To the best of our knowledge, this is the first study that has been conducted in Pakistan exclusively targeting the mental health of women during the pandemic, so filling a gap in the literature. Our study also highlights the need for help regarding mental health to immediately reach women during this period of social isolation. Women make an asset to this country and directly affect lives of other people here and availability of treatment options for their mental health is of paramount importance at the moment.

The sample chosen does not reflect the entire population of Pakistan and future researches can be conducted at a national level in this area. A validated questionnaire could be created accounting for personal factors to precisely assess depressive disorders and anxiety before and during the pandemic. Our research aimed at women living in an urban city, and there's no knowledge available on psychological health of women making up the rural population of this country and therefore any future researches involving them may prove beneficial. We recommend studies to be conducted to see how available and in reach are the psychological help options for women in this country during this pandemic, or otherwise.

CONCLUSION

This research shows the mental health of women in Karachi to be noticeably affected during the pandemic with an alarming finding of thoughts regarding self-harm. Younger females in our context were seen to be more vulnerable. Students due to a sudden break in their on-going education seem to be dealing with more depressive and anxious thoughts. Women suffering with chronic illnesses have had a higher mental impact than healthier women. Keeping in view these findings, essential assistance should be made available through online support groups, awareness though television or social media and telemedicine. Moreover, informative messages through short message services or call services may help reduce the overall public panic, and therefore help reducing the anxiety levels found in our population.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SA supervised the research and acted as the mentor. SG ran all the data analysis and statistical analysis. AA, MA, AQ, and SG drafted various sections of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2020.594970/full#supplementary-material

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Psychological Distress Among Women Healthcare Workers: A Health System's Experience Developing Emotional Support Services During the COVID-19 Pandemic

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Ensuring the mental health and well-being of the healthcare workforce globally, especially women healthcare workers (HCWs), is an ongoing challenge that has been accentuated by the novel coronavirus (COVID-19) pandemic. Already at high risk of experiencing symptoms of stress, burnout, and depression, women HCWs are now also facing the psychosocial impacts of the COVID-19 pandemic. Although different types of mental health interventions have been introduced to support HCW well-being, the current needs of women HCWs have not been emphasized and replicable processes for developing and implementing specific emotional support services for women HCWs have not yet been well-described in the literature. Therefore, in this perspective, we discuss the approach our institution (University of California, Los Angeles) took for developing emotional support services for women HCWs that incorporate aspects of disaster behavioral health models and address various barriers to support and treatment. In addition, we describe and illustrate the process that we utilized to develop individual-level and institutional-level emotional support services. Finally, based on our institution's experience, we share recommendations for developing emotional support services for women HCWs during the COVID-19 pandemic and other future crises.

Keywords: women, healthcare worker, mental health, emotional support, wellness, COVID-19

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Sanford J, Agrawal A and Miotto K (2021) Psychological Distress Among Women Healthcare Workers: A Health System's Experience Developing Emotional Support Services During the COVID-19 Pandemic. Front. Glob. Womens Health 2:614723. doi: 10.3389/fgwh.2021.614723

> The most precious thing I gained from the support I received was to understand the importance of scheduling time for my own self-care and self-compassion. I never realized that I spent most of my life caring for others and very little time on my own needs. The COVID-19 pandemic has brought us to an unpredictable time in history, but I am excited to report my self-care, self-compassion, and elevated level of self-awareness will be a few of my bright spots during this unsettling time.
> - Woman healthcare worker who received emotional support services from our institution

INTRODUCTION

Women healthcare workers (HCWs) experience a unique set of work and individual life stressors, often resulting in significant gender-related differences in mental health symptoms and outcomes. Factors that affect women HCWs' well-being include (a) role strain (b) difficulties establishing and maintaining work-life balance, (c) consequences associated with pregnancy and motherhood,

(d) gender bias and discrimination, (e) imposter syndrome, and (f) a lack of sufficient support systems (1–4).

These stressors often leave little time or opportunities for self-care or self-compassion, leading to lower levels of self-valuation among women HCWs (5). Moreover, with regards to the effects of these stressors on mental health conditions, in addition to high levels of stress (1), women HCWs experience significantly higher rates of burnout (4, 6, 7) and depression or depressive symptoms than their male colleagues (3, 8).

High rates of mental health problems among women HCWs are particularly worrisome, since HCWs are reluctant to seek regular healthcare for themselves and are often unwilling to engage with mental health treatment. For example, 35% of physicians (9) and nearly 20% of physician assistants (10) do not have an established, regular source of care for receiving preventive healthcare services. Moreover, physicians' use of mental health services is low (11), especially among females, as evidenced by the fact that nearly 50% of women physicians surveyed who believed they met criteria for a mental illness reported not seeking mental health treatment (12). Previous research has suggested that women HCWs frequently cite a lack of time, concerns related to confidentiality and stigma, and fear of professional consequences, including effects on licensure status, as barriers to engaging with mental health services (12, 13). Organizational barriers to accessing supportive services also include decentralized services and employee assistance or mental health treatment programs only offering appointments during normal business hours, impacting women HCWs who are working or assisting with childcare or educational responsibilities.

Recent global large-scale studies, systematic reviews, and meta-analyses examining the mental health outcomes of HCWs during the COVID-19 and prior pandemics have confirmed the aforementioned trends related to gender differences in HCW well-being. For instance, psychological distress during pandemics has been found to be associated with gender (14, 15) and compared to male coworkers, women HCWs reported experiencing higher rates of depression, anxiety, insomnia, and distress (16–23). Finally, considering the fact that barriers to accessing mental health services have likely intensified because of the pandemic, the current state of HCWs'-especially women HCWs'-mental health and well-being, is cause for concern and must be addressed.

Although various interventions to support the mental health of HCWs during the COVID-19 pandemic have been described in the literature (24) and calls to include a gender perspective when developing interventions have been made (25), there remains limited information on the specific needs of women HCWs during this challenging time and specific processes institutions can use to develop and implement emotional support services. Therefore, in this perspective, we (1) briefly review useful disaster behavioral health models that informed the development of emotional support services at our institution (University of California, Los Angeles); (2) present an online interactive screening program that assessed the impact of the COVID-19 pandemic on HCWs and served as a qualitative needs assessment; (3) provide qualitative needs assessment data from women HCWs that we referred to in the development of additional services at both the individual and institutional levels for this population; and (4) outline recommendations for developing emotional support services for women HCWs based on our institution's experience.

MODELS OF DISASTER AND CRISIS PSYCHOLOGICAL AND BEHAVIORAL HEALTH INTERVENTIONS

When our institution's COVID-19 wellness and mental health workgroup first convened to address HCW well-being during the COVID-19 pandemic, members reviewed disaster behavioral health models. These models subsequently informed the development of our COVID-19 emotional support and mental health response plan for all HCWs (26). Various models have been proposed for supporting individuals during crises or after disasters and while many models share certain aspects, our workgroup identified three models to utilize. One model recommended by the National Academy of Medicine describes a tiered public health approach, consisting of universal resources and information, targeted logistical and psychological interventions, and intensive mental health services. This model allows for triage to an appropriate level of care with tier-specific interventions, services, and resources (27). The second model was Psychological First Aid (PFA), developed by the National Child Traumatic Stress Network and the National Center for PTSD. Key, relevant tenants of PFA include information gathering to identify needs, offering assistance that addresses immediate needs and concerns, and connecting and linking individuals with social supports and other services (28). The third model was a specific set of COVID-19-related institutional recommendations, which also included a list of thematic requests that HCWs may direct toward their respective organizations. We reviewed the themes from the third model and aimed to ensure that our emotional support and mental health response plan for HCWs addressed many of these requests, especially HCWs' appeals to their organizations to feel heard, supported, and cared for during the COVID-19 pandemic (29). In sum, the three models emphasized the importance of conducting a needs assessment, providing emotional support services, and a healthcare system's response to addressing the specific needs of HCWs during crises.

DEVELOPMENT OF EMOTIONAL SUPPORT SERVICES FOR WOMEN HCWs DURING THE COVID-19 PANDEMIC

As part of our institution's overall COVID-19 emotional support and mental health response plan (26), we developed a variety of emotional support services for all clinical and non-clinical HCWs. After reviewing the relevant disaster behavioral health models, we conceptualized the flow of services to begin with HCWs accessing an online interactive screening program and providing qualitative data regarding their current psychosocial and mental health needs via a needs assessment. At our

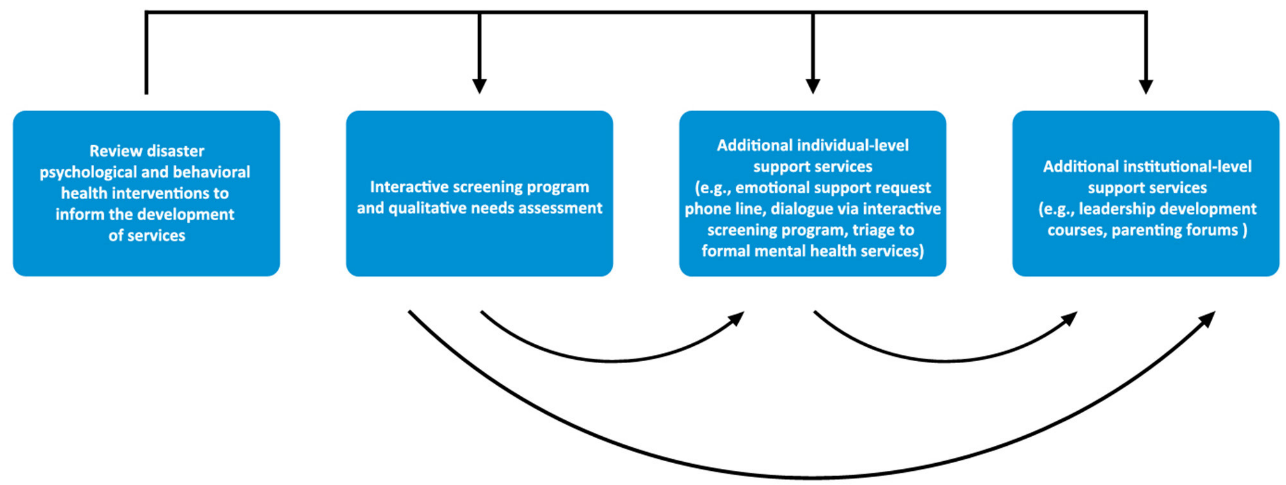

FIGURE 1 | Our institution's process of developing and introducing emotional support services for HCWs during the COVID-19 pandemic.

institution, as is typically found in mental health intervention research, the majority of participants were women. Therefore, we determined that, based on the feedback we received from women HCWs, we would develop tailored additional services for this population at both the individual and institutional levels. A pictorial description of the development and introduction of these services is outlined below in **Figure 1**.

Interactive Screening Program and Embedded Qualitative Needs Assessment

The online interactive screening program was developed in coordination with the American Foundation for Suicide Prevention and designed to both assess COVID-19-related anxiety, depression, and stress, as well as provide all HCWs with an opportunity to express their fears and concerns. The screening program totaled 16 questions, including the 12-item Coronavirus Impact Scale (30) and the 4-item Patient Health Questionnaire (PHQ-4) (31). The Coronavirus Impact Scale measures the extent to which the COVID-19 pandemic has changed one's life across multiple domains, including the following: routines, family income/employment, food access, medical health care access, mental health treatment access, access to social supports, COVID-19-related stress, familial stress/discord, and diagnosis of coronavirus among self, immediate family members, and extended family members and/or close friends (30). The PHQ-4 screens for anxiety and depressive symptoms (31). The qualitative needs assessment was embedded within the interactive screening program and asked program users to indicate (1) how they felt the current situation has impacted their lives, (2) what they were finding most challenging, and/or (3) what support they thought would be most helpful at the time. Since the majority of participants were women, our programmatic response to the needs assessment focused on addressing women HCWs' stressors and devising services specific to this population. Thematic analysis of ∼100 women HCWs' responses to the qualitative needs assessment resulted in the discovery of 10 main themes of concerns. The most commonly cited theme was related to workplace dynamics/duties, followed by concerns regarding family/friends, health (physical and emotional), anxiety, work-life balance, stress, finances, education (predominantly of their children), depression, and burnout.

Individual-Level Support Services

Confidential services available to all women HCWs were delivered by mental health professionals via phone (text, call) or web (email, screening program platform). Specific examples of services provided include hiring trained counselors to (1) engage in sustained, anonymous dialogue with users over the online screening program platform; (2) provide resources for logistical support (e.g., institutional, community, and governmental resources for securing childcare, food delivery, and vouchers for lodging to self-isolate from family members) via phone or web; and (3) via phone or web, refer participants to formal mental health services and assist them as they established care. We also launched an institution-wide emotional support request phone line staffed by mental health professionals (e.g., psychologists and psychiatrists). In addition to those that requested a check-in call after dialoguing with a counselor over the screening program platform, many women HCWs first engaged with our services by texting or calling the line to request an emotional support check-in call.

Institutional-Level Support Services

Four institutional initiatives related to high-risk units or departments, leadership development, community pods, and parenting forums were designed. Recognizing that any obstacle to engaging with needed support becomes magnified during disasters or crises, we matched high-risk clinical and non-clinical units, departments, or workgroups with mental health clinicians to serve as an embedded designated resource for emotional support and mental health concerns. Depending on their familiarity with their assigned workgroups, these clinicians joined regular, recurring staff huddles or held additional ones to introduce themselves, listen to staff concerns, and normalize the fear and stress associated with adjusting to the implications of new realities. These clinicians also escalated reported concerns to the workgroup leadership team, which resulted in further tailored institutional support. For example, after the embedded clinician for the Emergency Department learned that HCWs were experiencing symptoms of insomnia and sleep disturbances, the workgroup coordinated an educational and supportive session on sleep and insomnia among HCWs during the time of COVID-19. After learning that certain supervisors were finding it difficult to inspire, motivate, and manage their non-clinical HCW teams in the face of prolonged uncertainty and consistently changing protocols, we developed a series of department-specific leadership development courses. These sessions educated supervisors on the tenants of stress first aid and PFA, and provided them with opportunities for peer support and self-reflection in group sessions so that leadership personnel could then model what they experienced in these sessions with their own staff and teams. An additional noteworthy outcome of campus-wide feedback is the formation of community bubbles or pods that enable HCWs' families to connect with other families at our institution for shared childcare, educational opportunities, or socio-emotional experiences either virtually or safely in-person. Finally, parenting forums for all HCWs currently under development will provide content related to child development, child disaster behavioral health, and parenting strategies during disasters and crises. The forums will also offer parents a space to raise questions or concerns. These forums may prove to be especially helpful as many women HCWs' children return to school, albeit via new formats and with an uncharted set of circumstances.

DISCUSSION

Research shows women HCWs report high levels of psychological distress and more recent studies have shown this trend to remain constant or become exaggerated as a result of the COVID-19 pandemic (32). We found these findings from the literature to be reflected in the demand for emotional support services provided by our organization during the COVID-19 pandemic. As described here, this demand prompted us to focus on addressing the specific needs of women HCWs in our organization.

The significance of incorporating crisis behavioral health models in our work was made explicit by members of our workgroup leadership team, some of whom are experts in the field of disaster psychology themselves and oversee operations at a national center for trauma. Although the emphases of these disaster behavioral health frameworks slightly differ, they are complementary and we utilized aspects of each one in planning our emotional support services. For instance, we utilized the three-tiered approach for determining the levels of care we would provide and the associated level-specific interventions. We used PFA to establish the progression of our interventions, beginning with conducting a needs assessment, followed by offering practical assistance for addressing immediate needs, connection with social supports, and linkage with other services. Finally, throughout our work, we kept in mind the thematically classified requests of HCWs to their organizations during the COVID-19 pandemic to hear, support, and care for them.

The goals of the online interactive screening program were 2-fold: to provide individual-level emotional support and assess the needs of HCWs for future construction of additional individual-level and other institutional-level support services. Moreover, we sought to provide a service that addressed frequently identified barriers to accessing support and treatment among HCWs, including a perceived lack of time and concerns related to confidentiality. Since shorter questionnaires yield higher response rates among HCWs (33), we limited the length of the screening program by asking a total of 16 questions (excluding demographic questions) and utilized the PHQ-4, an abbreviated screening assessment for anxiety and depression. We also conceptualized the screening program to function in a dual capacity, since anecdotal evidence suggests that survey fatigue is already high among HCWs and workgroup members advocated for a time-efficient and streamlined process for HCWs to receive emotional support and provide feedback. Finally, seeking to address concerns related to confidentiality, we are enthusiastic that we were able to advertise this program as completely anonymous, since counselors are never made aware of user's personal information. Approximately 75% of program users were clinical HCWs and the assurance of anonymity and confidentiality may have contributed to this trend, since clinical HCWs are often very concerned about the confidentiality of mental health services and potential impacts of seeking such services on licensure (12, 13). A key lesson learned from the implementation of this program is the need for repeated, tailored outreach and messaging, since we experienced noticeable upticks in usage immediately following health system, department, or division-wide email and verbal virtual announcements. In addition to providing recurring reminders to our HCWs regarding emotional support, announcements were made on a staggered, rolling basis to ensure our counselors' capacity to provide sufficient support.

Based on the feedback we received from the online interactive screening program, we developed additional individual-level and institutional-level services, including an emotional support request phone line, embedded designated mental health clinicians, leadership development courses, and parenting forums. We also provided feedback in the larger institutional effort to launch community pods. At this time, the most utilized additional service has been the emotional support request line and among staff member callers, the proportion of HCWs with clinical or non-clinical duties has been fairly similar (40% non-clinical, 37% clinical, and 23% not specified). In addition, among women HCW callers, concerns have closely mirrored those identified in the interactive screening program. One of the most useful aspects of both the interactive screening program and the emotional support request line has been that, in addition to providing emotional support, counselors have been able to direct women HCWs to specific resources based on the concerns they raised. As is the case with large health systems, HCWs may seek support, but due to the fragmented nature of service development and hosting, many remain unaware of existing services that are available for use. By creating a centralized catalog for services and resources, we believe we were able to successfully direct HCWs to certain types of support they were seeking, but did not know existed. We began offering the leadership development courses for personnel managing and supervising non-clinical HCWs because many did not know how to best support their staff during crises, unlike leaders of clinical HCWs who have more experience supporting staff through stressful, adverse patient care outcomes. Although we piloted this service with non-clinical HCW leadership, based on positive testimonials, we hope to expand this offering institution-wide in the coming months. Finally, we anticipate high attendance for our upcoming parenting forums, since the themes of family/friends, work-life balance, and education, along with childcare, have consistently been cited by women HCWs.

Our work was made possible by utilizing a team-based approach and engaging HCWs and academic leaders with expertise in a variety of related disciplines, including disaster psychology, disaster behavioral health, peer support, and evaluation and delivery of mental health services to HCWs. Operating with workgroup members who have extensive experience in these fields enabled us to broaden the scope of our efforts and quickly mobilize to develop and provide additional support services, as requests from different HCW populations were made.

Compared to other mental health interventions for HCWs developed during the COVID-19 pandemic, as well as the Ebola and Severe Acute Respiratory Syndrome (SARS) outbreaks (15), our services were primarily focused on providing emotional support. Based on the review by Soklaridis et al. (15), while our intervention differed from others that increased availability to music therapy and group therapy sessions, our emotional support services did utilize aspects of other interventions that incorporated PFA and a warmline.

Several limitations of this perspective should be noted. Since our primary objective was to develop and introduce emotional support services to HCWs as quickly as possible, we were unable to measure women HCW well-being pre- and post-introduction of services. Additionally, the ratio of respondents to eligible clinical and non-clinical HCWs was not routinely tracked, as announcements of services were distributed on a regular basis to different groups within the health system. Finally satisfaction with services was not measured; however, as the testimonial at the beginning of this perspective indicates, we have received positive anecdotal feedback regarding our emotional support services.

RECOMMENDATIONS

Based on our experience developing emotional support services for women HCWs during the COVID-19 pandemic, we recommend that institutions:

- Incorporate evidence-based disaster behavioral health models in emotional support and mental health initiatives for women HCWs.
- Leverage existing resources and the expertise of key institutional wellness stakeholders when developing support services.
- Develop a variety of services that address commonly cited barriers and allow women HCWs to engage with services that correspond to their level of comfort.
- Introduce multi-purpose interventions that provide immediate emotional support, as well as assess the needs of women HCWs to inform the development of additional services.
- Partner with institutional leadership to ensure a consistent flow of information pertaining to available support services, since utilization was dependent on continual announcements being disseminated.

As the COVID-19 pandemic persists and women HCWs continue to face occupational hazards, the demand for emotional support and mental health services is expected to remain high for quite some time. In fact, research from previous infectious disease outbreaks has found that the psychological footprint of crises, like the COVID-19 pandemic, disproportionately impacts women HCWs and has the potential to affect HCW mental health for years. As a result, institutions should be taking a longitudinal approach to planning and launching initiatives to support the mental health and well-being of women HCWs. We believe the process we used to develop and introduce emotional support services to women HCWs can be a helpful guide for organizations seeking to support their staff during the COVID-19 pandemic and beyond. Women HCWs are committed to managing their current and future professional, patient care, familial, and personal responsibilities. The COVID-19 pandemic has afforded us an opportunity to both rethink the way we support women HCWs and demonstrate institutional commitments to ensuring their mental health and well-being.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JS and KM wrote the first draft. AA conceptualized the graphic representation included in the manuscript. All authors contributed important editorial feedback, as well as read and approved the final manuscript.

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Access to and Quality of Healthcare for Pregnant and Postpartum Women During the COVID-19 Pandemic

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Introduction: During the COVID-19 pandemic, obstetric care has adopted new precautions to ensure services can be maintained for pregnant women. The aim of this study was to describe access to and quality of obstetric care for pregnant and postpartum women during the COVID-19 pandemic and to identify factors that predict quality of care at this time.

Methods: Between May 3 and June 28, 2020, we recruited women who were pregnant or within the first 6 months after delivery to participate in an online survey. This included questions on access to obstetric healthcare (type and place of health care provider, changes to obstetric appointments/services, appointment preferences) and the Quality of Prenatal Care Questionnaire (QPCQ).

Results: Of the 917 eligible women, 612 (67%) were pregnant and 305 (33%) were in the first 6 months after delivery. Sixty-two percent ($n = 571$) reported that COVID-19 had affected their healthcare; appointments were rearranged, canceled or occurred *via* virtual means for 29% ($n = 166$), 29% ($n = 167$), and 31% ($n = 175$) of women, respectively. The majority preferred to physically attend appointments (74%; $n = 676$) and perceived the accompaniment of birth partners as important (77%; $n = 471$). Sixty-two percent ($n = 380$) were permitted a birth partner at delivery, 18% ($n = 111$) were unsure of the rules while 4% ($n = 26$) were not permitted accompaniment. During pregnancy, QPCQ was negatively associated with disruption to obstetric services including exclusion or uncertainty regarding birth partner permissions [$F_{(7, 433)} = 11.5$, $p < 0.001$, $R^2 = 0.16$] while QPCQ was negatively associated with inadequate breastfeeding support postpartum [$F_{(1, 147)} = 12.05$, $p = 0.001$, $R^2 = 0.08$].

Conclusion: Pregnant and postpartum have experienced disruption in their access to obstetric healthcare. Perceived quality of obstetric care was negatively influenced by cancellation of appointment(s), suspension of services and exclusion of birth partners at delivery. During this time, continuity of care can be fulfilled *via* virtual and/or phone appointments and women should receive clear guidance on changes to services including birth partner permissions to attend delivery.

Keywords: COVID-19, obstetric care, pregnancy, postpartum, quality of care

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INTRODUCTION

In January 2020, the World Health Organization declared a public health emergency in response to the rising incidence of the 2019 novel coronavirus (COVID-19) that was later declared a pandemic in March 2020. In the early stages of the pandemic, pregnant women were categorized as high-risk and advised to limit social interactions to protect themselves against contracting the virus. As a result, clinical care has adopted new precautions to ensure that services can be maintained for pregnant women. In the US, these precautions include the use of personal protective equipment, physical distancing, frequent hand washing, and limiting contact with others (1). This is similar in the UK alongside permission for asymptomatic partners to attend births (2). Despite this, emerging evidence indicates that for many women, services are being disrupted and include suspended and/or canceled appointments, restrictions regarding place of birth, continuity of care (3), and much ambiguity regarding birth partner permissions to attend delivery (4, 5). Disrupted access to healthcare appears to be a global consequence of the COVID-19 pandemic (6–11). This is of particular concern with respect to obstetric practice because limited access to services increase the risks of adverse health outcomes for both mother and baby (12).

In an effort to protect against COVID-19 transmission, many pregnant and postpartum women are fulfilling appointments by telephone and video teleconferencing. While this adaptation to continuity of care is extremely encouraging, it is plausible that reduced face-to-face interaction may invoke a perception of limited healthcare access among pregnant and postpartum women (13). In an effort to combat this plausible perception, women are encouraged to avail of information online regarding their pregnancy and associated COVID-19 risks (14). Women are also encouraged to engage with support groups to limit pandemic-related feelings of isolation (13, 15) that can have adverse outcomes for mother and baby (16). To ensure that such online resources and support groups are effective in benefitting women during this time, it is paramount to know the type and format of information women would like to receive.

Pandemic associated disruptions in accessing healthcare has negative consequences for quality of care (17, 18). According to Heaman et al. (19), prenatal quality of care is underpinned by constructs that include information sharing, anticipatory guidance, sufficiency, approachability, and availability. During the COVID-19 pandemic, it is plausible that these constructs are perturbed given the need for the maternity environment to rapidly adapt (3). For example, during the pandemic, obstetric caregivers are tasked with staying informed and adapting to guidance regarding the availability of services and the impact of COVID-19 on pregnant women and their babies (20). As the guidance emerges and evolves, it may not always be possible for caregivers to provide this information. Furthermore, the redeployment of midwives to general nursing roles, reductions in staff numbers due to COVID-19 related sickness, the implementation of virtual instead of face-to face appointments (3), restrictions on both home births (21), and community visits (22) may negatively impact the sufficiency of services, the approachability, and availability of staff. As a result, quality of care for pregnant and postpartum women may be directly impacted by the COVID-19 pandemic however this remains to be determined.

The primary aim of this study was to describe access to (e.g., appointment fulfillment, cancellations, virtual means, and service suspensions) and quality of obstetric care (e.g., information sharing, anticipatory guidance, sufficiency, availability, and approachability) for pregnant and postpartum women during the COVID-19 pandemic. A secondary aim was to identify factors that predict quality of care in pregnant and postpartum women. Lastly, we aimed to explore what information would benefit pregnant and postpartum women during a pandemic to help inform clinical and research practice. The study was approved by the Ethics Committee at York St. John University (Reference number: STHEC0011) and adhered to the ethical statements outlined in the Declaration of Helsinki apart from registry in a publicly accessible database.

METHODS

Sample Design

Between May 3 and June 28, 2020, women that self-reported as pregnant or in the first 6 months following delivery completed an online questionnaire advertised *via* social media platforms (Facebook, Twitter, Reddit) and shared publicly to facilitate snowball sampling. Women were ineligible to participate if not currently pregnant, or not within the first 6 months following delivery. Participants were made aware of the study aims, risks, and benefits alongside reassurance of freedom to withdraw from the questionnaire at any time-point. Electronic consent was requested before progressing to the survey.

Variables Assessed

Participants answered questions on demographic factors including their age, level of education, ethnicity, employment status, health, and reproductive history. They responded to questions about symptoms, testing, and diagnosis of COVID-19 they experienced during/following pregnancy. The authors liaised with a midwife to confirm aspects of healthcare access to be captured in the questionnaire. Participants were asked about their current level of access to obstetric healthcare, including (1) the type of health care provider (e.g., obstetrician, midwife, general practitioner, a combination of each), (2) the place at which they received their care (hospital, family practice, private clinic, or other), (3) any changes in obstetric appointments or services (e.g., unchanged, canceled, or modified schedule; ability of their partner to attend appointments; transportation to appointments), and (4) any appointment preferences they had (physical attendance, virtual, home visit, no appointment). Pregnant women were asked about the impact of COVID-19 on their birth plans including birth partner permissions to attend and their feelings about this. All women were asked an open-ended question about what type of pregnancy related information would be/had been useful for them during this time (i.e., during a global pandemic).

Quality of Prenatal Care Questionnaire

All participants completed a validated questionnaire to quantify quality of healthcare using the 46-item Quality of Prenatal Care Questionnaire (QPCQ) (19). While the questionnaire is predominantly intended for use during pregnancy, it has been deemed a valid and reliable instrument to assess the relationship between quality of care and maternal health outcomes (23–25). Pregnant and postpartum women were asked to complete the questionnaire with their most recent pregnancy related appointment in mind.

The QPCQ is a self-report instrument that quantifies quality of prenatal care using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). It is comprised of six subscales that include information sharing (9 items), anticipatory guidance (11 items), sufficient time (5 items), approachability (4 items), availability (5 items), and support and respect (12 items). The sum of the QPCQ subscales are calculated and presented as a total score ranging from 46 to 230 with higher values indicating better quality of care. The total score obtained is divided by 46, and the score of each subscale is divided by the respective number of questions within that subscale. The mean score obtained (total or subscale) can range from 1 to 5, again with the higher value representative of better care quality. Cronbach's alpha was applied to each of the six subscales ($\alpha =$ 0.91, 0.92, 0.92, 0.87, 0.89, and 0.97, respectively) and totaled score of the QPCQ for internal consistency ($\alpha = 0.97$). To contextualize participant QPCQ responses, the total score was expressed as a percentage of the possible maximum score (230), with scores at or over 70% indicating participant care was *good,* and scores under 70% indicating that care was *poor* (26). This percent score and dichotomous coding was used in subsequent statistical analyses.

Thematic Coding

The open-ended questions were analyzed by a researcher with an undergraduate degree in Psychology, who was blind to the study hypothesis and all other data on participants. The questions coded included, although were not limited to, items such as "How does [your partner being permitted/not permitted to attend the birth] make you feel?" A qualitative content analysis was conducted on six open ended questions separately in accordance with relevant guidelines (27). The researcher immersed themselves in the responses and devised a categorical coding scheme for each question to reflect emerging themes from the responses (e.g., "anxious," "relieved," "sad," "alone") to enable subsequent input into a statistical model. The coding scheme was reviewed by the first and second authors as a validity check. All participants' answers were then coded as having each of these themes present or absent. Approximately 20% of all responses were independently coded by the first author as a reliability check with almost complete agreement; any scoring differences, albeit negligible, were resolved through discussion.

Statistical Analysis

All data were checked for accuracy and invalid data (e.g., any responses that were not plausible) were removed. Statistical analysis was performed using IBM SPSS version 26 (SPSS Inc., Chicago, IL). Descriptive analysis was performed to examine the characteristics of the sample and the distribution of the quality of care related outcomes. Means and standard deviations were calculated for continuous variables while proportions were calculated for categorical variables. An independent samples *t*-test was performed to compare QPCQ subscales reported by pregnant and postpartum women during the COVID-19 pandemic. Pearson correlations were used to support the bivariate analysis, which aimed to verify the association between the independent variables (maternal and obstetric care characteristics as well as COVID-19 related outcomes) and the dependent variable (quality of care during the gestational or post-partum period, i.e., QPCQ percentage score). Multiple linear regression analysis was then used to determine which of the analyzed variables could be considered predictors of maternal quality of care during a pandemic where QPCQ percentage score was the dependent variable. No statistical analysis was performed on the qualitative responses; these were collated for observational purposes only.

RESULTS

Participant Characteristics

Of the 1,147 responses, 225 were removed due to incomplete consent ($n = 125$), ineligibility with regards to pregnant and post-partum status ($n = 15$) and/or no data being provided beyond consent ($n = 90$). Of the 917 eligible women, 612 (67%) were pregnant and 305 (33%) were postpartum. The mean age of participants was 31 $\pm$ 5.2 years ($n = 911$), 70% ($n = 458$) had at least 1 child already and 39% ($n = 355$) of the sample lived in cities. The majority of responses came from women educated beyond high school ($n = 789$), living in the United Kingdom ($n = 625$), of white ethnicity ($n = 873$), in a relationship ($n = 861$) and in full-time employment ($n = 488$; **Table 1**). Eighty-six percent ($n = 796$) of the sample rated their general health positively; 17% ($n = 156$) reported having $\geq$1 pre-existing health condition while 22% ($n = 201$) reported $\geq$1 pregnancy related complication. The prevalence of pre-existing and pregnancy related complications are illustrated in **Table 1**.

Five percent ($n = 44$) of the sample had experienced COVID-19 symptoms, 9% ($n = 78$) had received a COVID-19 test and <1% ($n = 5$) were diagnosed with a positive result. Forty-nine percent ($n = 445$) of the women had self-isolated of which 422 women clarified that the reason for this was due to medical reasoning (11%; $n = 46$), personal choice (62%; $n = 260$) and a combination of both (27%; $n = 116$). Of the entire cohort, 46% ($n = 419$) perceived themselves to be at higher risk in general because of COVD-19 compared to individuals who were not pregnant or in the first 6 months after delivery.

Access to Healthcare

Fifteen percent ($n = 141$) of women indicated that COVID-19 had impacted how they traveled to appointments. During the pandemic, sixty-eight percent ($n = 624$) of women report traveling to pregnancy related clinical appointments by car. Forty-eight percent ($n = 439$) of women reported receiving care from a midwife, 16% ($n = 143$) from an obstetrician, 0.5% ($n = 5$)

TABLE 1 | Participant characteristics.

Number (% out of 917) or ± standard deviation	
Degree	
Less than high school degree	6 (1%)
High school degree or equivalent	84 (9%)
College degree	182 (20%)
Bachelor degree	251 (27%)
Graduate degree	149 (16%)
Postgrad	207 (23%)
Other	25 (3%)
Prefer not to say	11 (1%)
Ethnic background	
White	873 (95%)
Black or African American	3 (0.3%)
American Indian	1 (0.1%)
Asian	17 (2%)
Native Hawaiian or Pacific Islander	21 (2%)
Country of residence	
Australia	12 (1%)
Bermuda	1 (0.1%)
Canada	25 (3%)
Germany	1 (0.1%)
India	1 (0.1%)
Indonesia	1 (0.1%)
Ireland	66 (7%)
New Zealand	2 (0.2%)
Pakistan	1 (0.1%)
UAE	5 (1%)
UK	652 (71%)
USA	129 (14%)
Relationship status	
Single	18 (2)
In a relationship/married, living together	861 (94%)
In a relationship/married, living apart	34 (4%)
Separated	1 (0.1%)
Widowed	2 (0.2%)
Employment status	
Student	17 (2%)
Self-employed	49 (5%)
Employed part-time	137 (15%)
Employed full time	488 (53%)
Homemaker/full-time parent	61 (7%)
Unemployed before COVID-19 and looking for work	5 (1%)
Unemployed before COVID-19 and not looking for work	10 (1%)
Employed before COVID-19 but have been laid off work during the pandemic	20 (2%)
I have been furloughed	100 (11%)
Other	29 (3%)
Pre-existing complications	
Cardiovascular disease	7 (1%)
Respiratory disease	35 (4%)
Type 1 diabetes	1 (0.1%)
Type 2 diabetes	2 (0.2%)

(Continued)

TABLE 1 | Continued

Number (% out of 917) or ± standard deviation	
Impaired glucose tolerance	6 (1%)
High blood pressure	16 (2%)
Neurological disorder	10 (1%)
Depression	175 (20%)
Anxiety	219 (24%)
Bone disease	4 (1%)
Other	60 (7%)
Average number of complications pre-pregnancy	0.58 ± 0.88
Pregnancy complications	
No complications	637 (70%)
Gestational diabetes	51 (6%)
Preeclampsia	27 (3%)
Eclampsia	1 (0.1%)
Placenta previa	22 (2.4%)
Pre-term labor	13 (1.4%)
Intrauterine growth restriction	12 (1.3%)
Twins	18 (2.0%)
Short cervix	6 (1%)
Pelvic girdle pain	108 (12%)
Depression	31 (3%)
Anxiety	63 (7%)
Bone disease	1 (0.1%)
Other	43 (5%)
Average number of pregnancy related complications	0.43 ± 0.78

from a family doctor and 23% ($n = 210$) from a combination of services. Twenty-nine percent ($n = 265$) of pregnancy related appointments took place at a general practice, 33% ($n = 302$) at hospital, 8% ($n = 77$) at private clinics while 19% ($n = 176$) indicated *other* on the questionnaire (**Table 2**).

Nine percent ($n = 82$) of women reported changing their healthcare provider because of COVID-19. Sixty-two percent ($n = 571$) of women reported that COVID-19 had affected their healthcare. Of this 571, 29% ($n = 166$) reported that at least one appointment had been rearranged, that at least one appointment had been canceled (29%; $n = 167$), 31% ($n = 175$) of women had their appointment over the phone or *via* virtual means while 10% ($n = 57$) reported *other* although did not disclose how their care was affected. Appointment cancellations/rescheduling on behalf of the clinic occurred for 41% ($n = 372$) of pregnant and postpartum women while 9% ($n = 81$) of women canceled appointments themselves predominantly due to childcare issues ($n = 34$) and concerns around availability of personal protective equipment ($n = 28$). Of the pregnant cohort, 36% ($n = 223$) reported that pregnancy-related services had been suspended because of COVID-19 that may have included, although not limited to, blood pressure, blood, and urine tests. The suspension of these services caused women to feel anxious ($n = 84$), neglected ($n = 46$), neutral ($n = 39$), sad ($n = 31$), and frustrated ($n = 24$) about this (**Table 3**). Seventy-four percent ($n = 676$) of respondents prefer to physically attend clinical appointments,

TABLE 2 | Type and access to obstetric care during the COVID-19 pandemic.

Type of healthcare provider	Number (% out of 917)
Midwife	439 (48%)
Obstetrician	143 (16%)
Family doctor	5 (0.5%)
Combination of services	210 (23%)
Place of healthcare	
General practice	265 (29%)
Hospital	302 (33%)
Private clinic	77 (8%)
Other	176 (19%)
Impact of COVID-19 on obstetric services	
COVID-19 affected healthcare	571 (62%)
At least one appointment rearranged	166 (29%)[a]
At least one appointment canceled	167 (29%)[a]
Appointments fulfilled *via* or virtually means	175 (31%)[a]
Appointment cancellations on behalf of clinic	372 (41%)
Appointment cancellations on behalf of patient	81 (9%)
Scheduled appointments had taken place *(albeit type may be different)*	639 (70%)
Pregnancy services suspended	223 (36%)[b]
Pregnant and postpartum women prefer to:	
Physically attend appointments	676 (74%)
Have phone appointment	120 (13%)
Have a virtual appointment	85 (10%)
Have a home visit	77 (8%)
Miss appointments	16 (2%)

[a]Subgroup of n = 571; [b]Pregnant cohort only.

13% ($n = 120$) would prefer a phone appointment, 10% ($n = 85$) would prefer a virtual appointment, 8% ($n = 77$) would prefer a home visit while only 2% ($n = 16$) would prefer to miss their appointment during this time. These findings illustrate that the majority of women did not want to reduce the number of medical appointments, but due to clinic factors or their own personal circumstances, the number of appointments had reduced for around a third of women.

Access to Birthing and Postpartum Services

Of the pregnant cohort, 72% ($n = 441$) planned to have a vaginal birth with 83% ($n = 507$) reporting that COVID-19 had not influenced delivery mode. Pregnant women mostly planned to deliver in hospital (77%; $n = 470$) with 10% reporting that the COVID-19 pandemic had altered plans about where they would deliver. Only pregnant women were asked about their birth partner; 85% ($n = 518$) confirmed they had a birth partner and 77% ($n = 471$) reported that having birth partners present at delivery was viewed as important. Four percent ($n = 22$) of pregnant women were permitted accompaniment of birth partners to clinical appointments, 62% ($n = 380$) were allowed have their birth partner at delivery, 18% ($n = 111$) were unsure of the rules regarding partner attendance, while 4% ($n = 26$) were not permitted to attend delivery. For pregnant women unsure about their birth partners permissions or not permitted accompaniment ($n = 137$), feelings of anxiety (65%; $n = 89$), sadness (39%; $n = 54$), and loneliness (9%; $n = 12$) were reported while those permitted to have birth partners present expressed feelings of relief (33%; $n = 124$) (**Table 4**). A total of 66% ($n = 401$) women planned to breastfeed, with 47% ($n = 289$) expecting

TABLE 3 | Example responses when participants were asked how they felt about services being suspended/canceled.

Feeling	Example quotes
Anxiety	"As this is my first baby, I am extremely anxious. I am not from the U.K. (my husband is) and definitely feel that my care would have been better elsewhere" (P46). "Nervous—lack of reassurance & information" (P93). "Anxious and angry" (P225).
Neutral	"Ok, not ideal but the best of a difficult decision I think" (P590). "Feeling perfectly fine so have no concerns" (P919). "It reduces my contact with other people so it's preferable at this stage" (P302).
Sad	"Sad. This is my first baby, and I don't feel I'm getting the same experience regarding antenatal care as would be usual in normal circumstances" (P314). "Upset as haven't heard my baby's heartbeat at all" (P373). "Very unhappy about the safety my pregnancy especially after previous delivery problems" (P428).
Frustrated	"Frustrated and nervous that important appointments will be taken away from me. If grocery stores are deemed essential, how is it that many Dr. appointments get canceled? They are essential services!" (P459). "Frustrated and disappointed. I have had no support or contact from the community midwife team. My hypertension diagnosis was almost missed due to lack of appointments" (P666). "It made me very frustrated. I understood why but I felt like I wasn't able to make fully informed decisions or know if I would need further testing or not" (P445).
Neglected	"A bit abandoned as first pregnancy and would like confirmation that all is ok" (P87). "Neglected. Not getting the care I was originally told I needed" (P214). "I have never actually spoken nor met my assigned midwife, for all appointments I have had to chase or ascertain whether they were going ahead, and *via* which means" (P952).

TABLE 4 | Example responses when participants were asked how they felt about their partners restricted access or permission to attend delivery.

Feeling	Example quotes
Anxiety	"He's only allowed in once I'm 7 cm dilated & I'm worried about that. I want him there from the start as I think I'll panic without him" (P93). "I'm being induced, and he can't attend until I am in labor so very scared and worried as it is my first baby" (P241). "Nervous and worried about not having support with me" (P315).
Relieved	"Reassured. I know I will need the support" (P34). "Yes, thank God, he can be there. I am so relieved I won't be alone and that he can share this huge transition in our lives with me" (P66). "I am very glad I will be allowed one support person in the delivery room" (P63). "I'm glad he is able to be with me as I do not want to be on my own and do not want my husband to miss the birth of our first child" (P104).
Sad	"This will probably be our only baby and that he hasn't been able to come to my scans has been very disappointing and upsetting" (P291). "Upset as I wish to have him there throughout the whole time" (P373). "Upset and angry" (P649).
Loneliness	"They can only be present for the very end stage of labor and cannot visit afterwards. I feel alone, extremely anxious and devastated" (P9). "It makes me feel scared that I will have to go through such a beautiful and scary time all alone especially it being a first child" (P412) "He won't be allowed to join until 3 cm—this makes me feel lonely and isolated" (P786).

TABLE 5 | Quality of Prenatal Care Questionnaire subscale and total scores for the entire sample, pregnant and postpartum cohort.

Subscale	Entire group	Pregnancy	Postpartum	*p*-value
Information sharing	4.1 ± 0.7	4.1 ± 0.7	4.2 ± 0.8	0.13
Anticipatory guidance	3.4 ± 0.9	3.3 ± 0.8	3.6 ± 0.9	<0.001
Sufficiency	3.6 ± 0.9	3.5 ± 0.9	3.7 ± 0.9	<0.001
Approachability	3.8 ± 0.9	3.8 ± 0.9	4.0 ± 0.8	0.04
Availability	3.7 ± 0.9	3.7 ± 0.8	3.8 ± 0.9	0.42
Support	4.0 ± 0.8	3.9 ± 0.7	4.1 ± 0.8	<0.001
Total Score (out of 5)	3.7 ± 0.8	3.7 ± 0.7	3.7 ± 0.8	0.24
Total Score (% of maximum)	74 ± 16	74 ± 14	76 ± 19	0.05

adequate support. Forty-nine percent ($n = 300$) pregnant women expected to receive a home visit by a community midwife. Of the postpartum cohort, 50% ($n = 150$) chose to breastfeed and 21% ($n = 64$) of respondents reported they did not receive adequate help. Forty-nine percent ($n = 149$) of post-partum women received a community visit postpartum with a negligible number of women uncomfortable with this (1%; $n = 4$).

Quality of Care

The subscales and overall scores of the QPCQ are displayed in **Table 5**. Of the entire cohort, 620 completed the QPCQ of which $n = 453$ were pregnant while $n = 167$ were postpartum. Of those that completed the QPCQ, 66% ($n = 297$) of pregnant and 75% ($n = 126$) of postpartum respondents perceived their quality of care as *"good"* (>70%), while 34% ($n = 156$) of pregnant women and 25% ($n = 41$) of the post-partum women reported their quality of care as *"poor"* (<70%). This equates to overall, 68% of women reporting good quality of care with 32% reporting poor quality of care. Postpartum women scored significantly higher on approachability ($p = 0.04$), anticipatory guidance, sufficiency, and support compared to pregnant women ($p < 0.001$; **Table 5**).

A number of factors within the pregnant cohort were significantly correlated with the QPCQ percentage score including the country within which participants lived ($r = -0.95$, $p = 0.05$). To allude further, QPCQ score differed for those living in Australia (83 ± 12%; $n = 8$), Canada (80 ± 14%; $n = 14$), Ireland (72 ± 10%; $n = 23$), UAE (72 ± 15%; $n = 4$), UK (72 ± 14%; $n = 314$), and USA (77 ± 15%; $n = 73$). Self-rated health was significantly correlated with QPCQ score ($r = 0.14$, $p = 0.002$), with positively rated health favoring good quality of care.

Respondents that received obstetrician and midwife care yielded perceived quality of care to be favorable ($r = -0.11$, $p = 0.02$) over those receiving care from a family doctor or a combination of services. Service cancellations ($r = 0.23$, $p < 0.001$), suspension to services ($r = 0.18$, $p < 0001$) and changes made to planning delivery mode ($r = 0.15$, $p = 0.001$) were all significantly correlated to QPCQ score whereby those that were negatively impacted, reported lower quality of care. Quality of care was significantly correlated with birth partners permission to attend birth ($r = -0.21$, $p < 0.001$) whereby those permitted to be accompanied reporting good quality of care (76 ± 14%) compared to those not permitted (63 ± 10%) and those that were unsure (69 ± 14%). In contrast, birth partner attendance to clinical appointments was not associated with quality of care ($r = -0.06$, $p = 0.19$).

These outcomes collectively generated a significant multiple linear regression model, with QPCQ score as the dependent variable; $F_{(7, 433)} = 11.5$, $p < 0.001$, $R^2 = 0.16$ (**Table 6**). Of these factors, birth partners attendance and appointment cancellations significantly contributed to the QPCQ score ($p < 0.001$) as did self-rated health, type of healthcare received, suspension to services, and changes to delivery mode ($p < 0.05$). For postpartum women, the only factor associated with the QPCQ result was the support available to breastfeed ($r = 0.28$, $p = 0.001$) which contributed significantly to the overall QPCQ score according to linear regression analysis; $F_{(1, 147)} = 12.05$, $p = 0.001$, $R^2 = 0.08$ (**Table 6**).

Future Information

A subset of pregnant women ($n = 296$) responded to an open question asking what information would be useful for them to have during a time where physical distancing is in place. Of this subset, respondents indicated that it would be beneficial to

TABLE 6 | Multiple Regression Predicting Quality of Care for pregnant and postpartum women.

	β (95% CI)	*p*-value
During pregnancy		
Country residing	−0.08 (−0.6, 0.01)	0.09
Self-rated general health	0.11 (0.4, 3.5)	0.01
Type of healthcare	−0.09 (−2.4, −0.1)	0.04
Clinic canceling or rescheduling	0.18 (2.5, 7.7)	<0.001
Services suspended	0.12 (0.6, 4.6)	0.01
Delivery mode influenced by COVID-19	0.13 (1.7, 9.2)	0.004
Birth partner attending delivery	−0.21 (−5.1, −2.0)	<0.001
Post-partum		
Adequate help breastfeeding	0.28 (4.63, 16.9)	0.001

receive information on the risks associated with COVID-19 for mother and baby (17%; $n = 50$), remain updated on changes made to services pertaining to scheduling (what appointments to expect next), cancellations, and clarity on rules for birth partners to attend routine appointments including delivery (28%; $n = 84$). Women would benefit from guidance on delivery options including pain relief, induction, birth plans, and home births (28%; $n = 78$), antenatal classes available to meet other pregnant women (7%; $n = 21$), breastfeeding (5%; $n = 16$), and mental health (2%; $n = 46$). The majority of women reported that they engaged with Facebook for pregnancy related information (88%; $n = 260$) with Instagram (18%; $n = 53$) and Mumsnet (5%; $n = 14$) also used. The preferred form of information varied between an infographic (35%; $n = 105$), leaflet (30%; $n = 88$), video (29%; $n = 85$), and an online Q&A (19%; $n = 55$).

A subset of post-partum women ($n = 155$) responded to an open question asking how post-partum care could be improved or altered during a time where physical distancing is in place. Twelve percent ($n = 18$) of women stated no improvement in care was necessary, 40% ($n = 62$) proposed virtual appointments would be useful while 15% ($n = 24$) indicated that more PPE to allow for face-to-face appointments would be beneficial. Lastly, 29% ($n = 45$) said they would benefit from more support that could be achieved with less rushing and canceling of appointments.

The same subset indicated that recently pregnant women would benefit from more information regarding risks related to COVID-19 and advice on how to stay safe during pregnancy (21%; $n = 33$), more general pregnancy related information (including antenatal and postnatal classes, labor, delivery and any reference to support that is available) (27%; $n = 42$), updates regarding any changes to services as a result of COVID-19 (27%; $n = 42$), and advice on how to cope with loneliness following birth particularly in the absence of peer contact that has been removed because of the pandemic (17%; $n = 27$). Postpartum women predominantly engaged with Facebook (12%; $n = 35$) for pregnancy related information while Instagram and Mumsnet were preferred for others (6%; $n = 19$ and 2%; $n = 6$, respectively).

DISCUSSION

This study demonstrated that patient-reported perceptions of obstetric health care quality was negatively impacted by disturbances to services (cancellations and suspensions) and ambiguity regarding birth partner permissions to attend delivery during the COVID-19 pandemic. The majority of women indicated a willingness to continuing to attend appointments in person. Finally, women identified a need for clearer communication predominantly regarding any changes to maternity services (scheduling, cancellations, and services available), clear guidance on birth partner permissions to attend routine appointments including delivery and clarity regarding the associated risks of COVID-19 for mother and baby.

Access to Healthcare

In this study, the majority of scheduled pregnancy related appointments were fulfilled, however, more than one-third of women experienced suspension to services and consequentially, anxiety, frustration, and sadness (**Table 2**). In support of fulfilling services and avoiding suspensions and cancellations, healthcare providers can benefit in knowing that although half of the respondents in this study felt at higher risk because of COVID-19 compared to a non-pregnant or non-post-partum woman, most wanted to physically attend appointments. The suspension of services may be due to inadequate personal protective equipment (PPE) supplies (28) to protect women and healthcare staff against contracting COVID-19 (29, 30). In situations where this is not feasible, alternative strategies could be adopted to alleviate associated stress and anxiety for women and may include virtual appointments, phone calls or where feasible, a home visit. These strategies, that appear to be accepted by many, offer greater flexibility for healthcare professionals to ensure services can be maintained in an effort to avoid suspensions and cancellations to obstetric care.

Birth partners have been heavily impacted by the COVID-19 pandemic with many excluded from or unclear about their permissions to attend appointments and including delivery. According to respondents, it is important to women to have the accompaniment of their birth partner at delivery (**Table 4**). It is noteworthy that high quality of care was associated with having a birth partner at delivery, although not associated with accompaniment to regular clinical appointments. This interesting observation highlights the importance of prioritizing birth partner attendance at delivery over all other appointments which could potentially alleviate the anxiety and loneliness for those giving birth during the COVID-19 pandemic. The rules vary greatly between countries (31); in the United States, many clinical settings are excluding birth partners or requesting a choice between a doula and birth partner (4), while in the UK, asymptomatic birth partners are permitted to be present for labor and birth whilst wearing a face mask, unless performed under general anesthetic (2). Indeed, such precautions are in place to minimize the risk of COVID-19 infection to the mother and infant. However, support from partners and caregivers have many positive effects on maternal health and well-being at delivery (4) including reduced labor pain, reduced stress, shorter duration of labor, less medication need, increased maternal satisfaction, and a positive attitude toward motherhood (32, 33). Furthermore, emotional support has shown to reduce the length of stay in hospital and the need for delivery by cesarean section (34). Therefore, the absence of maternal support in an effort to protect against COVID-19 contamination may adversely affect other aspects of maternal and childbirth outcomes that could have long lasting implications. Birth partners are also helpful for hospital staff who have reported that they feel bad when they are unable to provide one-to-one support during the pandemic in the absence of birth partners (4). This is reaffirmed by one respondent in this study who stated that "I feel it is important for my partner to be there for his baby's birth and feel that pressure will be taken off of midwives if a partner is there to assist" (P955). Based on the positive outcomes that birth partner attendance can have on maternal and infant outcomes as well as alleviating pressures for hospital staff, facilitating birth partner attendance to delivery seems imperative.

Quality of Care

Disruption to obstetric services including suspensions, cancellations, changes to delivery plans, restricted birth partner access, and inadequate breastfeeding support were associated with reduced quality of care during pregnancy and the postpartum period. Despite this, the overall influence of these factors in collectively predicting quality of care was low. This may in part be explained by the understanding that quality of care is a multi-dimensional concept and includes a variety of characteristics including safety, efficacy, timely, efficiency, equity, and a people-centered approach to care (35). While this study primarily focused on the timely aspect of care (reducing delays in providing/receiving healthcare), it is plausible that other factors, for example, safety (delivering healthcare that minimizes risks and harm to service users), may have impacted quality of care to a greater extent particularly during the COVID-19 pandemic. In agreement with a previous study, our findings highlight that post-partum women would benefit from increased breastfeeding support (36). This may be of unique value to healthcare professionals to ensure bonding between mother and baby particularly at a time where anxieties and psychological vulnerability are heightened (37–39).

Future Information

This study has provided insight into what pregnant and postpartum women would like to know during a pandemic. Pregnant women want to be informed about the logistics of having a baby during a pandemic, including site specific changes to services and rules regarding birth partners permission to attend delivery. As aforementioned, these factors were associated with quality of care; it is plausible that if women received sufficient information about service changes and birth partner permissions, the psychological burden of COVID-19 on pregnancy related care could be lessened. Virtual appointments seemed acceptable by postpartum women and the logistics of this have previously been described (40). Postpartum women also want to receive guidance on reducing loneliness that appears to be a common feeling for this population during the COVID-19 pandemic (41). This warranted information could be shared *via* social media platforms with no clear preference identified by participants regarding the format of delivery.

Limitations and Future Directions

This study is limited by a reliance on participants to self-report their eligibility (pregnant or within 6 months after delivery) to participate. Secondly, although this survey was distributed with intention of reaching a global audience, the majority of respondents were white and from developed countries including the United Kingdom, Ireland, and the United States. This limits the generalizability of findings to all pregnant and/or recently post-partum women. Lastly, to the authors knowledge, no valid questionnaire exists to quantify access of healthcare specifically among pregnant and postpartum women. Although all constructs of healthcare access have been described, it may limit the replicability of this outcome.

This study converges with previous authors whereby healthcare services become disrupted during a pandemic and that these disruptions are negatively associated with quality of care (17, 18). The research has also provided agreement that women feel anxious during this time (42) and that this is likely exacerbated by birth partner restrictions (4). To the authors knowledge, this is the first study during the COVID-19 pandemic to attempt to quantify access to and quality of obstetric care. Lastly, this study offers novel insight into the information and guidance wanted by pregnant and post-partum women during this time. While suggestions were made by Jago et al. (13) regarding what this information could be, this study presents primary data to support their suggestions. Given that this [information sharing] is a construct of prenatal quality of care (19) and can be achieved by an online distribution of resources, it is an important confirmation from respondents that could ease in part, the burden of the COVID-19 pandemic on pregnant and postpartum women. To advance on this work further, insight is necessary to understand access to, and quality of care for pregnant and post-partum women from the black and ethnic minority community and from countries not captured in this study.

CONCLUSION

During this global pandemic, many pregnant and postpartum many women have experienced a disruption in their access to healthcare. Patient perceptions of the quality of their obstetric care was negatively influenced by cancellation of appointment(s), suspension of services and exclusion of birth partners at delivery. Accordingly, ensuring the continuity of care *via* virtual and/or phone appointments and providing clear guidance on birth partner permissions to attend delivery may help improve quality of obstetric care during this time.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee at York St. John University (Reference number: STHEC0011). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB had access to the data in the study and takes responsibility for the integrity, the accuracy of data, and statistical analysis. FL data analysis. HJ and MD study concept and design. All authors data interpretation, drafting, and revisions of manuscript for important intellectual content.

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REVIEW
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Predisposition of Women to Cardiovascular Diseases: A Side-Effect of Increased Glucocorticoid Signaling During the COVID-19 Pandemic?

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The novel coronavirus disease 2019 (COVID-19) pandemic has created a significant health crisis worldwide. To mitigate this disease's spread, "social distancing" and "shelter in place" have been implemented. While these actions have been critical to controlling the pandemic, they have short- and long-term mental health consequences due to increased stress. There is a strong association between mental stress and cardiovascular disease (CVD). Young women (pre-menopausal) are at high risk of developing CV events in response to mental stress compared to age-matched men. The mechanisms underlying women's increased reactivity and response to stress are mostly unknown. The present review summarizes the known physiological consequences of mental stress in women's CV health and the latest molecular findings of the actions of the primary stress hormones, glucocorticoids, on the CV system. The current data suggest a clear link between psychological stress and heart disease, and women have an increased sensitivity to the harmful effects of stress hormone signaling imbalances. Therefore, it is expected that with the given unprecedented levels of stress associated with the COVID-19 pandemic, women's CV health will be significantly compromised. It is critical to widen our understanding of the direct contribution of mental stress to CVD risk in women and to identify biochemical markers with predictive value for CVD in female patients with/without cardiovascular conditions who have experienced significant mental stress during the current pandemic.

Keywords: COVID-19, pandemic, women, cardiovascular risk, stress, glucocorticoids, heart

INTRODUCTION

An outbreak of a novel coronavirus that started in December 2019 in Wuhan, China, has resulted in a horrifying pandemic (1). Worldwide, the health and economic effects of the coronavirus disease 2019 (COVID-19) have been exacerbated for women, in particular for young-middle aged women, who are struggling to combine their professional and family responsibilities (2–4). Disparities in job security, wages, and social pressure to stay home to care for children and older family members have significantly heightened psychological and physical pressure for women as compared to their male counterparts (5). Moreover, with the deepening pandemic situation, the restricted movement and social isolation measures have led to an exponential increase in gender-based violence (6). Therefore, women are currently suffering from an unprecedented level of psychological and physical stress.

Exposure to acute and chronic mental stress has been associated with an increase in the causation of pathological conditions for both men and women; however, women are more susceptible to the deleterious effects of stress compared to men (7, 8). Depression and anxiety are associated with an increased incidence of obesity, autoimmune disorders, and atherosclerosis in women (9). Clinical studies have highlighted the connection between elevated mental stress and adverse cardiovascular events in women, including myocardial ischemia (MI) and stroke (10–12). Mental stress–induced MI (MSIMI) is twice as common in women under 50 years old than similarly aged men (13). Moreover, among patients with coronary artery diseases (CAD), women, especially younger women, are more likely to develop MSIMI than men, despite less severe obstructive CAD and a relatively similar profile of traditional CAD risk factors (14). Despite these mentioned clinical evidences, the molecular pathways underlying the deleterious effects of stress in women are unknown. In the present review, we summarize the known sex-specific molecular and physiological effects of stress (crosstalk between sex and stress hormones) on the cardiovascular system and discuss the clinical manifestations of mental stress on the female heart. We also review the potential implications of the elevated mental stress associated with the COVID-19 pandemic in context of future cardiovascular risks in women.

STRESS HORMONE SIGNALING AND PHYSIOLOGICAL EFFECTS

Any stimulus, intrinsic or extrinsic, that evokes a biological response can be considered as stress (15). These stress stimulating factors can be environmental, inflammatory, psychological, or physical. Exposure to stress leads to the activation of the hypothalamic-pituitary-adrenal (HPA) axis. The effect of stress on the central nervous system (CNS) was first demonstrated in 1968 when studies by Bruce McEwen showed the effects of adrenal hormones on reconfiguring network connections on the brain (16). McEwen's work provided a direct evidence of the chronic effects of cortisol (primary stress hormones in humans) on mental function regulation and coined the term "allostatic load" as the process by which the body prepares and responds to stress to restore homeostasis. His work demonstrated that chronic exposure to stress lead to major changes in neuronal network connections that triggered a neuroendocrine response associated with multi-organ effects (17). McEwen's pioneer work also indicated that chronic stress exposure contributed to neurodegenerative diseases and that stress had sex-specific effects on the CNS (17). The classic primary endocrine mechanism of a body in response to stress encompasses the production of glucocorticoids.

Regulation of Glucocorticoid Secretion and Molecular Signaling

Glucocorticoids are steroid hormones that are essential for life and are synthesized in the adrenal cortex in response to signals from the hypothalamus (**Figure 1**). Stress stimulates the paraventricular cells in the hypothalamus to produce the corticotropin-releasing hormone (CRH). CRH is then released into the pituitary portal vein that stimulates corticotrophs in the anterior pituitary gland for the synthesis and release of adrenocorticotropic hormone (ACTH). ACTH then binds to G protein-coupled receptors located on the zona fasciculata and zona reticularis of the adrenal cortex, which then leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA). PKA in turn phosphorylates and induces hormone-sensitive lipase to hydrolyze cholesteryl esters into cholesterol (18) as well as activates the steroidogenic acute regulatory protein (StAR) (19–21), which then transports cholesterol into the mitochondria, where glucocorticoids are synthesized in a process known as steroidogenesis.

Chronic production of high levels of cortisol results in Cushing syndrome, also known as hypercortisolism (22), while insufficient amounts of adrenal hormones (cortisol, or cortisol and aldosterone) can lead to Addison's disease (23). Both of these conditions involve the dysfunction of HPA axis signaling and have been linked to immune, metabolic, cardiovascular, and mental conditions such as melancholic depression and chronic anxiety (24, 25). Therefore, tight control of glucocorticoid secretion is critical to maintain homeostasis. Glucocorticoid levels are regulated by a negative feedback loop at the level of the hypothalamus and pituitary gland. Following the hormone secretion, bioavailability of glucocorticoid is regulated by binding to corticosteroid-binding globulins (CBGs). It is estimated that 80% of circulating cortisol is bound to CBGs (26). At target tissues, glucocorticoid availability is further modulated by the action of two enzymes: 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) which oxidizes cortisol into the inactive metabolite cortisone, whereas 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) converts cortisone to cortisol (**Figure 1**). After release from CBGs, free glucocorticoids can diffuse through the cell membrane, and, once inside the cell, glucocorticoids bind their receptor, the glucocorticoid receptor (GR, NR3C1) (**Figure 1**).

Glucocorticoid receptor (GR, NR3C1) is a member of the nuclear receptor family of ligand-activated transcription factors, which is expressed in almost every cell in the body (27). Binding of glucocorticoids to GR results in the receptor-glucocorticoid complex translocation into the cell nucleus where GR directly (biding to DNA) or indirectly (interaction with other transcription factors) regulate the expression of target genes (28). Glucocorticoids via GR binding can regulate a vast array of genes involved in controlling the development, metabolism, immune response, and the cardiovascular system (29). Endogenous and some synthetic glucocorticoids can also bind to closely related mineralocorticoid receptor (MR, NR3C2), which is not as widely expressed as the

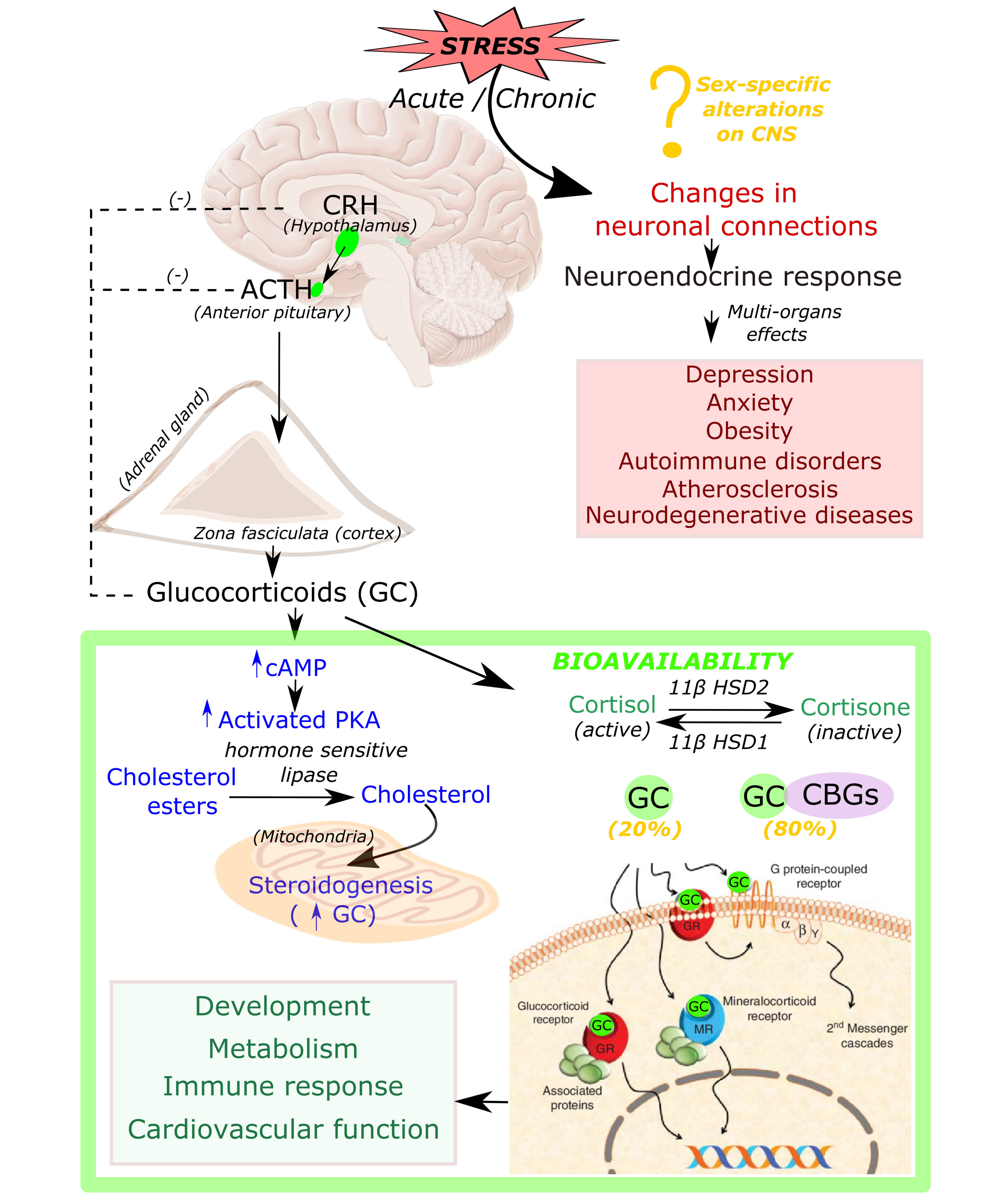

FIGURE 1 | Synthesis, bioavailability and role of glucocorticoid hormone in response to stress. Acute and chronic exposure to stress stimulate hypothalamus to release corticotropin releasing hormone (CRH). CRH then triggers the secretion of the adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which

(Continued)

FIGURE 1 | binds to its receptors located on the cortex of the adrenal gland that leads to production of intracellular cyclic adenine monophosphate (cAMP). cAMP then activates protein kinase A (PKA). This activated PKA phosphorylate cAMP response element-binding protein (CREB), eventually promotes production of steroidogenic proteins that transport cholesterol into the mitochondria, where glucocorticoids (GC) are synthesized (steroidogenesis). Biologically active form of GC is present in the unbound form (20%), whereas 80% remains in inactive condition bound to corticosteroid-binding globulin (CBGs). Free active GC binds to glucocorticoid receptor (GR) or mineralocorticoid receptor (MR) which leads to further downstream signaling responsible for many physiological processes such as development, metabolism, immune response, and cardiovascular function. Chronic stress also leads to changes in many neuronal connections leading to pathological conditions such as depression, anxiety, obesity, autoimmune disorders, atherosclerosis as well as neurodegenerative diseases.

GR, but high levels of MR has been observed in cardiovascular tissue (30). The main ligand for MR is aldosterone. However, giving the fact that cortisol circulates at ~100 times higher concentrations than aldosterone, in certain tissues that lack 11βHSD2, glucocorticoids have been found to significantly occupy MR (30). In the context of the cardiovascular system, glucocorticoid activation of GR has been found to be beneficial for the body to restore homeostasis; however, binding to MR has been shown to exacerbate cardiac dysfunction and failure (31). However, no studies have been performed to evaluate the sex-specific effects of glucocorticoids signaling through MR or GR. The structure and function of the GR gene and protein, and mechanisms of gene regulation are discussed in detail in a recent review by Scheschowitsch et al. (32).

Glucocorticoids and the Cardiovascular System

Glucocorticoids have positive effects on the cardiovascular (CV) system. Treatment with synthetic glucocorticoids can provide beneficial therapeutic effects on conditions such as myocarditis, cardiac conduction defects, as well as vascular conditions such as angina and acute myocardial infarction (33). However, due to the existence of severe side effects in off-target organ systems, the therapeutic use of glucocorticoids is limited.

In normal physiology, both excesses, and deficiencies of glucocorticoids can lead to cardiovascular disease (CVD) (34). Hypertension and cardiomyopathies are commonly found in Cushing Syndrome patients (35, 36). However, hypotension and cardiac dysfunction are regarded as signs of cortisol insufficiency. Polymorphisms of the GR gene are also reported to influence the progress and prognosis of CVD in humans (37–44). The actions of glucocorticoids on the vasculature and the heart are summarized in **Figure 2**.

In the vascular system, glucocorticoids have been shown to be involved in blood pressure regulation through the modulation of inflammatory and oxidative stress molecular pathways (29, 44–46). In addition, as discussed above, glucocorticoids have been confirmed as vital hormones in the regulation of blood pressure (BP) (36, 47), and there is strong evidence that GR is present in both vascular smooth muscle (VSM) (47) and endothelial cells (48). Also, clinical and animal studies have shown that glucocorticoid signaling is critical in the heart (31, 33, 36, 49–52). Antenatal exposure to glucocorticoids increases the expression of endothelial nitric oxide synthase (eNOS, critical for the production of nitric oxide, which is one of the most important endogenous vasodilators) in the large vessel endothelium, large airway, and small airway epithelium of fetal rat lungs (53, 54). In adult animal models, exogenous glucocorticoid administration leads to hypertension by suppressing nitric oxide synthase III (NOS) and inducible nitric oxide synthase (iNOS) expression (47, 55–57). Glucocorticoid treatment also inhibits nitric oxide (NO) biosynthesis in the endothelium (48). In addition, glucocorticoids increase the expression of angiotensin II type I receptors in smooth muscle cells, and the influx of Na^+ and Ca^{2+} into vascular smooth muscle affects contractility and therefore leads to alterations in blood pressure (58). Moreover, glucocorticoids are known to exert actions on the vasculature by their effects on immune cells, including on macrophages, dendritic cells, and neutrophils (29, 59–62). It is still controversial whether glucocorticoids' actions on the vasculature are mediated through GR or MR. Future studies are needed to fully elucidate if glucocorticoids can contribute to hypertension via GR or MR.

In the last decade, a number of studies have been focused on understanding the direct effects of glucocorticoid signaling on the heart. Studies have shown that glucocorticoids signaling through GR or MR play a critical role in regulating cardiac function in health and disease (63). In addition, glucocorticoid signaling through GR contributes to heart development. Using mouse models lacking GR in cardiomyocytes and vascular smooth muscle cells indicated that structural, functional, and biochemical maturation of the fetal heart is dependent on intact glucocorticoid signaling (64). Studies on adult mice with cardiomyocyte GR deficiency have also exhibited that an intact glucocorticoid signal is critical for the regulation of systolic function in a post-natal heart. Cardiomyocyte GR deficiency in adult mice leads to early death due to pathological cardiac hypertrophy that progresses to dilated cardiomyopathy and heart failure (50). These effects seem to be associated with the GR regulation of genes involved in cardiac contractility (ryanodine receptors 2, RyR2), cardiomyocyte survival (prostaglandin D2 synthase, Ptgds), and the inhibition of inflammation (lipocalin 2, Lcn 2) (50). MR deficiency does not lead to any major structural or functional abnormalities, and it seems to be protective against myocardial injury (65, 66). GR overexpression in the heart leads to bradycardia and a chronic atrioventricular block in mice (49) but not arrhythmia or premature death. In contrast, MR overexpression and increased signaling in the heart leads to major ECG abnormalities, cardiac arrhythmias, dysregulation in Na^+ and K^+ currents, and a high death rate (67). Whether glucocorticoid effects in the heart are mediated via GR or MR is a topic of controversy. However, recent novel studies by Oakley et al. (31) provide direct evidence that glucocorticoid signaling through MR in the absence of GR in cardiomyocytes seems to mediate most of the negative effects of glucocorticoids in the heart. Glucocorticoids signaling via cardiomyocyte MR leads to cardiac pathology, whereas glucocorticoids signaling through GR

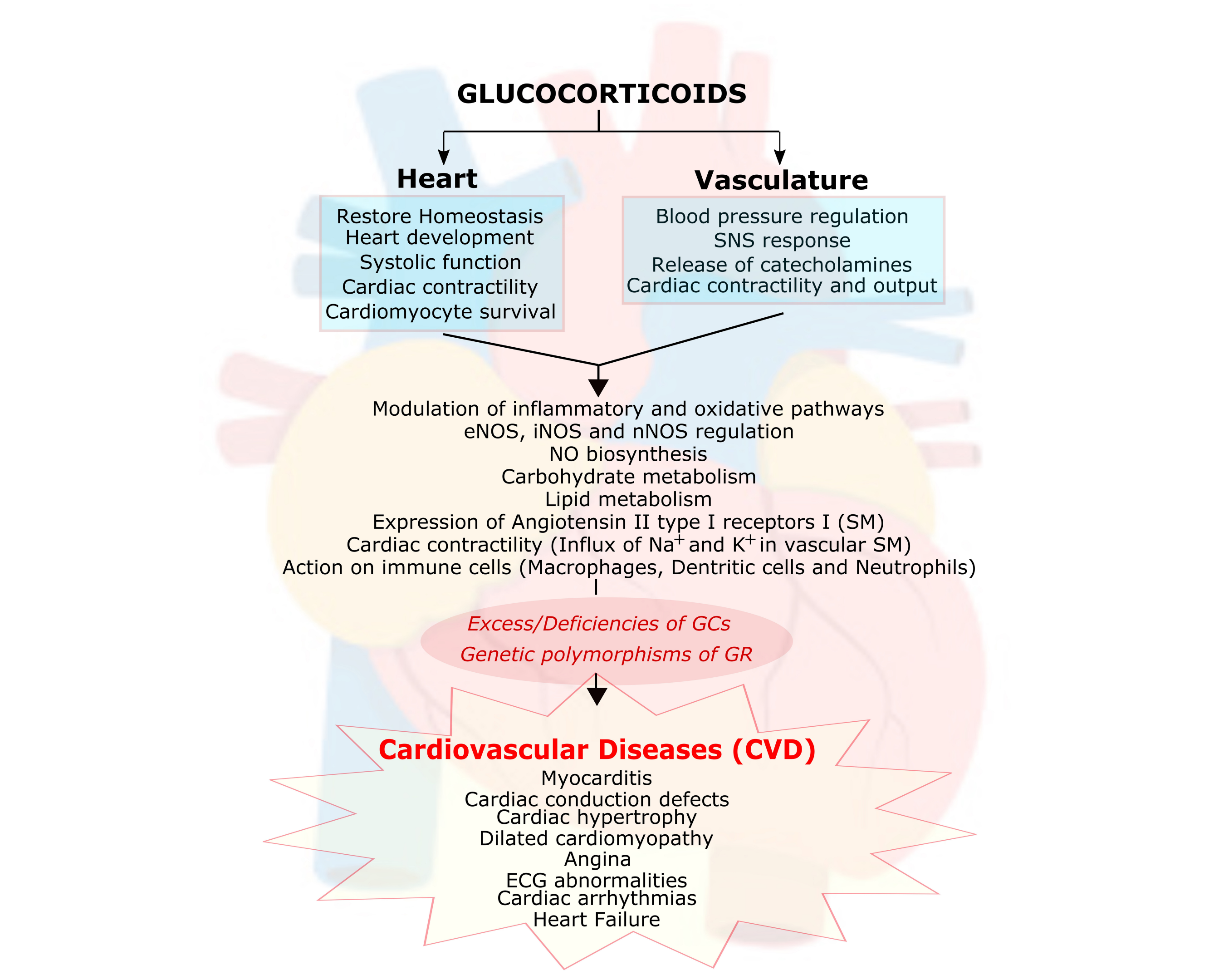

FIGURE 2 | Essential role of glucocorticoids in cardiovascular function. Glucocorticoids (GC) play an essential role in heart and vasculature. It is involved in signaling important functions such as maintaining the cardiac homeostasis, cardiac development, cardiac contractility, cardiac rhythm, modulation of inflammation and oxidative stress, cardiomyocyte survival, carbohydrate and lipid metabolism, inhibiting nitric oxide (NO) biosynthesis, modulating expression of angiotensin II type I receptors on smooth muscle cells (SM) as well as interaction with immune cells (macrophages, dendritic cells and neutrophils). Abnormal function of (GC) due to its excess/deficiencies or due to genetic polymorphism in its receptor leads to many cardiovascular diseases. GC, glucocorticoids; GR, glucocorticoid receptors; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase; SNS, sympathetic nervous system; ECG, electrocardiogram.

have been observed to be cardioprotective. Thus, these results suggest that the balance between GR and MR is critical in heart disease. However, it remains to be clarified whether the effects of glucocorticoid signaling on the heart are sexually dimorphic.

Glucocorticoid Signaling Cross-Talk With Sex Hormones

The sexually dimorphic actions of glucocorticoid regulation of gene expression were observed to contribute to the dimorphic basis of inflammatory disease in a study by Duma et al. (68). In this study, comparison of number of genes involved in inflammatory disorders between sexes revealed that glucocorticoids have more profound anti-inflammatory effects on males as compared to females, suggesting that females have additional factors that may inhibit/alter the response to glucocorticoids (68).

GR exhibits female-biased expression in several preoptic and thalamic nuclei, thus indicating that glucocorticoids have a greater influence on physiology and behavior, mediated by specific neuropeptides more so in females than in males (69). Since the brain plays an important role in governing the stress response, this may contribute to gender differences in CV response to stress. The CV system is susceptible to emotional stress, and young and middle-aged women appear to be especially vulnerable to psychosocial risk factors (11, 13, 70–72). Depression, trauma, and perceived stress are disproportionately common in women as compared to their male counterparts or older patients and can be considered predictors of CV risk (14, 73–75). However, no studies have been performed to investigate whether exposure to severe mental stress for a considerable period of time leads to irreversible gene programming and epigenetic changes that predispose or increase the risk for CV complications, despite going back to a period of "normal" stress levels.

Regarding the sexual dimorphic effects of glucocorticoid on the heart, animal studies have demonstrated that the deletion of GR in cardiomyocytes leads to systolic dysfunction and heart failure in both male and female mice (52). However, this phenotype appears early in males as compared to females and is associated with dysregulation of different cardiac gene networks (52). These differences may arise from the effects of sex hormones on the heart. Ovarian hormone (in particular, estrogen) signaling may be compensating initially for the lack of GR in the heart, whereas androgens may be exacerbating the deleterious effects of GR deficiency in cardiomyocytes (52, 68, 69, 76–78). Future studies are needed to fully elucidate the mechanisms behind the sex differences in the physiological consequences of GR signaling in the heart. However, more work is needed to clarify whether glucocorticoid signaling in heart results from GR cross-talk with androgen receptors (AR) or estrogen receptor (ER) signaling and whether if these interactions play a role in male and female differential sensitivity to the effects of exposure to higher stress levels as it relates to cardiovascular and heart disease. Moreover, studies are needed to further define the role of MR in glucocorticoids' sex-specific effects on the heart.

In addition, chronic stress has been shown to increase the risk of hypertension for both men and women (79, 80). Most studies have associated stress and hypertension with the stimulation of the sympathetic nervous system response, in which the release of catecholamines leads to increased heart rate, cardiac output, and altered blood pressure (80). However, future studies need to focus on investigating the direct contribution of glucocorticoid release in response to stress in blood pressure regulation, with special emphasis on characterizing the gender-specific effects of chronic stress and pathological hypertension.

In the next section, we briefly discuss how trauma-related mental health disorders during the COVID-19 pandemic might alter glucocorticoid signaling in the female heart, and the potential CV side-effects of the increased activation of GR signaling associated with the COVID-19 pandemic for women.

THE PRICE OF THE COVID-19 PANDEMIC ASSOCIATED STRESS ON WOMEN'S CV HEALTH

The COVID-19 pandemic has led to unprecedented levels of mental and emotional stress (81). The uncertainty due to the fear of infection, economic losses, and isolation due to quarantining has triggered a substantial decline in mental health for both men and women. However, women's mental health appears to be disproportionally affected. Emerging data show that women are suffering more than men from the pandemic-associated stressors, and that there is a higher self-reported symptoms of anxiety, depression, post-traumatic stress disorder, and poor psychological well-being in them (82–85). Moreover, since women are already at a higher risk for depressive and anxiety disorders, the current environmental stress has intensified the severity of these disorders for women (86).

There is a strong association between psychological stress and cardiovascular disease (70, 87–90). Exposure to stressors such as natural disasters has demonstrated an increase in cardiovascular risk associated with prolonged emotional trauma due to human and economic losses and changes in the daily routine. Studies show that sudden changes in heart rate and increases in blood pressure are common in populations that have experienced an earthquake and are facing uncertainty (90, 91). Moreover, a dramatic increase in pulmonary embolism and myocardial infarction (MI) has been observed in the wake of an earthquake (91). Similarly, other natural disasters, such as hurricanes, floods and tsunamis, that disrupt the fully functioning lives of the victims and cause loss for individuals, families and communities have highlighted the association between CVD risk and mental stress (92, 93). A recent study also revealed that the number of trauma-related mental health disorders has increased significantly during COVID-19 quarantine (83, 94). Therefore, a substantial increase in mental health conditions and associated sequelae is expected to be a consequence of this pandemic worldwide. Given the link between mental stress and CVD risk, it is critical to investigate the biological pathways underlying the stress response and the CV system to identify patients at risk (prevention) and to discover novel therapeutic targets.

Traditionally, it has been assumed that premenopausal women have a lower cardiac risk than men (95). This decreased risk has been attributed to estrogen, which has anti-atherosclerotic effects (96–98). Data from the Framingham Heart Study suggested a strong association between low estrogen levels (menopause) and increased cardiovascular risk in women (99). However, while some studies show that low estrogen dose therapy has been shown to be beneficial for cardiovascular health in post-menopausal women (100), the data remain controversial regarding whether long-term estrogen therapy improves cardiovascular outcomes for women (101). Moreover, recent clinical evidence has also shown that although there has been a decrease in heart disease mortality for both men and women over 65 years of age in the last three decades, the incidence of cardiovascular events has significantly increased among premenopausal women (102). These results suggest that additional risk factors have a differential impact on women's cardiovascular health compared to men.

Women differ from men in a multitude of ways (**Figure 3**), including genetic differences in immunity (103, 104), coagulation (105, 106), and hormonal factors (107), all of which can influence the risk for CVD and related outcomes. Many studies have highlighted sex differences in delayed hospital arrival and lack of sufficient awareness of women in the context of CVD (108, 109). Along with these factors that has been associated with increased mortality for women, abnormal levels

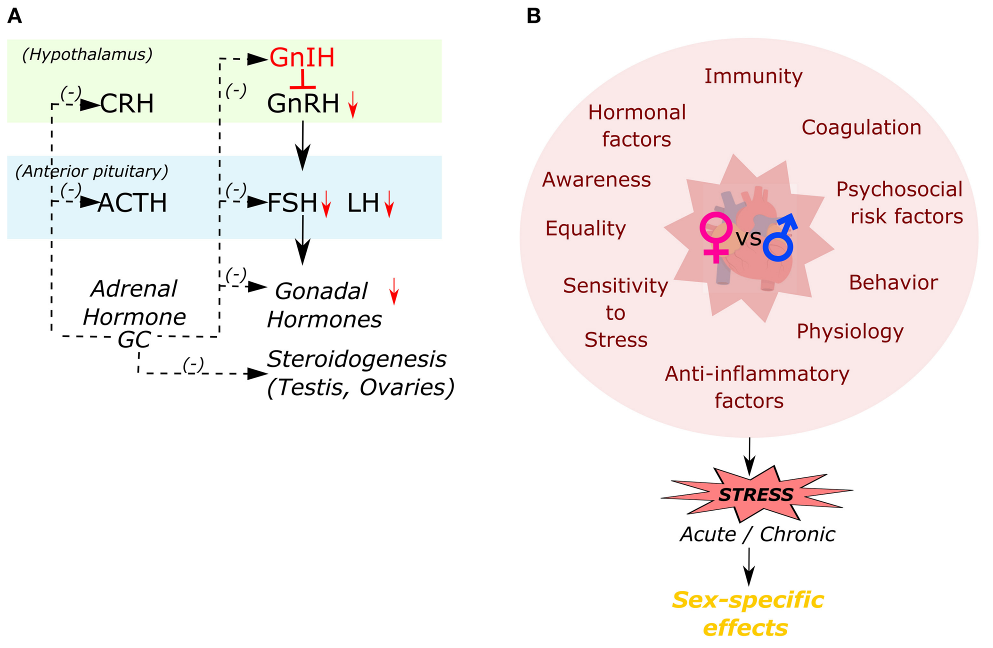

FIGURE 3 | Inter-relationship of different factors responsible in causation of sex-specific effects to stress. **(A)** Interactions among the hypothalamo-pituitary-adrenal (HPA) and hypothalamo-pituitary-gonal (HPA) axes by glucocorticoid hormone (GC). **(B)** Different factors influencing female's cardiac health compared to males in developing a sex-specific effect in response to stress.

of glucocorticoids have also been known to increase CV risk for women (7, 11, 75, 110–112). However, surprisingly, very little has been explored about the direct role of glucocorticoid signaling on the female heart.

CONCLUSIONS AND FUTURE PERSPECTIVES

The COVID-19 pandemic has exponentially raised anxiety and depression in vulnerable populations due to economic and social pressure, uncertainty, isolation, and feelings of immobility/constraint due to social distancing measures. Young and middle-aged women are among the most affected due to the lack of balance between demanding job schedules and family responsibilities.

The mechanisms responsible for the sex-specific effects of stress hormones on the CV system are still unclear. Women have an increased vascular reactivity to glucocorticoids, which may account for their increased risk of mental-stress-induced ischemia (73, 113). However, the molecular pathways underlying this reactivity are unknown. A potential mechanism for the sex-specific effects of stress is the crosstalk between glucocorticoids and sex-hormones signaling. A better understanding of such interactions will open up new potential avenues for risk assessment and prevention for women. It will be particularly be important to study whether exposure to chronic mental stress for a period of time leads to gene reprogramming that may predispose women to CV complications, exacerbate the effects of additional comorbidities, and negatively impact the aging process. Assessment of mental health status, in addition to traditional risk factors, has become more important than ever. There is a clear connection between psychological stress and heart disease and understanding this connection will aid in preventing and improving cardiovascular outcomes for the general population and women.

AUTHOR CONTRIBUTIONS

All authors contributed to writing the manuscript, critically revised the work, and approved the final version.

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REVIEW
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Susceptibility to COVID-19 in Pregnancy, Labor, and Postpartum Period: Immune System, Vertical Transmission, and Breastfeeding

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The new coronavirus (SARS-Cov-2) was first identified in late 2019 as the new RNA virus in the coronaviridae family responsible for causing COVID-19 in the residents of China's Hubei province. In mid-March 2020 WHO declared the pandemic caused by this virus as a result of thousands of people infected all over the world. Epidemiological evidence obtained from other pandemics, such as influenza and ebola, suggest that pregnant women are more susceptible to serious complications and death from viral infection. Physiological changes in the anatomical structure of the respiratory system as well as in the immune system during the pregnancy-puerperal period seem to contribute to this greater risk. Thus, pregnant women are more susceptible to be infected by the SARS-COV-2 or other viruses and to have serious COVID-19 disease. In fact, COVID-19 can alter immune responses at the maternal-fetal interface, affecting the well-being of both mother and her fetus. There is still no sufficient evidence in the literature to support the occurrence of vertical transmission and through breastfeeding, but the prevalence of prematurity was high among pregnant women infected by SARS-Cov-2. In this review, the changes in the immune system that may increase susceptibility to SARS-Cov-2 are discussed as well as the possible mechanisms involved in the transmission of the virus to the fetus by vertical transmission and during breastfeeding.

Keywords: COVID-19, pregnancy, immunity, vertical infection transmission, breastfeeding

INTRODUCTION

The disease caused by the new coronavirus (COVID-19) is currently the most serious public health problem that the world has faced (1). According to a recent report from the World Health Organization, until August 13th of 2020, 20,439,814 cases of COVID-19 have been registered with 744,385 deaths (2).

SARS-Cov-2 can infect newborns, children, young adults, pregnant women and elderly (3). This virus is more contagious than the coronavirus that causes severe respiratory distress syndrome (SARS), which had infected ∼8,000 people and caused 800 deaths so far. The combination of inadequate immune response and high infectivity can contribute to the SARS-CoV-2 widespread.

Contagion occurs mainly through droplets and aerosols spread in the environment by the infected people (1) (**Figure 1**).

Once in contact with the body, SARS-CoV-2 binds to a cell surface receptor, invades the endosome and eventually fuses viral and lysosomal membranes. In mature viruses, the spike protein is present as a trimer, with three S1 receptor-binding heads, sitting on top of an S2 membrane fusion rod. Like SARS-CoV, SARS-CoV-2 recognizes the angiotensin-converting enzyme 2 (ACE2) as its receptor (4).

During pregnancy, the maternal immune system faces some challenges which includes establishing and maintaining tolerance to the fetus, as well as preserving the ability to fight against viruses and bacteria, therefore, a healthy pregnancy depends on immune adaptations. In fact, the maternal immunological system adapts and changes with the growth and development of the fetus at the different stages of pregnancy, which goes from a pro-inflammatory state (beneficial for embryo implantation and placentation) in the first trimester to an anti-inflammatory state (useful for fetal growth) in the second trimester. In the third trimester, it reaches a second pro-inflammatory state (in preparation for the start of childbirth) (3, 5).

The immune system of a pregnant woman is well-prepared to defend against the invasion of pathogens in such a way that innate immune cells like NK cells and monocytes respond more strongly to viral challenges. On the other hand, some adaptive immune responses are negatively regulated during pregnancy. In addition, the high levels of estrogen and progesterone induce the upper part of the respiratory tract to swell which, in addition to the restricted lung expansion on the last gestational trimester, make the pregnant woman more susceptible to respiratory pathogens such as SARS-CoV-2 (3, 5) (**Figure 2**).

Previous reports have shown that SARS infection during pregnancy can lead to premature birth, intrauterine growth restriction and spontaneous abortion. However, there is still no strong evidence of vertical transmission of SARS-Cov-2. Therefore, it seems that these complications are caused by the direct effect of this virus on mothers. Although current evidence is limited regarding the transmission of the new coronavirus during pregnancy and lactation, the potential risk of vertical transmission must not be rule out (3, 6, 7).

In this review, the main changes in the immune system that occur during pregnancy, which may increase susceptibility to SARS-Cov-2 infection, are discussed as well as the possible mechanisms involved in the transmission of the virus to the fetus by vertical transmission and during breastfeeding.

SARS-COV-2: MECHANISMS OF CELL INFECTION AND IMMUNE RESPONSE

Coronaviruses infect host cells through protein-mediated fusion on their surface (spike protein—S). Although unusual, the spike protein can be activated by furins, which are proteases with high expression levels (8). The genomes of coronaviruses evolve through gains or losses of genes. Such genes have high plasticity, which means that the longer the genome is the greater the probabilities of adaptive mutation are, thus generating high diversity for the spike protein to change and adapt to other cell receptors (9).

The horseshoe bats work as natural hosts and are reservoirs for SARS-CoV (10). Since the first step in the viral replication cycle is mediated by protein S, it offers several potential therapeutic targets. Protein S uses the angiotensin-2 converting enzyme (ACE2) and sialic acids linked to gangliosides on the cell surface to enter the cell (11). Therefore, cell penetration by coronaviruses requires the activation of protein S by cellular proteases, which affects the cleavage of protein S, thus allowing the fusion of viral and cellular membranes. The SARS-S receptor becomes involved with ACE2 as an input receptor (12) and releases the cellular serine protease TMPRSS2 to activate the S protein (13, 14) (**Figure 3**).

Even though SARS-S and SARS-2-S share 76% of amino acid identity, no study has shown how SARS-2-S or SARS-S uses ACE2 and TMPRSS2 to adhere to the target cell (15, 16). In this context, the transmembrane serine protease TMPRSS2 activates the coronavirus peak protein (17). Since other coronaviruses use ACE2 as a cell receptor, it seems that host factors other than ACE2 may contribute to the highly efficient zoonotic transmission of SARS-CoV-2 from person to person (18, 19). In addition, it has been evidenced a lower expression of cytokines and chemokines in mice deficient in TMPRSS2 in comparison to those that had TMPRSS2 activity after coronavirus infection. Viral replication is probably one of the main causes of the high levels of inflammatory chemokines observed in mice, even though the TMPRSS2 involvement in the inflammatory reactions has also been evaluated. Thus, activation of coronavirus S proteins by target cell proteases are essential for viral entry into the cells and encompasses protein S cleavage at S1/S2 and S2 sites. The S1/S2 cleavage site of SARS-2-S houses several arginine residues, which indicates high cleavage activity (20).

The physiological immune response against SARS-CoV-2 is usually initiated at the cellular level after viral replication. Cellular detection is mediated by a family of intracellular receptors that detects aberrant RNA structures that usually form during virus replication. Initially, there is an engagement of cellular antiviral defenses, mediated by the transcriptional induction of type I and III interferons (IFN-I and IFN-III), followed by a sub-regulation of IFN-stimulated genes (ISGs). Antiviral response also involves recruitment and coordination of specific subsets of leukocytes, orchestrated mainly by the secretion of chemokines (21). Immune responses play an essential role in determining the progression of SARS-CoV-2 infection, as damaged lung cells induce a local immune response, which recruits macrophages and monocytes to respond to infection (22) (**Figure 4**).

The relocation of NK cells, macrophages and plasmacytoid dendritic cells (pDC) to the lungs has been associated with increased levels of cytokines and chemokines. In fact, dysregulation of immune responses commonly occurs in severely affected patients, which includes excessive secretion of inflammatory cytokines and imbalances in the proportion of naive helper T cells, memory helper T cells and regulatory T cells. SARS-CoV-2 can induce dysregulation of immune responses in susceptible individuals, as demonstrated by the decrease in lymphocytes, especially T cells, increased leukocyte count and

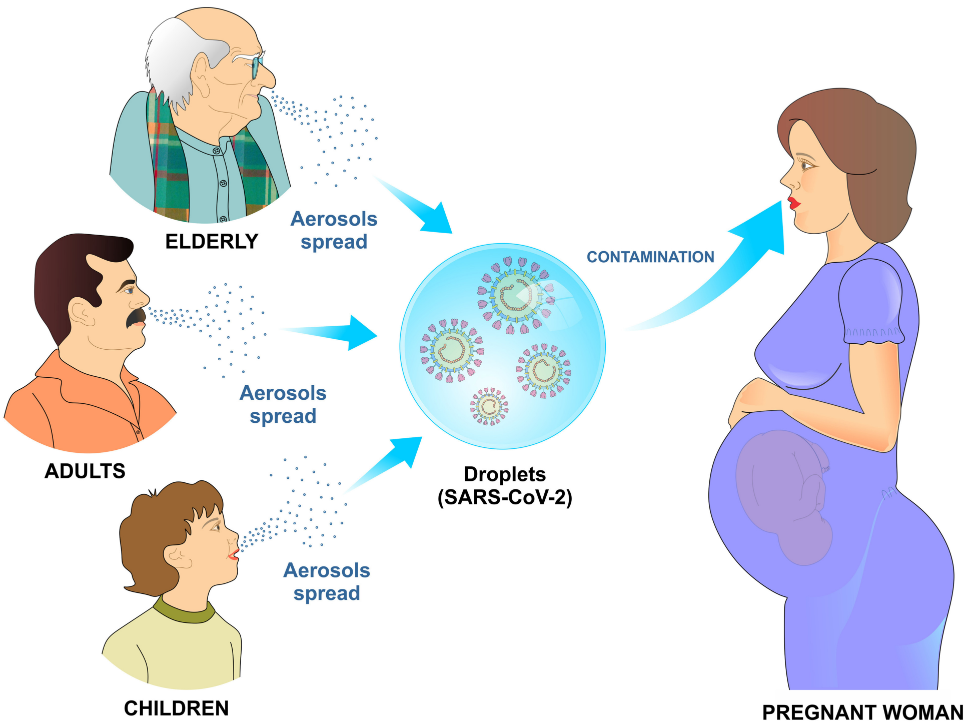

FIGURE 1 | Transmission mechanism of SARS-CoV-2 by air. Infected children, adults, and elderly disseminate viral particles by sneezing or coughing. Upon reaching the mucosa of the upper airways or alveoli, the SARS-CoV-2 viral particles bind to specific receptors on the cell surface and initiate the process of cell penetration and subsequent viral replication.

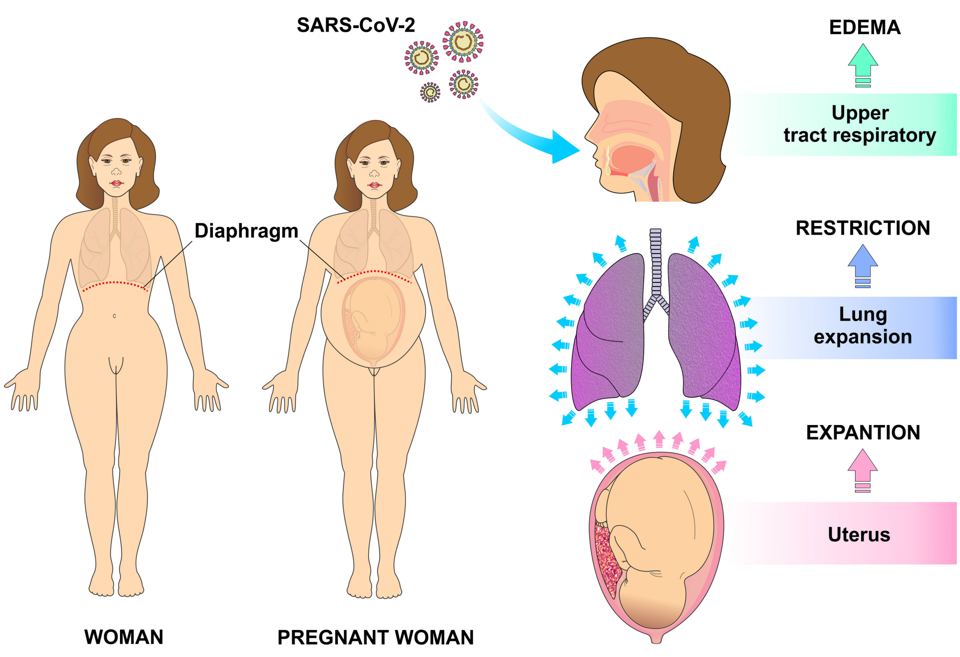

FIGURE 2 | Physiological changes in the respiratory system during pregnancy that make it more vulnerable for infection. The high levels of estrogen and progesterone result in edema of the upper respiratory tract also contribute to higher risk of infections. With uterine expansion, the diaphragm is displaced superiorly, making pulmonary expansion difficult and therefore decreasing the respiratory reserve capacity.

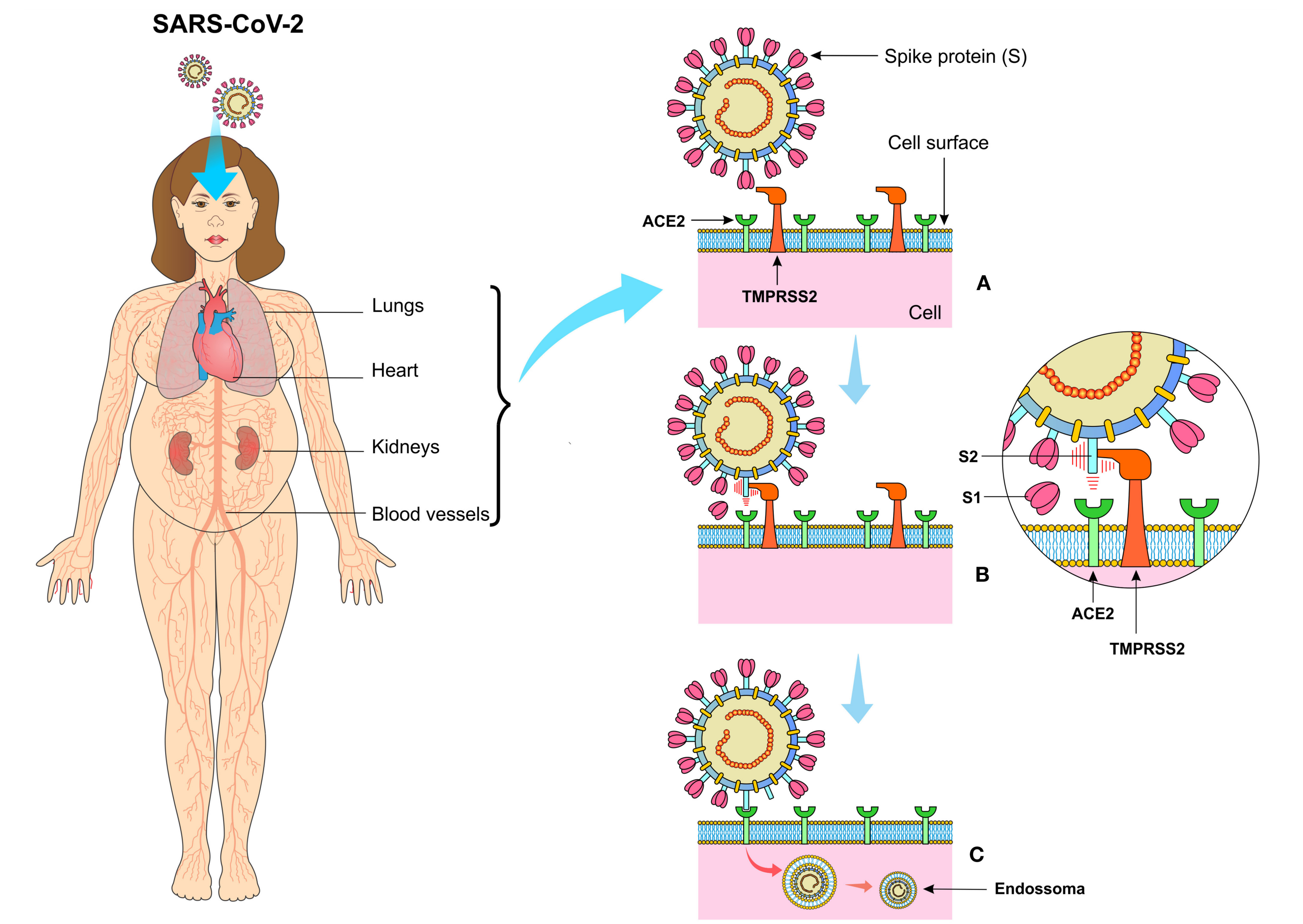

FIGURE 3 | (A) The SARS-CoV-2 virus presents the spike protein (S) on its surface, expressed in the form of a spike that binds to angiotensin-converting enzyme 2 (ACE2) present on the surface of cells especially in the lungs, kidneys, heart, vessels, and adipose tissue. **(B)** Transmembrane Serine Protease 2 (TMPRSS2) cleaves protein S in units S1 and S2, making it possible for the virus to bind to ACE2. **(C)** The viral particle is enclosed by the cell membrane creating the endosome, which after the proteolytic action of the structural components of the virus, the viral RNA is released in the cytoplasm of the infected cell.

neutrophil-lymphocyte ratio as well as other imbalances in the immune cell population. In addition, severely affected patients are accompanied by a significant increase in the proportion of naive T helper cells as well as by a reduction in memory T helper cells and regulatory T cells (23, 24) (**Figure 5**).

A recent study involving Chinese patients with SARS-CoV-2 showed high plasma concentrations of IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFN-γ, IFN-γ (IP)−10-induced protein, monocyte chemotactic protein 1 (MCP1), MIP1A, MIP1B, and TNF-α. The authors reported significant overproduction of IL-2, IL-7, IL-10, GCSF, IP-10, MCP1, MIP1A, and TNF-α. Deregulation of cytokine levels has been demonstrated in almost all patients, but clear differences have been reported in the levels of various cytokines between severely affected patients and those with moderate or mild symptoms (20). These massive cytokine outbreaks result in a severe immunopathological condition known as "cytokine storm," which can lead to several pathological consequences including extensive pulmonary edema, acute respiratory distress syndrome and multiple organ failure (24, 25).

Severe and lethal cases of SARS-CoV and MERS-CoV manifest with greater accumulation of neutrophils and monocytes-macrophages in the lungs. In fact, this was the main mechanism involved in lung damage in both viral infections. It has been hypothesized that in SARS-CoV and MERS-CoV infections the delay in the IFN type I response compromised the control of viral replication. This, in turn, would lead to an increase in the influx of neutrophils and monocyte-macrophages (26). Increased accumulation and persistent activation of these cells would cause lung damage with clinical manifestations that include pneumonia and severe respiratory distress syndrome (27).

Like many other pathogens, SARS-CoV-2 develops mechanisms that help to evade the host's immune system. One of these mechanism is the persistent activation of the NLRP3 inflammasome (NACHT, LRR, and PYD domains

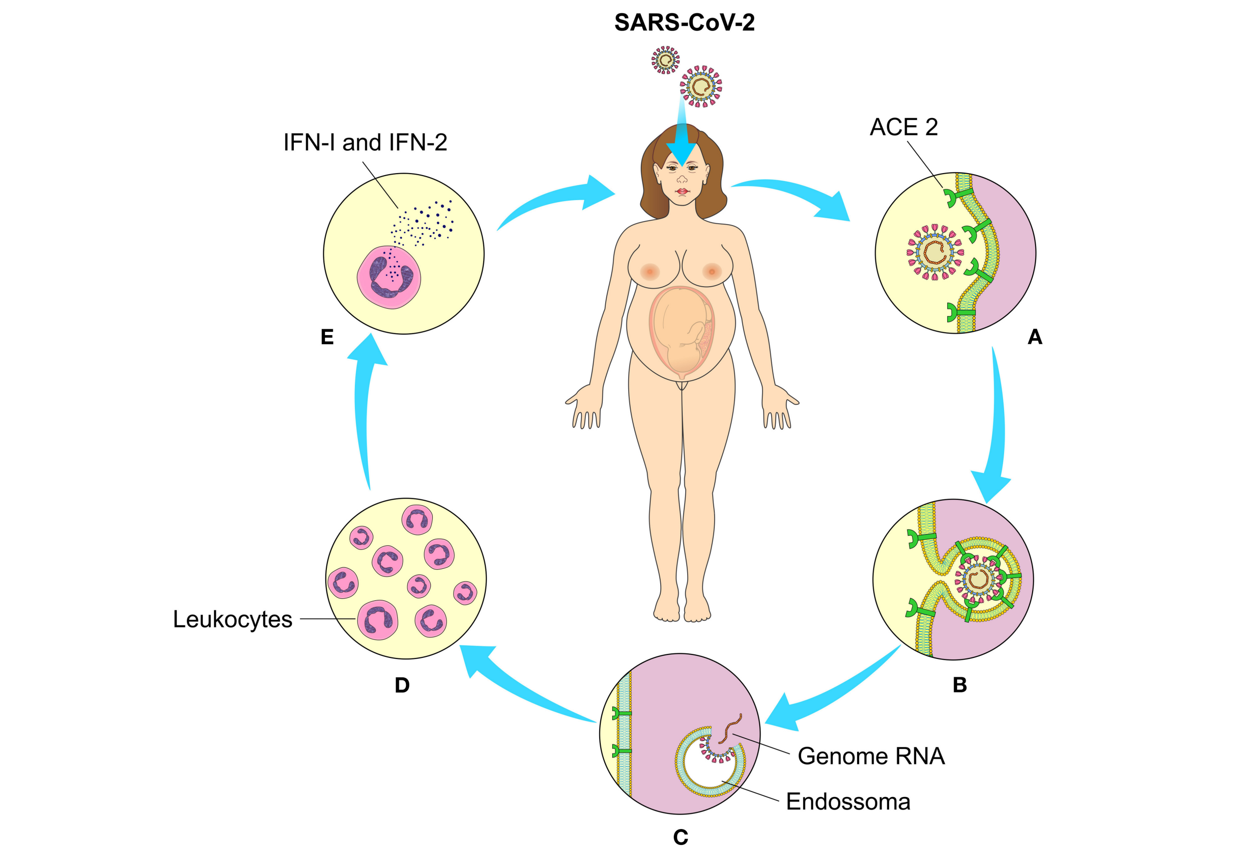

FIGURE 4 | Cell binding, interiorization, and cellular response to SARS-CoV-2. **(A)** Through their binding to angiotensin 2-converting enzyme (ACE2) on the cell's surface, **(B)** the viral penetrates inside the cells and **(C)** after the enzymatic action of the endosomes release their genetic material (RNA) for the production of the structural components of new viral particles. **(D)** Intracellular receptors detect viral RNA replication and mediate leukocyte chemotaxis and **(E)** interferon production (IFN-I and II).

containing protein 3), which is a component of the innate immune system that induces the activity of caspase-1 and pro-inflammatory cytokines such as interleukin (IL)−1β and secretion of IL-18 in macrophages (28).

Recent reports have shown that lymphopenia was a frequent finding in most patients with COVID-19 who required hospitalization, which might be due to the migration of T cells to the lungs (27). Such clinical findings were evidenced by chest radiographs and lung computed tomography (29, 30). This migration of lymphocytes accompanied by macrophages, causes interstitial damage that impairs the gas exchange and therefore, compromises oxygenation. This is why hypoxemia and dyspnea are two of the main predominant characteristics of COVID-19 infected patients. Therefore, the development of the respiratory distress syndrome observed in these patients may be a reflection of these clinical conditions (30).

The lungs of COVID-19 infected patients exhibit characteristics consistent with a non-specific inflammatory response, such as intense infiltration and edema (29, 30). Other characteristics found in these patients include thickening and damage of the alveolar septa, severe desquamation of alveolar epithelial cells and infiltration of the alveolar space. This intense inflammatory process eventually leads to necrosis, infiltration, and hyperplasia (31, 32).

PREGNANCY, IMMUNOLOGY, AND SUSCEPTIBILITY TO SARS-COV-2

Human decidua during pregnancy involves a high number of immune cells, predominantly macrophages, natural killer (NK) cells, and regulatory T cells (Treg). During the first trimester of pregnancy, macrophages and natural killer (NK) cells accumulate around the trophoblastic cells, which results in a protective effect, preventing abortion of the allogeneic fetus (33, 34). The maternal immune system protects the mother from aggressors coming from the environment and prevents damage to the fetus. On the other hand, the fetus activates the immune response that changes the way the pregnant woman responds to the environment, which makes the immune response very unique during pregnancy.

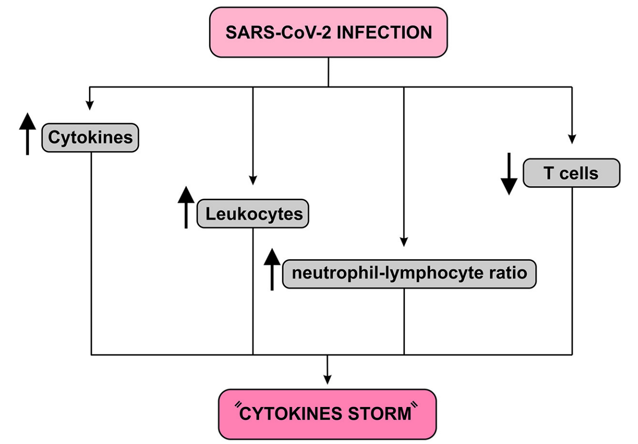

FIGURE 5 | Immune response to SARS-CoV-2 infection diagram. This infection causes a fall in T cells and an increase in leukocyte count and neutrophil-lymphocyte ratio. In addition, it increases the release of cytokines resulting in a condition known as "Cytokines storm," which may lead to pulmonary edema, severe hypoxia, respiratory failure and, finally, multiple organ failure.

Therefore, this particular immune system must be characterized by a modulated immune condition, rather than a suppressed one (33).

In pregnancy, progesterone has immunomodulatory properties that in addition to preventing the mother from recognizing the fetus as an antigen, it can influence the evolution of autoimmune diseases with improvement in conditions such as rheumatoid arthritis. During pregnancy, there is an increase in anti-inflammatory molecules such as interleukin-1 receptor antagonist (IL-RA) and tumor necrosis factor-α receptor (TNF-R), whereas a decrease in IL-1b and tumor necrosis factor-α (TNF-α) are observed (35). In the human placenta, the trophoblast expresses pattern recognition receptors (PRRs) that act as sensors to detect external aggressors. Through them, the trophoblast is able to recognize bacteria and viruses, and then secrete cytokines and interferons. Interferons are potent antiviral proteins that also have important immunomodulatory functions (34, 36). In addition, active transport of antibodies of the IgG class produced by maternal humoral immunity occurs through the placenta after 16 weeks of pregnancy, resulting in increased fetal immunity against microorganisms (34).

Immunity undergoes some changes during pregnancy that avoids an exacerbated immunological response against the allogeneic fetus, but maintains an adequate immune response against invading microorganisms (3). Aghaeepour et al. described how a "immune clock" occurs during pregnancy through a progressive increase in the release of CD25+FoxP3+ Treg cells, naive and memory CD4+ and CD8+ T cells as well as γδ T cells (37). Considering that pregnant women are in a pro-inflammatory state in the first and third trimester, the SARS-CoV-2-induced cytokine storm may result in a more severe inflammatory state in these women. In addition, the occurrence of maternal inflammation as a result of viral infections during pregnancy can affect various aspects of the fetal brain and can lead to a wide range of neuronal dysfunctions and behavioral phenotypes (7) (**Figure 6**).

However, changes in the levels of estrogen and progesterone from the first gestational trimester cause respiratory, cardiovascular and immune changes that make pregnant women more susceptible to SARS-Cov-2 infection, in addition to an increased risk of developing severe acute respiratory syndrome (SARS). The effect of progesterone on the nasal mucosa facilitates the adhesion of the virus and hinders its elimination. Moreover, the increase in oxygen consumption due to vascular congestion and the decrease in the functional residual capacity of the lung contribute to an increased risk for severe respiratory symptoms in infected pregnant women (38).

Such changes in the levels of estrogen and progesterone in the first trimester cause a reversible degeneration in the thymus, with a decrease in CD4 + and CD8 + T cells. In addition, the activity of these cells significantly reduces, contributing to a greater susceptibility to infections during pregnancy (38). Another risk factor involves the angiotensin converting enzyme 2 (ACE2) receptor, to which the virus binds before infecting the cell and it is upregulated during pregnancy. As a result of higher ACE2 expression, pregnant women may be at an elevated risk of complications from SARS-CoV-2 infection (39). Previous studies have reported an increase in these receptors in the kidneys of pregnant women, which may contribute to the efficient regulation of blood pressure during pregnancy. However, it can favor the binding of the virus and therefore, facilitating its entry into the host's cells (38) (**Figure 7**).

SARS-COV-2 IN PREGNANCY, CHILDBIRTH, AND ITS VERTICAL TRANSMISSION

Despite the low rates of morbidity and mortality from SARS-CoV-2 infection in children and women of reproductive age, these groups can be disproportionately affected by the collapse of health care services, especially in developing countries, with a possibility of increasing the prevalence of maternal mortality up to 38.6% in the worst case scenario as a consequence of this pandemia (40). A study involving 978 cases of pregnant and postpartum women infected by SARS-Cov-2 in Brazil revealed that 207 (21.2%) were admitted to the intensive care unit and among them 124 died. The authors pointed out that the high mortality due to COVID-19 in that country can be explained by the low quality of prenatal care, the insufficient resources for the management of critical patients in emergencies and the barriers imposed by the pandemic for access to the public health system (41). A recent report revealed that maternal mortality in Brazil was much higher than that in Iran, Mexico, United Kingdom, France and United States, in which 7, 5, 1, and 16 deaths by Covid-19 have been recorded during pregnancy and puerperium, respectively (42).

The physiological consequences of SARS-CoV-2 infection in pregnancy, especially in the cardiovascular and respiratory systems, are a result of the high levels of estrogen and

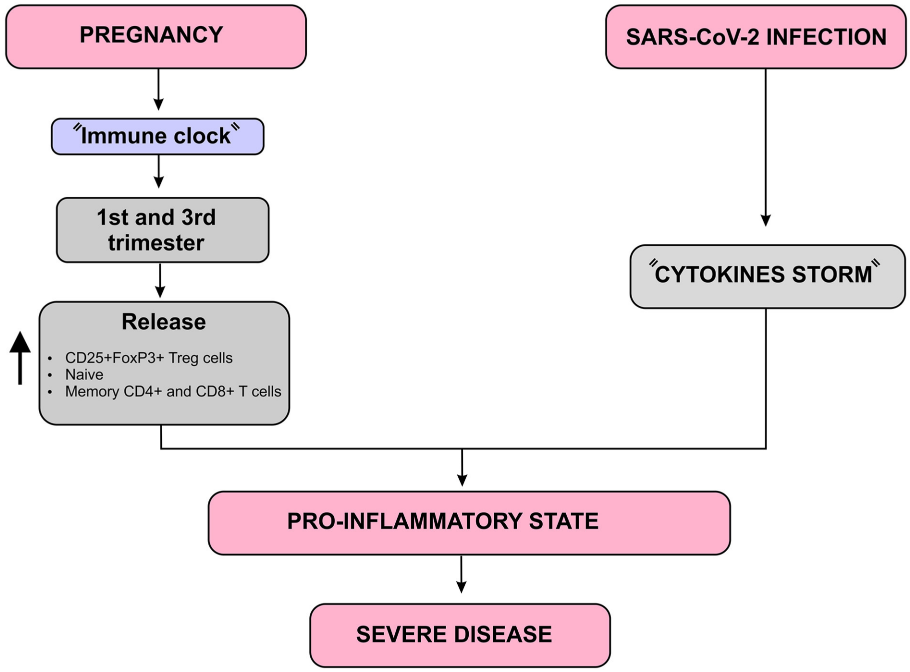

FIGURE 6 | Immunological complications that may worsen the SARS-CoV-2 infection prognosis in pregnant women diagram. In addition to the "Cytokines storm" induced by SARS-CoV-2, there is a natural increase in pro-inflammatory mediators such as CD25 + FoxP3 + Treg cells, naive and memory CD4 + and CD8 + T cells during the first and third trimesters of pregnancy, which is known as "Immune clock." These two aspects together lead to a more severe pro-inflammatory state which may worsen the SARS-CoV-2 infection, especially during the first and third trimesters of pregnancy.

progesterone, as well as immunological suppression and increased blood volume, heart rate, oxygen consumption and uterine volume. The upper respiratory tract tends to swell and the lung expansion is restricted with the progression of pregnancy, which may increase the susceptibility to respiratory infections and therefore, a greater need for intensive care and mechanical ventilation occurs during pregnancy in case of a respiratory virus infection (43). Data published by the Center for Disease Control (CDC) revealed that 31% of 8,207 pregnant women with SARS-CoV-2 infection needed hospitalized and after adjusting for age, race and comorbidities, pregnant women had a significantly higher risk than the other women admitted to the intensive care unit needing mechanical ventilation. However, mortality rate (0.2%) in pregnant women aged from 15 to 44 years old was identical to that found in non-pregnant women (44) (**Figure 8**).

In order to prevent high maternal and neonatal morbidity and mortality, the International Federation of Gynecology and Obstetrics (FIGO) has published recommendations on the four main aspects of pregnant and postpartum women care that have been infected with SARS-CoV-2: outpatient prenatal care, care in obstetric screening centers, intrapartum care and post-natal care, childbirth and neonatal care. However, before the pandemic, access to services specialized in maternal and child care was already precarious in many countries, which has worsened with the increased demand for intensive care beds due to COVID-19 (41, 45).

Despite the increased risk of complications due to immunological status and physiological changes in pregnancy as well as IFGO recommendations, data from seven systematic reviews (46–52) about COVID-19 in pregnant women point out that the prevalence of severe respiratory distress syndrome is not different from that found in the infected population and that the mortality is equally low during pregnancy and childbirth. These reviews included 637, 538, 385, 324, 136, 92, and 51 pregnant women infected with SARS-CoV-2. All these studies showed that the most common signs and symptoms were fever and cough, with the minority presenting severe respiratory distress syndrome and requiring intensive care as well mechanical ventilation. The prevalence of cesarean sections varied between 69.4 and 84.7% in the studies, with the most common maternal complication being preterm delivery and a 1.6% of maternal mortality rate as reported in the study conducted with the largest number of pregnant women, while the others reported none or just one death. Turan et al. (51) concluded that maternal age, obesity, diabetes mellitus, and elevated D-dimer and interleukin-6 are predictive of poor pregnancy outcomes in those with COVID-19.

These results are similar to those reported by a prospective population-based study involving 194 maternity hospitals in the United Kingdom with 427 infected pregnant women in which only 10% needed ventilatory support and five (1%) died from Covid-19 (53). Another study conducted in New York revealed that among 70 pregnant women whose viral RNA

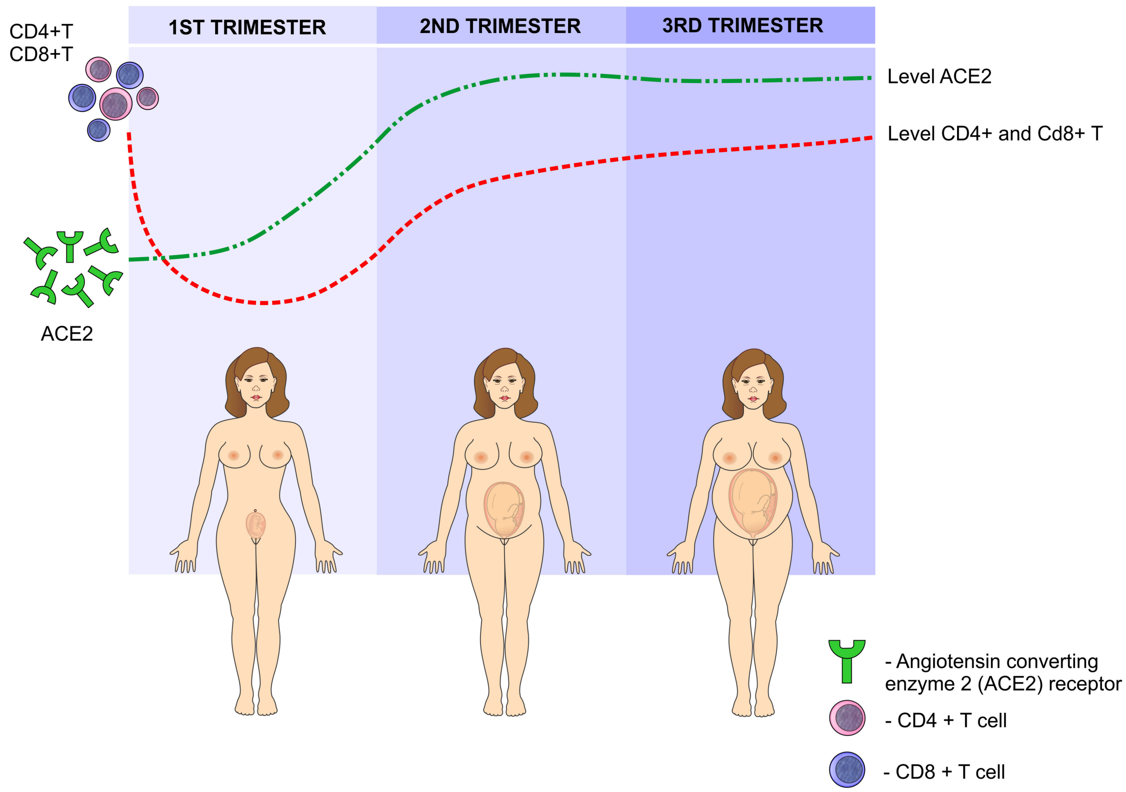

FIGURE 7 | SARS-CoV-2 infection during pregnancy: In the first trimester of pregnancy, the levels of angiotensin-converting enzyme 2 (ACE2) increase, peaking in the second trimester and reaching a plateau in the third semester. This enzyme facilitates the binding of the virus to the cells. On the other hand, due to the presence of paternal antigens foreign to the mother's body, immunity is modulated by reducing the levels of CD4 + T and CD8 + T lymphocytes in the first trimester, gradually increasing in the second and third trimesters.

was detected by RT-PCR, 55 (78%) were asymptomatic. The most common complaints among symptomatic women were cough and fever with only 3 presenting hypoxia, whereas none required mechanical ventilation and only one was admitted to the intensive care unit without any death (54).

SARS-CoV-2 can be identified by RT-PCR and serological tests from upper airway smears and blood from pregnant women and newborns. Differentiating the vertical transmission of the virus from contamination in the neonatal period is of paramount importance, but the data in the literature are still controversial about the occurrence of intrauterine infection (55).

RT-PCR has been the most frequently used method for diagnosis of COVID-19 in pregnant women and newborn, as shown by several systematic reviews that studied the vertical transmission of this virus (46–49, 51, 52). A swab collection took place on newborns on the first and second days of life and the polymerase chain reaction was positive for SARS-CoV-2 in only 1, 4, 5, and 8, respectively, with the authors concluding that there is a need for more studies that can prove if there is vertical transmission of the virus. However, in another systematic review the authors revealed that of 936 neonates born from COVID-19 infected mothers, 27 were viral RNA positive for SARS-CoV-2 (nasopharyngeal swab) and that SARS-CoV-2 viral RNA testing in neonatal cord blood was positive in 2.9% (1/34), 7.7% (2/26) of placenta samples and 9.7% (3/31) of fecal/rectal swabs, concluding that there is evidence of SARS-CoV-2 vertical transmission when the infection occurs in the third trimester of pregnancy (56).

Likewise, a systematic review investigated 50 studies involving a total of 606 neonates with the purpose of assessing evidence on vertical transmission of SARS-CoV-2 (57). The authors point out that only 20 newborns presented clear evidence of viral infection (17), where the virus was detected in 8 placentas, in 3 samples of breast milk and 1 in the amniotic fluid. Despite these findings pointing to the possibility of transmission during pregnancy, they conclude that further studies need to be conducted through analysis of the virus in larger numbers of placenta, milk and amniotic fluid.

Algarroba et al. reported a case of severe respiratory distress syndrome in a pregnant woman at 28 weeks in which it was possible to detect SARS-CoV-2 in the placental syncytiotrophoblast. However, PCR detection in amniotic fluid or placenta has not been investigated yet. In addition, swabs collected from the newborn in the second and third days of life

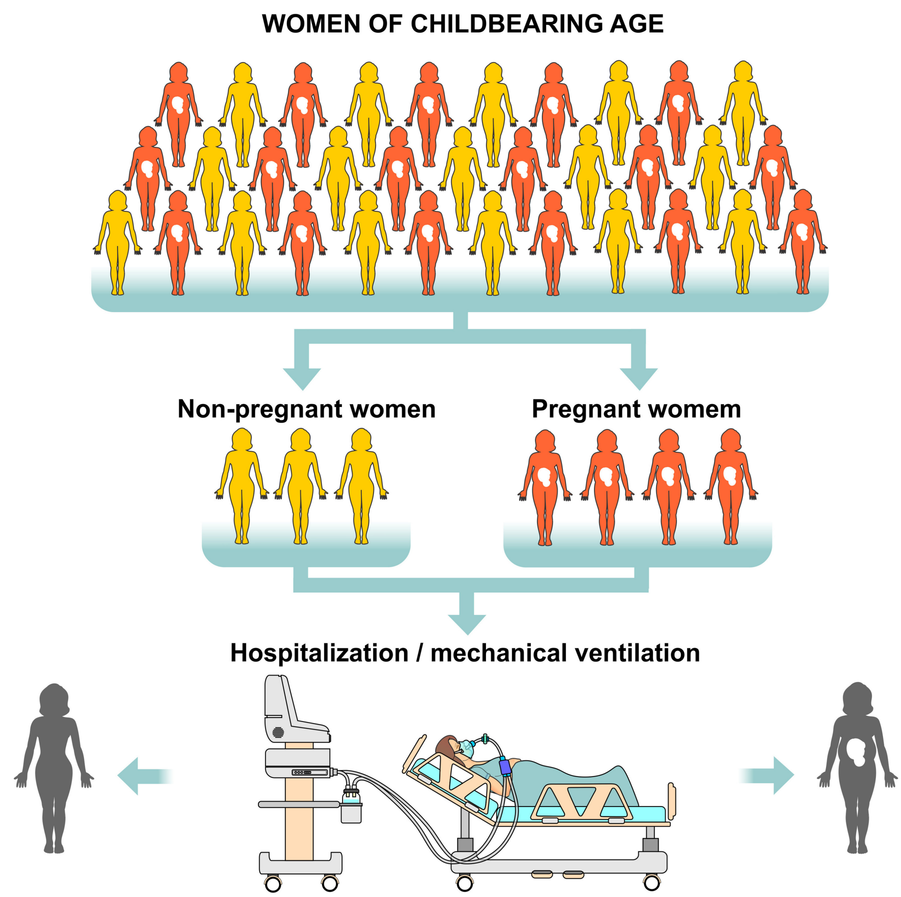

FIGURE 8 | Risk of hospitalization and need for mechanical ventilation in women of childbearing age with SARS-CoV-2. Considering all women of childbearing age (pregnant and non-pregnant) who are positive RT-PCR (Reverse Transcription Polymerase Chain Reaction) for the virus, pregnant women are at greater risk of being hospitalized and requiring mechanical ventilation. However, the mortality rate is identical in both pregnant and non-pregnant groups.

did not report the presence of the virus (58). Facchetti et al. analyzed post-partum placentas and neonates who presented positive PCR and SARS-CoV-2 pneumonia shortly after birth and found an elevated expression of viral proteins S and N in the placental tissue. Thus, the authors claim to have provided some evidence for maternal-fetal transmission of SARS-CoV-2 (59). Likewise, Fenizia et al. analyzed through nasopharyngeal and vaginal swabs the presence of viral RNA by PCR in 31 infected pregnant women and in their respective newborns. In addition, they investigated specific anti-SARS-CoV-2 antibodies and the expression of genes involved in inflammatory responses in placenta, breast milk, amniotic fluid and in maternal and umbilical cord plasma. The authors found viral genome and antibodies against SARS-CoV-2 in samples of umbilical cord blood and breast milk, which seems to support the hypothesis of *in utero* vertical transmission of SARS-CoV-2 (60).

Sisman et al. reported a case of vaginal delivery occurring at 34 weeks of gestation in a pregnant woman with positive RT-PCR reagent for SARS-CoV-2. They state that the newborn was immediately separated from the mother after delivery, being admitted to a neonatal intensive care unit. Nasopharyngeal swabs were collected at 24 and 48 h of life in which the results were positive for SARS-CoV-2 infection and the neonate presented fever, tachypnea and 78% oxygen saturation in room air on the second day after birth. The authors performed an immunohistochemical study to detect the virus in the placenta. They further evaluated the placental tissue by electron microscopy and detected viral nucleocapsid protein and viral-like particles in the cells of the syncytiotrophoblast. However, the authors did not perform PCR in breast milk, amniotic fluid and umbilical cord blood (61).

Vivanti et al. claim to have proven placental transmission of SARS-CoV-2 to a neonate who had brain injury similar to that of infected adult patients. The virus was transmitted from a mother who was infected during the last gestational trimester. In this case, placental infection was confirmed by immunohistochemistry and RT-PCR. The viral genes E and S were detected in the amniotic fluid collected during the cesarean procedure. In addition, viral RNA was detected by RT-PCR in

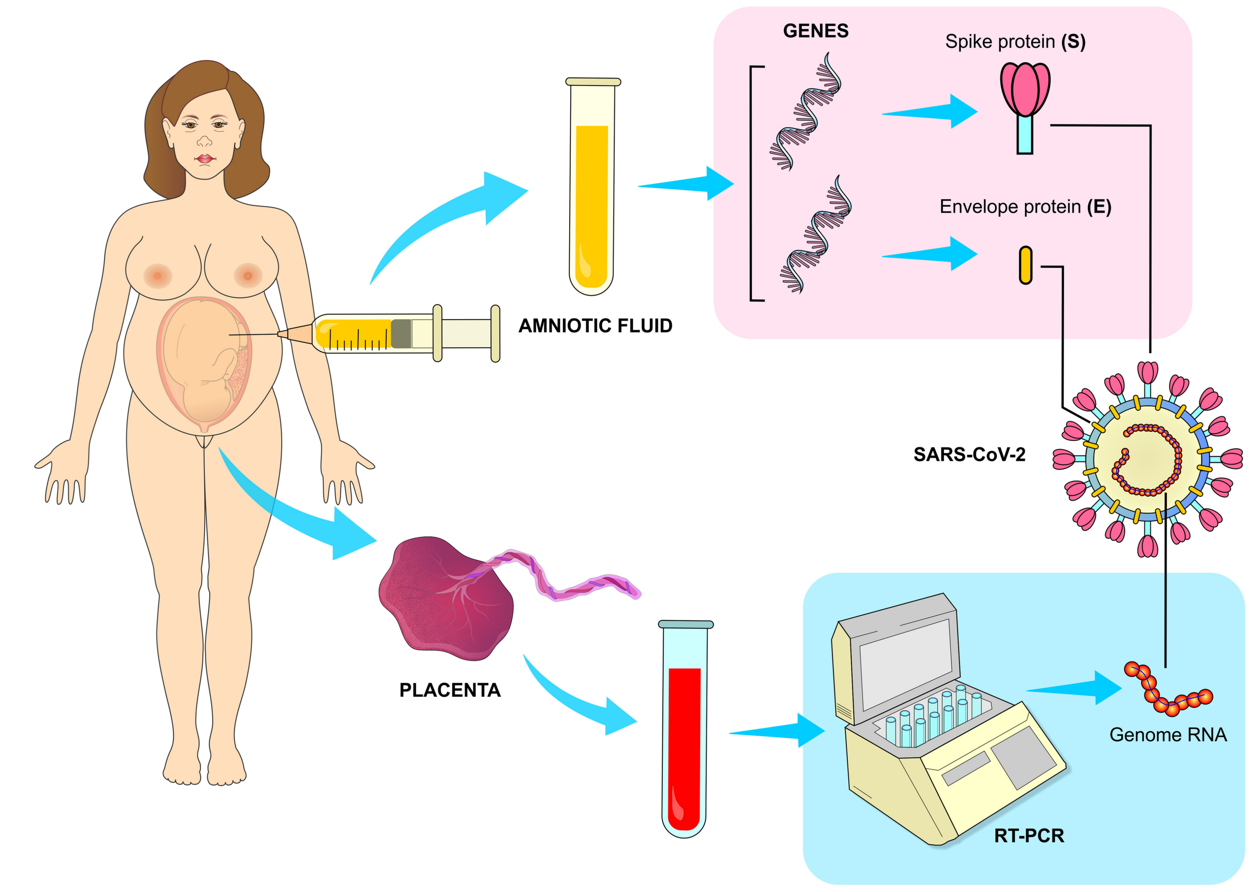

FIGURE 9 | Vertical transmission of SARS-CoV-2. The transmission of the virus from infected mothers to fetus has been confirmed by RT-PCR (Reverse Transcription Polymerase Chain Reaction) method, which has detected a high viral load in the placenta. The presence of viral genes responsible for translating structural proteins E and S were also detected in samples of amniotic fluid collected during cesarean surgeries of infected mothers.

the blood and bronchoalveolar lavage fluid of the newborn (62) (**Figure 9**).

In a recent study carried out in New York, swabs were collected in the first 24 h of life in 71 newborns of infected pregnant women in which no SARS-CoV-2 virus was detected by RT-PCR. Placental pathology was performed in 28 infected and 99 non-infected parturients, with a greater presence of thrombi and meconium in the placentas of women with Covid-19 (54). On the other hand, a population-based study involving 427 pregnant women with Covid-19 carried out by Knight et al. found positive RT-PCR in 12 (5%) among 265 newborns, with six being detected in the first 12 h of life (53).

A review study conducted by Lamouroux et al. reported the diagnosis of neonatal infection in 4 out of 71 newborns in the first 48 h of life. The authors pointed out that in 2 cases the PCR was negative on the sixth day of life, which is unexpected in cases of congenital infection by any pathogen. SARS-CoV-2 was detected by PCR in umbilical cord blood, amniotic fluid, placenta, vagina, and breast milk in 12, 10, 5, and 3 samples, respectively (55).

In another review (63), swabs were collected from 179 newborns from pregnant women infected in the third trimester of pregnancy with SARS-CoV-2 being detected in only six. In addition, the virus was searched in 37 samples of amniotic fluid and 48 samples of umbilical cord blood from these parturients and all were negative. Thus, the authors concluded that more evidence is needed to prove whether there is a risk of congenital COVID-19 infection.

Finally, the ideal gestational age for birth and the route of delivery must be determined by maternal conditions that can be aggravated by infection and fetal vitality. Pregnant women who have been infected in the first trimester must wait for the evolution for the delivery at term. For those infected in the third trimester and who are in the recovery phase, postponing childbirth until the mother is fully recovered seems to be the best choice. Early delivery by cesarean section is only indicated for pregnant women with severe respiratory distress syndrome, while among those who have developed mild symptoms without compromising fetal vitality, vaginal delivery is safe and recommended. Transmission of SARS-CoV-2 person-to-person in the delivery room through the healthcare team should be avoided through protective measures for both patient and staff (64).

SARS-COV-2 IN THE POSTPARTUM

In the immediate postpartum period, a minimum distance of two meters from the cradle to the bed of the mother infected with SARS-CoV-2 is recommended. Isolation with a screen or curtains and use of masks by both parturient and companion are also advised. However, a systematic review study including 666 neonates did not show high rates of postnatal SARS-CoV-2 infection after vaginal births, breastfeeding and mother-baby interaction (65) (**Figure 10**).

The RT-PCR detection of SARS-CoV-2 in umbilical cord blood has not been proven to be the best target for virus detection in both vaginal and cesarean delivery. Thus, there is no reported increased risk of vertical transmission with umbilical cord clamping between 1 and 3 min after birth (64).

Breastfeeding in patients infected with SARS-CoV-2 is not contraindicated, as long as they have the desire to breastfeed and have stable clinical conditions. Factors such as severity of the symptoms, hygiene of the breasts, use of mask, and respiratory hygiene must be considered before and during breastfeeding. A study carried out by German researchers evaluated by RT-PCR the presence of the virus in milk samples from 2 infected women. In the four samples collected from one of the mothers, the tests were negative for SARS-CoV-2, whereas the milk collected from the other mother had viral RNA detected for 4 days consecutively. However, the authors claim that more studies need to be carried out to determine whether the virus can be transmitted during breastfeeding (45, 66) (**Figure 11**).

Hand and Noble state that the anti-inflammatory and anti-infective factors that are present in breastmilk becomes especially important in mitigating infectious conditions, as shown by a recent report that found a strong sIgA antibody SARS-CoV-2 immune response in breastmilk from 12 out of 15 mothers (80%) previously infected with COVID-19 (67).

Mothers infected with SARS-CoV-2 are usually asymptomatic or have mild symptoms. A prospective study investigated 70 pregnant women who had reactive PCR on admission for delivery and of these, 12 (13%) had complications in the puerperium, with 3 being admitted to intensive care unit 7 days after delivery due to hypoxia and tachypnea with signs of multifocal pneumonia and need for oxygen through nasal cannula (54).

One of the first retrospective studies conducted in China reported that between December 2019 and February 2020 nine children aged up to 1 year old were tested positive for SARS-CoV-2. Country data had just reported over 31,000 confirmed cases of Covid-19 in the same period and this study found that at least one member in the family of each child had the infection. In addition, most children had fever and mild respiratory symptoms even though more undiagnosed cases were certainly present in this population, as only hospitalized children were included in the study (68).

A prospective study also conducted in China involving 33 newborns from mothers diagnosed with Covid-19 revealed that only 3 were PCR positive for SARS-CoV-2, two were born at 40 weeks of pregnancy by cesarean sections, which were indicated due to fetal distress and severity of maternal pneumonia. After collection of nasal and rectal swabs, both newborns had the infection confirmed on the second day after birth and presented fever, lethargy and radiological signs of pneumonia. The third child was born by cesarean section at 31 weeks after acute fetal distress and had to be resuscitated. Finally, the latter presented a condition suggestive of neonatal sepsis with positive blood culture for Enterobacter and pneumonia on the chest x-ray (69).

In another prospective study, the authors compared stillbirths, birth weight, Apgar score and number of admissions to the neonatal intensive care unit among newborns from infected ($n = 69$) and non-infected ($n = 599$) women. The results showed no significant difference between these groups with only 1 stillbirth at 37 weeks of gestation from an infected mother with decompensated diabetes (54). In New York, an observational study conducted in 3 hospitals identified 120 neonates born from 116 mothers positive for SARS-CoV-2. All neonates were tested at 24 h of life and none were positive. Eighty-two neonates completed follow-up at day 5–7 of life. All mothers were allowed to breastfeed and 79 of 82 neonates repeated PCR test at 5–7 days of life with negative results in all of them. After 14 days of life, 72 (88%) neonates were also tested and none were positive. None of the neonates had symptoms of COVID-19 (70).

Literature review investigated the clinical characteristics of 25 neonates with positive RT-PCR in the first 28 days of life. The newborns had an average gestational age of 37 weeks and 4 days and an average birth weight of 3,041 grams. The most common signs and symptoms were fever, vomiting and cough, there were no deaths and the average hospital stay was 15 days, ranging from 5 to 40 days (71) (**Figure 12**).

DISCUSSION

In this review, it was found that the increased risk of SARS in pregnant women infected with the new coronavirus can be explained by physiological changes in the respiratory system and by peculiarities in the immune response in this specific population. Studies in the two countries with the highest number of cases of COVID-19, Brazil and the United States, showed higher maternal mortality in the former country and a higher risk of admission to intensive care units in the latter (41, 44).

However, systematic reviews (46–52) that evaluated pregnant women with COVID-19 in different countries reported that the majority were infected in the last two gestational trimesters while presenting the asymptomatic form of the disease or mild symptoms such as fever and cough, with maternal mortality above 1.5% in only one study (51). This fact is probably explained by the average age of infected pregnant women, which does not fit the age group that is mostly affected by the severe form of COVID-19. A review study about the epidemiology of COVID-19 points out that the majority of those infected have mild flu-like symptoms and only 2 to 5% of the cases evolve to SARS (72).

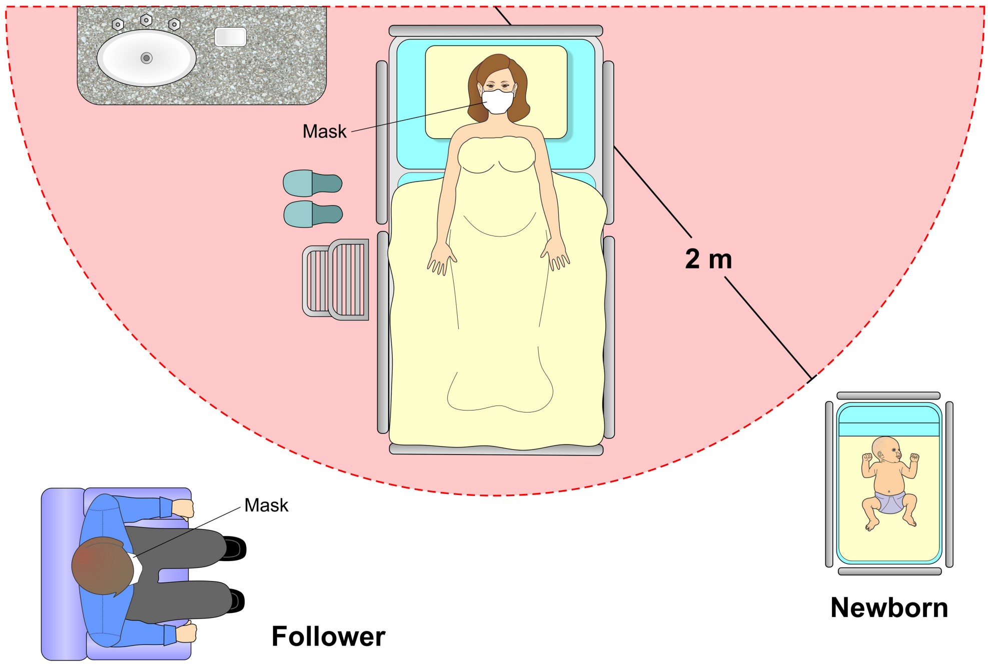

FIGURE 10 | Postpartum care. If the mother is in good health condition and does not require intensive care, it is recommended that the newborn remain in an appropriate cradle at a distance of 2 meters from the mother. The puerperal woman must always remain with a protective mask with an adequate filtering index and obey strict methods of hand hygiene. The presence of a companion is also allowed, following the rigor of hand hygiene with 70% alcohol and the use of an appropriate mask.

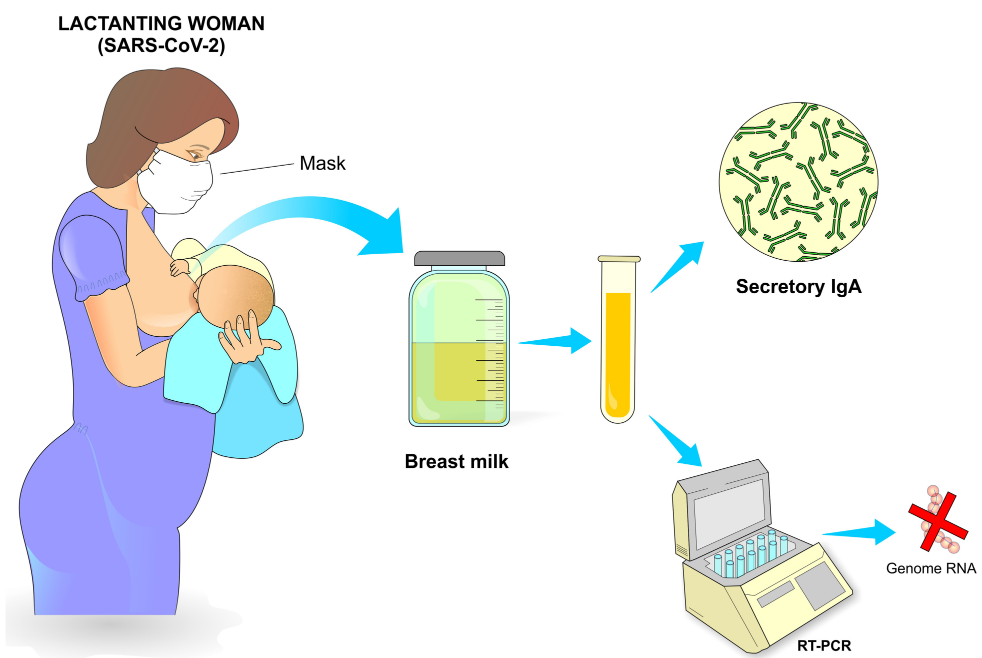

FIGURE 11 | Postpartum care. Breastfeeding is recommended as long as the conditions of the infected mother are appropriate, which include adequate breastfeeding procedure, use of a mask with adequate filtering, cleaning of the breasts and nipples and general care that minimizes contamination of the newborn. Milking can also be carried out, preferably with an appropriate suction pump after previous hygiene of the breasts and with subsequent adequate storage. The presence of secretory IgA in breast milk represents an important passive protection transmitted from the mother to the newborn through breastfeeding.

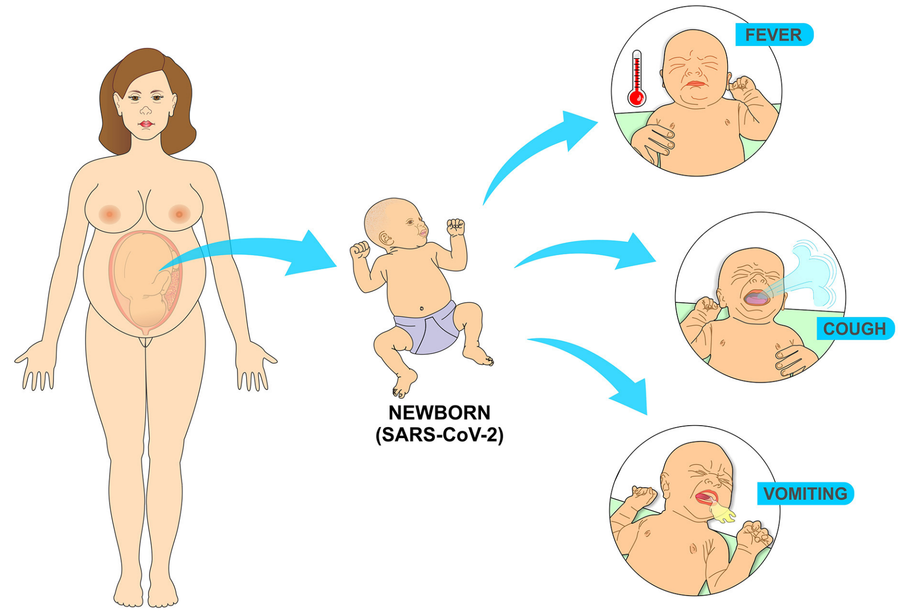

FIGURE 12 | Most common symptoms in the newborn infected with SARS-CoV-2 come from the replication of the virus in the cells of the respiratory tract. Fever results from the immune response to the presence of the virus, while vomiting comes from coughing as a result of the infectious process in the airways.

The studies included in this current review showed a higher prevalence of cesarean section and prematurity among pregnant women infected with SARS-CoV-2, which seems to be due to changes in the placental circulation induced by this virus that results in acute or chronic fetal distress and fetal hypoxia. Studies that carried out histopathological analysis of the placentas of pregnant women with the disease have demonstrated a greater presence of thrombi, villous edema, inflammatory infiltrates, poor perfusion in the fetal face and meconium in the placental tissue, which are associated with impaired fetal oxygenation (54, 73).

Vertical transmission of SARS-Cov-2 needs to be proven by studies with a larger sample of infected pregnant women and with a greater number of molecular tests performed on the placenta, amniotic fluid, umbilical cord blood and newborns. In this review, most studies (46–49, 51–53) detected the virus by performing RT-PCR analysis on placental tissue, umbilical cord blood and amniotic cavity. However, the possibility of SARS-Cov-2 being transmitted during pregnancy and childbirth cannot be ruled out as a recent systematic review including fifty studies reported that the virus was detected in newborns as well as in the placentas and amniotic fluid of infected mothers (57).

Likewise, only a single study (64) has detected the presence of the virus in breast milk so far. A review that included eight studies that analyzed the presence of SARS-CoV-2 RNA in the breast milk of 24 pregnant women infected with this virus during the third trimester of pregnancy demonstrated that no breast milk samples were positive for SARS-CoV-2 (74). The World Health Organization (WHO) recommends that women with suspected or confirmed cases of COVID-19 can breastfeed, based on the idea that through breastmilk the babies would get antibodies and anti-infective factors that help protect newborns from getting infections (75). Thus, it seems likely to conclude that there is no restriction for pregnant women with Covid-19 to breastfeed if respecting the recommendations for hand washing and mask use.

In addition, the studies evaluated in this current review indicated that the prevalence of preterm delivery and cesarean sections was high among pregnant women with Covid-19, in which most of them had the asymptomatic or mild form of the disease, with low mortality and with few cases of infected neonates shortly after delivery. In infected newborns, mortality was similarly low, with a mild form of fever and cough, with a low rate of hospitalization. Most studies covered in this review involved pregnant women diagnosed in the last two trimesters of pregnancy, which seems to prevent the infection from being associated with a higher risk of miscarriage. Moreover, research involving neonates had a very short follow up, impairing the assessment of the effects of the virus on children's health in the first year of life. Further studies are needed to prove vertical transmission and to ensure that the virus is not present in the placenta, amniotic fluid, umbilical cord blood and breast milk.

AUTHOR CONTRIBUTIONS

AV wrote the topics SARS-Cov-2 in pregnancy, childbirth, and its vertical transmission and SARS-Cov-2 in the postpartum. AF wrote the topic SARS-Cov-2: mechanisms of cell infection and immune response and was responsible for organizing the references and citations. FG wrote the topic Pregnancy, immunology, and susceptibility to SARS-Cov-2. FP was responsible for designing all the figures in this manuscript. EdA was responsible for translating the manuscript to English and for revising the entire manuscript. RC wrote the topic SARS-Cov-2 in pregnancy, childbirth, and its vertical transmission, was responsible for the concept of this work, and also helped writing the abstract, introduction, and discussion sections. All authors contributed to the article and approved the submitted version.

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Between a Rock and a Hard Place: Considering "Freebirth" During Covid-19

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Background: The global coronavirus (Covid-19) pandemic concerns all people, but has a specific effect on those who are expecting a baby during this time. The advice in the UK changed rapidly, with 14 different sets of national guidance issued within 1 month. Individual NHS Trusts released various guidance relating to the withdrawal of homebirth services, the closure of birth centers, restrictions on the number of birth partners (if any) allowed during labor, and whether any visitors were allowed to attend after birth. With the landscape of maternity care changing so rapidly, research was carried out to provide real-time data to capture the lived experiences of expectant families.

Methods: A mixed methods online survey was carried out over 2 weeks between 10th and 24th April 2020. The survey was open to those in the third trimester of pregnancy, those who had given birth since the beginning of the "lockdown" period in the UK, and the partners of pregnant women and people who were in these circumstances. The survey asked questions about how respondents' holistic antenatal experiences had been affected, whether their plans for birth had changed, and the effect of these changes on respondents' emotional wellbeing. Of the 1,700 responses received, 72 mentioned that they had seriously considered "freebirthing" (giving birth without a healthcare professional present).

Findings: An analysis of the respondents' reasons for considering freebirth was conducted, finding that reasons for considering freebirth were complex and multifaceted. Lesbian, bisexual, pansexual, and queer women were more likely to have considered freebirth than heterosexual people ($p < 0.001$).

Conclusions: Considering giving birth without a healthcare professional present is unusual in the Global North and represents an emerging field of study. The literature examining the reasons that people consider freebirth shows a variety of underlying motivations. A global pandemic represents a new factor in such considerations. The findings from this research can help inform maternity service planning in future crises.

Keywords: freebirth, pregnancy, choice, COVID-19, maternity, childbirth, LGBTQ+

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INTRODUCTION

The global coronavirus (Covid-19) pandemic concerns all people but has a specific effect on those who are expecting a baby during this time. Perinatal care, like emergency medical care, is time-sensitive, and cannot be delayed and then accessed later. In the first days of the lockdown in the UK, rapid response research was planned to understand the real-time social and cultural impact on the lived experience of people accessing maternity care in the UK. Our research question was:

> What are the experiences of perinatal care of those who are due to have a baby in the first months of lockdown in the UK, and how do they feel about these experiences?

Our article is drawn from this wider research project, which used an online survey of parents. The survey comprised of three main elements: capture of demographic information; a psychometric tool that was administered to those who had given birth; and a series of open-ended questions. The survey opened on 10th April 2020 and closed on 24th April 2020.

One of the themes that emerged from the open-ended questions was that 72 respondents had given serious consideration to freebirthing. This paper specifically discusses the experiences of those respondents, examining both why they considered this option, and their feelings about freebirth.

Freebirth

Freebirth occurs when someone:

> "intentionally giv[es] birth without health care professionals (HCPs) present in countries where there are medical facilities available to assist them (1)."

Although legal in the UK, freebirth is typically viewed as a non-mainstream and stigmatized birthing decision. The subject is under-researched and there is a paucity of academic literature on the phenomenon. Existing studies are largely qualitative and focus on the motivations of women in Western nations such as USA (2), UK (3), Ireland (4), Canada (5), Australia (6), Norway (7), and The Netherlands (8).

Such studies highlight that women decide to freebirth for a range of reasons. These include a previous traumatic birth (6), dissatisfaction with the care offered by perinatal services (7), and an inherent belief in the undisturbed physiological processes of birth (3). An inability to access care based on "logistics" and geographical distance to a maternity unit (9) and limitations on homebirths have also played a role in women's decision-making (4).

Freebirth and the Covid-19 Pandemic

In the first weeks of lockdown in the UK, the advice for expectant parents changed rapidly. On the 9th March 2020 the Royal College of Obstetricians and Gynecologists (RCOG) issued guidance suggesting pregnant women were not at greater risk from coronavirus that the general population. However, a week later, the UK Government guidance stated pregnant women were one of the most vulnerable groups. Within a few days, RCOG advised NHS Trusts to consider closing smaller maternity units (10).

Despite the proven safety of out of hospital settings for low-risk births (11, 12), in the first days of lockdown individual NHS Trusts released different guidance relating to the withdrawal of homebirth services, and the closure of birth centers and midwife-led units (MLUs). Restrictions were also placed on the number of birth partners—if any—allowed during labor, and whether any visitors (and who they were) were allowed to visit after birth.

The uncertainty and confusion around this advice meant that pregnant people became concerned as to how these restrictions would impact their rights and experiences during labor and birth. As a result, national human rights charities such as the Association for Improvements in the Maternity Services (AIMS) and Birthrights, published a range of literature to support people impacted by these restrictions [e.g., (13, 14)]. Further, it became apparent to midwives that some women were contemplating removing themselves entirely from NHS perinatal care and freebirthing their babies. Concerned by this, on 30th April 2020 the Royal College of Midwives (RCM) issued a clinical guidance note for midwives advising on how to support women intending to freebirth (15).

Quantitative data about freebirth is almost non-existent. It is unknown, for example, how many people per year freebirth their babies in the UK. Demographics relating to freebirthers' socio-economic background, ethnicity, age, and parity do not exist. In short, within the UK context, there has never been a quantitative study undertaken that attempts to collect such data. Given this lack of statistical data relating to freebirth, the rates of increased interest in freebirthing due to the COVID-19 pandemic remain unclear. However, communities such as the Freebirth and Emergency Childbirth Support Group—a UK fee-based Facebook group—have been created on social media during the pandemic. This group provided information to almost 300 expectant parents, healthcare professionals and birth supporters. The emergence of groups such as this during lockdown suggests a genuine interest from a range of people in learning more about freebirth.

METHODS

Data Collection

An online survey was undertaken to capture the experiences of those in the UK who had given birth, or were due to give birth, between the 9th March 2020 and the 3rd July 2020, or whose partners had given birth or were due to give birth between these dates. The dates chosen ensured participants had either recently become parents or were in the third trimester of pregnancy at the time of the research. The survey collected demographic data, used a psychometric tool to measure support in labor and birth, and included a large number of open-ended questions about respondents' experiences.

Participants were asked to indicate whether they or their partner was pregnant, their baby's date of birth or due date and their local healthcare service trust. Participants were also asked to indicate their ethnicity, age, disability, sexual orientation, and gender. The main part of the survey consisted of free text boxes which asked when participants became aware of Covid-19, and when they understood that it might impact their pregnancy and birth plans. It also asked about their plans for birth and whether they had changed, whether they were accessing private healthcare providers, whether other elements of perinatal care had changed, and how they felt about becoming a parent during a pandemic. A psychometric scale for those who had given birth was also included, but the results are not discussed in detail here. All questions after the consent and birth/due date were optional. The questionnaire tool is attached at **Supplementary Table 1**.

The survey was promoted and carried out entirely online due to the practicalities of the pandemic, and also to allow as many people to respond as possible. An advert with a hyperlink to the survey was shared on Twitter from both the first author's personal account and a King's College account. On Facebook, the advert was shared in generic birth groups, "due in" groups, homebirth groups, cesarean birth groups, parenting groups and locality-based birth groups. Two human rights charities, Birthrights and the Association for Improvements in Maternity Services (AIMS) were involved in helping design the survey, and in promoting it through their online social media. The questionnaire was open from 10th to 24th April 2020, and 1,754 responses were received.

Case Selection

This article reports in detail on the responses that related to freebirth. The psychometric scale data was removed, and a textual search of the full responses was carried out in the Excel spreadsheet for the terms:

"Freebirth"
"Unattended"
"Unassisted"
"Free [AND] birth"

The last search term produced a high number of false positive results such as "stress free birth," so all results for this search were manually checked before being included. The word "alone" was searched for (in the spreadsheet) but returned too many vague results. The mention of fear related to giving birth alone may refer to freebirthing, but is more likely to refer to giving birth without a partner, a situation many respondents were unhappy with.

Responses which included these terms were then read in full by the lead researcher (MG), and included in the freebirth dataset if they indicated that the participant or their partner had considered freebirth at any point, or if they had had a freebirth. This resulted in responses from 72 people who had considered or had a freebirth being included in the dataset. The full responses (excluding the psychometric scale) from these participants were then uploaded into NVivo. Two responses which mentioned freebirth were excluded from the analysis as these responses mentioned that the participants were too scared to consider freebirth, or that they were concerned other women might choose to freebirth. A second check of the full database was conducted by the second researcher (SPG) to ensure that all cases had been correctly identified.

TABLE 1 | Themes identified.

Theme	Subtheme
Planned place of birth	
Non-NHS support available/considered	Doula
	Independent midwife (IM)
Reasons for considering freebirth	Avoid hospital
	Previous traumatic birth
	Coercion
	Birth partner potentially excluded
	Uncertainty
	Access to water
	Childcare
	Distance/access to transport
	Timing

Analysis

The demographic data from the full dataset were compiled so as to compare with those considering freebirth. The dataset of 72 responses was then thematically analyzed using NVivo. Thematic analysis is a methodology often used within qualitative research in the social sciences, because it can generate rich detail from the data, whilst also providing an overall organizational structure to compare and discuss the data within. It is used for "identifying, analyzing and reporting patterns (themes) within data" [(16), p. 79].

As the aim of this research was to capture the real-time lived experiences of expectant parents during lockdown, we wanted to employ an analytical methodology that would provide a rich description of the dataset rather than a theoretically driven methodology.

Six stages of analytic process are described by Braun and Clarke (16) as part of a robust thematic analysis process. These are: familiarization, initial coding, searching for themes, reviewing themes, naming and describing themes, and producing a report. Reading and re-reading the responses which mentioned freebirth to determine whether they should be included in the analysis provided the necessary familiarization for the researchers. The dataset was then transferred to NVivo, and the lead researcher used an inductive approach to generate initial codes from the open-ended questions. This initial coding was organized into themes, providing a map of the data, which were reviewed by the second researcher (SPG).

Each theme was then named and described, drawing on the data to ensure that participants' voices remained the center of the analysis. The themes are presented above in **Table 1**, and a full codebook of the themes is available at **Supplementary Table 1**. The three main themes are: where birth was planned to happen before the pandemic; what non-NHS support respondents considered; and respondents' reasons for considering freebirth.

The findings above use the themes identified to form the structure of this article. Simple quantitative analysis was also undertaken with the freebirth dataset, firstly to produce descriptive statistics of the demographics of the participants, but also to turn qualitative answers into quantitative ones by turning open-ended answers into closed ones. Turning qualitative data into quantitative data can be one of the purposes of qualitative research (17).

RESULTS

Quantitative Findings

This section begins by identifying the demographic characteristics of the participants who had considered freebirth. We then go on to examine participants' plans for birth before the pandemic.

Of the 72 participants who said they had seriously considered freebirth during the pregnancy, 69 were women who were pregnant at the time of the research. Two participants were women who had given birth since the 9th March, and one participant was a man whose partner was pregnant. This division in the types of participant is roughly in line with the total dataset, where 1,385 were still pregnant at the time of the research, 336 had given birth, and 33 were the partner of someone who was pregnant or had given birth.

The majority of participants were white, heterosexual women, as is shown in **Figures 1**, **2**.

The youngest woman was 19, and the oldest was 41. The man was 42, but his partner's age is unknown. The average age was 31.4 ± 5 years, and the spread of ages are shown in **Figure 3**. The same person who declined to indicate their ethnicity or sexuality, also declined to indicate their age.

In terms of geographic distribution, participants considering freebirth were not confined to any particular location in the UK. There is representation in England, Scotland, Wales and Northern Ireland (see **Table 2**). There is largely no clustering in any of the NHS healthcare trusts, with the exception of three cases in the Nottingham University Hospitals NHS Trust.

The demographic characteristics of those considering freebirth were similar to the demographic characteristics of the entire dataset, with the exception of sexual orientation. Bisexual, lesbian and pansexual respondents made up 4.2% of all survey respondents, but 13.9% of the respondents considering freebirth. Sexual minority women were therefore more likely than heterosexual participants to be considering freebirth. Contingency table testing was used to determine if this difference was statistically significant. Fisher's Exact test was applied to the data, comparing the number of LGBQ+ participants in the full dataset with the number of LGBQ+ participants in the subset who had considered freebirth. This test showed that there was a difference between the groups, with LGBQ+ people being more likely to have considered freebirth ($p < 0.001$).

Although we did not collect demographic data about the profession of either the pregnant person or their partner, several respondents mentioned it within their responses to the open questions. One woman was a senior medical professional, two others work clinically within the NHS, two are non-clinical birth workers, another's partner is a GP, and one's husband is a Registered General Nurse (RGN). It is interesting both that so many people with professional experience in either birth or healthcare were considering freebirth, and that they felt it was important to provide this information in their answers. For those with partners who are in current clinical practice, this also presents a challenge to the definition of freebirth as a birth "without health care professionals (HCPs) present (1)." We will consider this further in the discussion.

Plans Before the Pandemic

Interestingly, only one person who answered the survey had been planning to freebirth before the pandemic. The other participants had a range of birth plans. Many had been intending to birth at home (60). In England and Wales, around 2% of babies are born at home each year, meaning that those who had planned a homebirth are over-represented in this cohort (18). A significant proportion of respondents had also been considering giving birth in either a freestanding birth center, or an alongside midwife-led unit (11), whilst two women had been intending to give birth on the labor ward, and one woman had been intending to have a planned cesarean birth. Many respondents described that they had flexible plans for birth:

> "If pregnancy remains low risk to go to [named] Birthing Center. Is [sic] any complications developed to go to [named] Hospital."

Although all of the participants had seriously considered freebirth or were currently considering it at the time they completed the survey, there were a mixture of current plans for birth. Only two women had given birth before the survey, and of these, one woman had had a freebirth, whilst the other had seriously considered freebirth, but in the end had been able to obtain the midwifery care that she had been told would not be available. She explained that although the homebirth service was officially withdrawn:

> "when my husband rang whilst I was in labor, they initially said no one could come, but after my husband asked to speak to the head of Midwifery, they said they could send someone out to do "checks" prior to transferring in. In the end, though, the midwife turned up with all the gear be and was happy to stay. Birth was extremely straightforward and fast (30 min after midwife arrived)."

Of the other 70 respondents whose babies had not yet been born, some were definitely intending to freebirth, whilst others remained undecided in their plans, and one woman was clear that she had previously seriously considered freebirth but was currently intending to give birth in hospital. The majority of expectant parents considering freebirth during the pandemic experienced negative feelings. Positive feelings seemed to be more prevalent amongst participants who had made the decision to have a freebirth, whilst those who were still undecided did not seem to share these positive feelings. Once the decision to freebirth had been made, participants described a returning sense of safety and security: "I feel safe in my own home."

Qualitative Findings

This section will use the qualitative data to explore the two remaining themes relating to the birth care and support

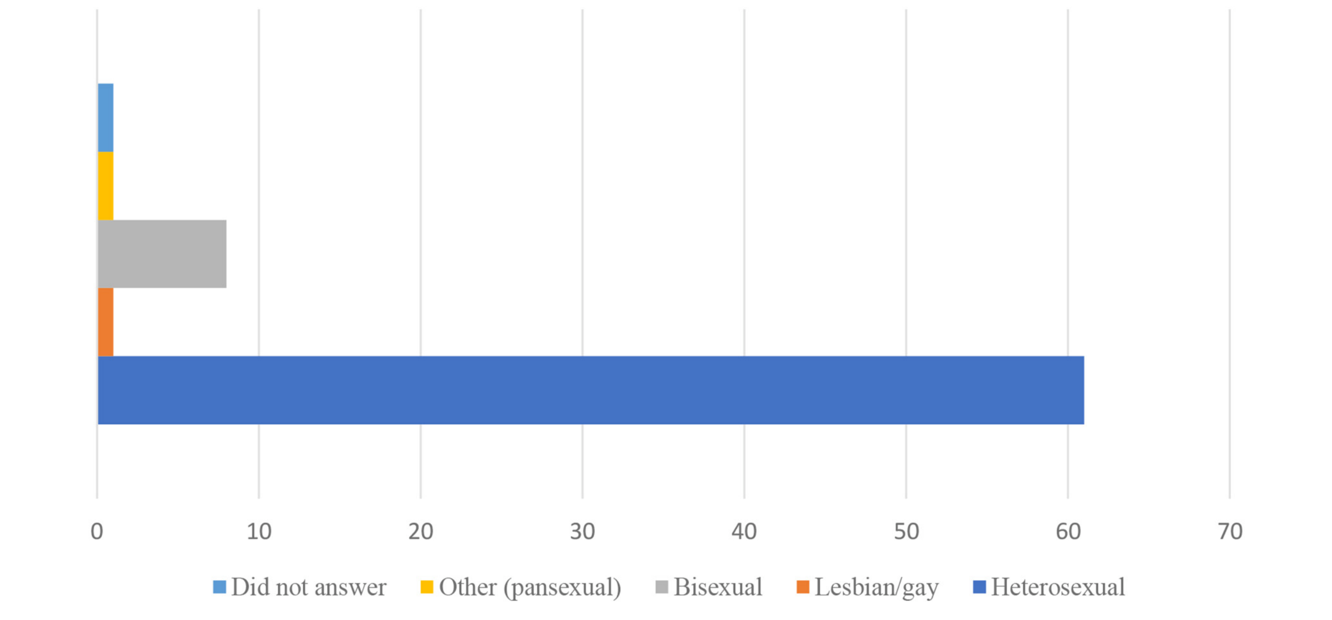

FIGURE 1 | Sexual orientation of participants considering freebirth.

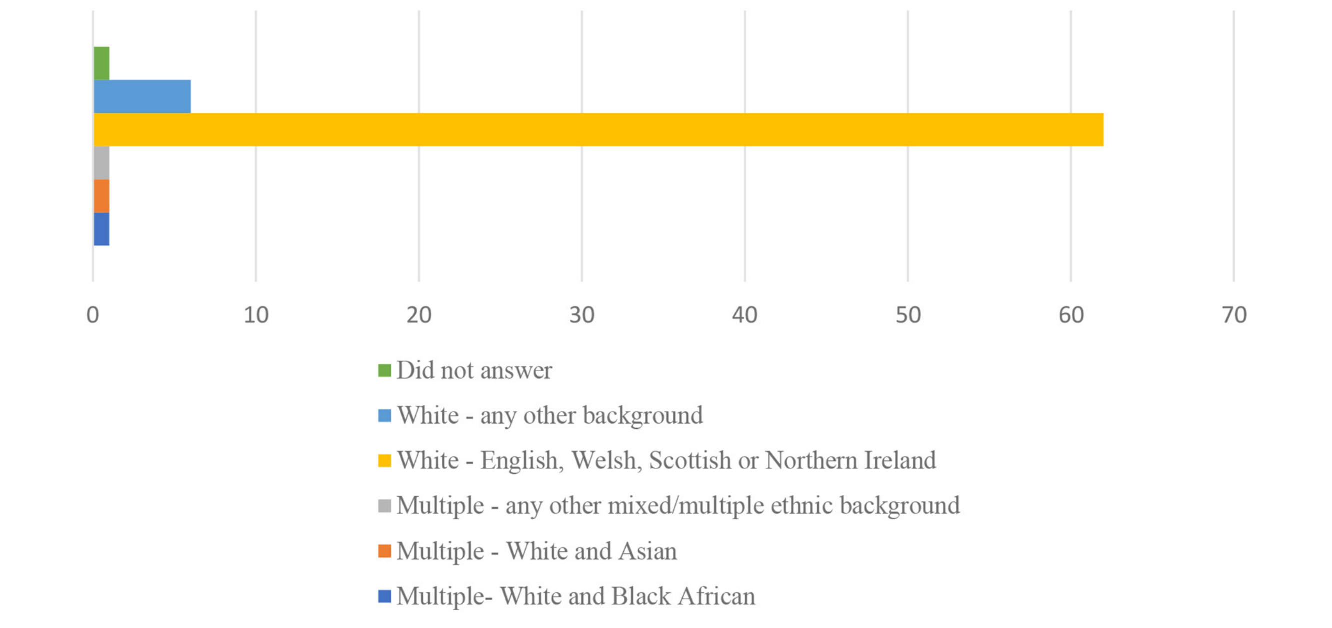

FIGURE 2 | Ethnicity of participants considering freebirth.

respondents considered, and the reasons that respondents considered freebirth.

Options Considered

Expectant parents in this study had a range of different first choices for birthplace, including homebirths, birth centers and MLUs, labor wards, and elective cesarean births. When expectant parents' plans for birth changed because of lockdown, a freebirth was not always their second choice for birth either. Some women's second preference was to give birth in a different NHS setting, which they had been informed was not available to them. These difficulties are shown by this participant, as she explains why her second choice of birthplace was not available to her, for reasons unconnected to Covid-19:

> "I have been told that the home birth service has been pulled and I won't be eligible for a midwife unit led birth as my BMI was too high at booking in so I am now planning to freebirth."

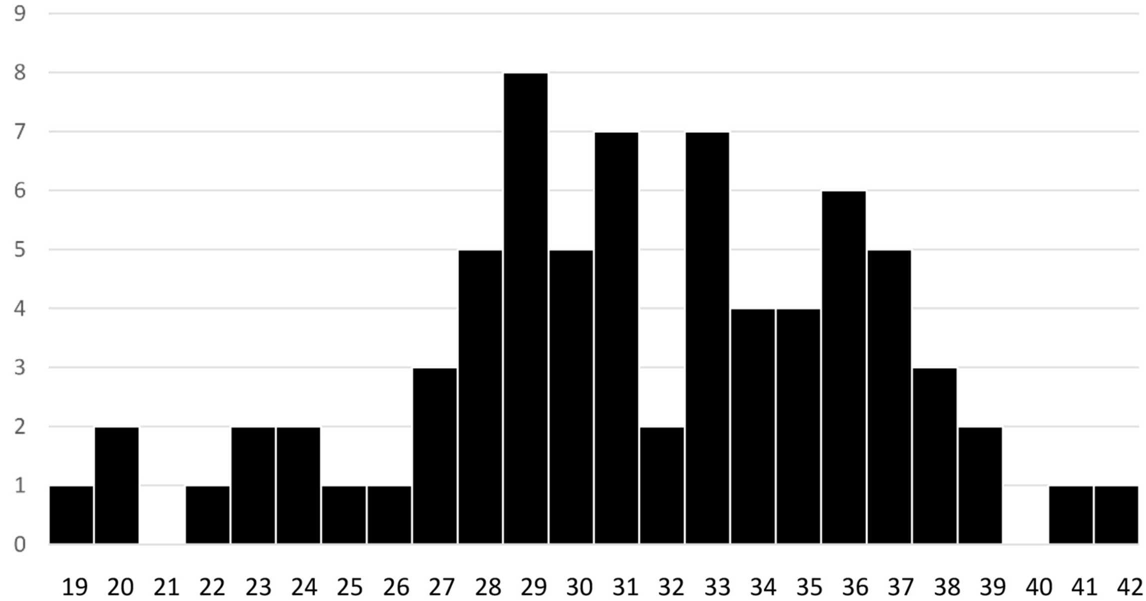

FIGURE 3 | Ages of participants considering freebirth.

Thirteen women in the study had considered using an independent or private midwife. These are fully qualified midwives, who are registered with the Nursing and Midwifery Council in the same way as NHS midwives. Independent midwives are self-employed, whilst private midwives are employed by private companies. Four women had hired an independent midwife, at the time of the survey. However, more women commented that they were unable to hire an independent midwife. For most, this was because they could not "afford it," whilst for others it was because the independent midwives had no availability. One woman had considered hiring an independent midwife before lockdown, but had spoken to their maternity services who had reassured her they would be supportive of a home vaginal birth after cesarean with the result that she decided not to hire an independent midwife.

Unfortunately, the local homebirth service had then been suspended, and the independent midwife no longer had any availability. The participant commented, "I feel the decision has been made too quickly without thorough troubleshooting." In another case, a respondent recalled that the local NHS Trust had:

> "[I]n their infinite wisdom decided to cancel indemnity for all independent midwives in the area....Combined with the cancellation of NHS home births, women in my area are left with few choices of any."

This meant that independent midwives were not legally able to attend births at that time.

The majority of participants who were considering freebirth because of Covid-19 had considered at least one other option subsequent to the changes in their original birth plans. Freebirth was therefore not a first or second choice for the majority of participants who were considering it.

Reasons for Considering Freebirth

Given that freebirth was the first choice of only one participant and was not even the second choice for many people, understanding the reasons why participants were considering it is important for healthcare services. The reasons given by expectant parents were varied. As **Table 3** shows, they can be divided into three overarching categories: a desire to avoid hospital, birth preferences, and practicalities.

These reasons were not mutually exclusive, and many participants expressed several reasons for considering freebirth. Some of the reasons were also connected, for example:

> "I will have to go into hospital alone as my husband doesn't drive and will have to look after our eldest daughter; there is no one else who can take her and she's not allowed to visit either."

This section will explore each of the three main themes for considering freebirth.

Avoiding Hospitals

Thirty-nine participants said they were considering freebirth partly or wholly because they wished to avoid going into the hospital to give birth. For some this was due to past experiences giving birth in hospitals. For others, the potential of catching Covid-19 whilst in hospital felt too much of a risk to take. Rather than hospitals being a place where they and their babies would be safe, they had become places of potential danger and contamination for some women.

Some participants feared what would happen if they went to hospital for this birth. Women described being afraid of being

TABLE 2 | Geographical distribution of participants considering freebirth.

England	**54**
North West	6
North East	1
Yorkshire and Humber	4
West Midlands	4
East Midlands	12
East	6
London	5
South East	11
South West	4
Scotland	**8**
Highlands and Islands	3
Mid East Scotland	2
South East Scotland	1
South West Scotland	2
Wales	**4**
South Wales	3
North Wales	1
Northern Ireland	**2**
Other	
Guernsey	2
Did not fill in	1

TABLE 3 | Reasons why participants were considering freebirth.

Avoiding hospital	Birth preferences	Practicalities
Traumatic last birth	Birth partner excluded	Lack of childcare
Fear of hospitals	Access to water	Previous fast labor
Last baby died in the hospital	Desire for certainty	Distance to hospital
Concerned about cascades of intervention		No access to suitable transport
Fear or experience of coercion		
Risks of contracting Covid-19		

coerced into interventions they did not want if they were in hospital or treated badly in other ways. These fears were not unrealistic, as they were often based on their previous experiences of hospital births:

> "Despite having quick births 'easy' births I have been treated awfully during labor and for that reason only feel I have had one positive birthing experience. I was hoping this birth would be healing...."

Other women's fears were based on their experiences of care during this pregnancy, where they felt that coercion and "bullying" had already happened to them. These fears were compounded by the idea that they might be in hospital without a partner "to advocate for me."

Hospital policies around the admission of partners to the labor ward were felt to be coercive by some women. Two women explained that their hospitals were only allowing partners in when labor was established. They had been informed that this would be judged by cervical dilation. However, cervical dilation can only be established by a vaginal examination. Two women described that they intended to decline the offered vaginal examinations but were scared that doing so would mean their partners were not allowed into the labor ward. The very fact that the stated policy made a partner's presence conditional on the women accepting an intervention made them feel that coercion was openly advertised as being integral to choosing a hospital birth.

For women whose partners or children were in the high-risk groups, going into hospital meant not only a risk to their own health and their newborn baby's health. It also meant that they potentially became contaminated, and a danger to their families. The dual hospital risks of interventions and the risk of contracting the virus were interrelated:

> "I fear the changes are going to lead to [more] unnecessary interventions. And an increased risk therefore of having to stay in hospital, increasing the chance that me, baby and my husband's will be exposed to the virus. My husband has a heart condition so I fear the worst."

Birth Preferences

Most NHS Trusts adopted a policy of only allowing one birth partner into labor wards, MLUs and birth centers during established labor. This created fear in some women that they would not have a known person with them for some or all of their labor. As well as wanting partners to be present at the birth to advocate for them, women described needing their support. This was especially the case when the journey to this birth had been difficult:

> "[M]y partner is a great support for me, we have gone through IVF and a miscarriage together and I couldn't imagine doing any of this without him...."

Some NHS Trusts adopted a policy that the sole birth partner had to be someone the woman lived with, ostensibly to reduce the potential for Covid-19 transmission to healthcare professionals (19). This caused specific problems for single mums, those whose partners needed to stay with older children, and those whose partners had jobs where the risk of being affected by Covid-19 was high:

> "[What] if my husband becomes locked down at work (possibility as he is [a] prison officer, when it hits the prisons they plan on literally locking the gates—in or out)...."

Many of the women who were in this position had planned their support carefully. Until just a few weeks before the survey, they had expected to be able to have a birth partner who they did not live with support them during birth—usually a doula (a non-medical birth worker who provides emotional and practical support), though one participant had intended to have her mother as her birth partner. Some of these women had intended to give birth in hospital or in birth centers and MLUs, with the support of their non-resident birth partner. They were very aware that they suddenly faced the real possibility of giving birth with no-one they knew present to support them.

In some NHS Trusts, the rules about who could be present at a birth were extended to homebirths as well. This created an impossible situation for one participant who is a single parent:

> "Home births so far are still going ahead in my trust, however I wouldn't be allowed my doula or my kids in the room. I have no childcare and no other birthing partner."

This situation had forced her into considering a freebirth, despite the fact that a homebirth service was still available.

For three women, access to water as a form of pain relief was an essential part of their birth plan. One participant was clear that she would have considered a waterbirth on the labor ward, but the only room with a pool was reserved for women who were Covid-19 positive or Covid-19 symptomatic[1].

The number of changes and the uncertainty over which services might be available were mentioned by three participants as a factor in their consideration of freebirth. Different NHS Trusts have made changes to the services available at varying times. Service changes impacted expectant parents' plans, as they made new choices depending on the services available. A participant who had changed her plans several times already in response to the withdrawal and reinstatement of birth support by her NHS Trust said she was now considering freebirth because she did "not want to change my birth plans [again]."

A sentiment which was repeated by many participants was the feeling that they had been left with no choices by their perinatal services, with 26 participants describing feeling trapped, and forced into decisions that they did not want to make. They characterized the choices that they had, due to a combination of personal circumstances and local Trust policies as being "no choice" or an "impossible choice." There was a sense that the decision to freebirth was one which the NHS services were making for them: "I feel I am being backed into a free birth."

Practicalities

Some expectant parents were considering freebirth because of practical reasons, which were often multifaceted. Lockdown restrictions, and elderly parents shielding had restricted the childcare options available for older children for some families. If the partner was the only person available to take care of the children, and the homebirth service had been withdrawn, that meant being without known support during birth. For those whose partner could not drive, or without access to a vehicle, simply getting to the hospital could be a logistical problem. This was especially the case if a homebirth service had been withdrawn and local birth centers were closed, or not available because the pregnant person was not "low risk." In rural areas, some women were faced with a significant journey to the only available NHS support for birth: "hospital 45 miles away."

Even with access to a car and a driver, this is a daunting journey to undertake in labor. Without that access, options were very restricted:

> "We don't have a car, and the idea of taking a taxi in mid labor, during a virus outbreak, was unthinkable."

Concern about the distance that might need to be traveled whilst in labor was compounded by previous birth history when women had had fast labors. The woman who lived 45 miles from the hospital said one of her main reasons for considering freebirth was that:

> "My last baby was born in less than an hour and a half so I'm worried I wouldn't make it to the hospital."

In total, eight participants mentioned that a previous history of precipitous labor was a factor in their consideration of freebirth. All of these women had previously planned a homebirth, or a birth in a birth center with close proximity to their home. They did not perceive that they were making a choice between giving birth in a hospital and freebirthing, but rather between freebirthing and "End[ing] up having an accidental unassisted birth."

DISCUSSION

This is the first large scale study to capture the demographics of people contemplating freebirth within the UK. It is also the first study to identify LGBTQ+ people considering freebirth. Importantly, freebirth was contemplated by people throughout the UK suggesting that this decision was not motivated by the actions of a few restrictive NHS trusts, but rather that the issue was far more widespread. Furthermore, as far as we are aware, this is the first freebirth study to capture data from all four countries of the UK.

Characteristics of Those Who Considered Freebirth

Notably, this is also the first time that a UK study has shown that NHS health care professionals have contemplated stepping outside of the NHS maternity system in order to freebirth their babies. As no respondent mentioned other, unconnected professions, it appears that respondents may have been justifying their choice to consider freebirth by constituting themselves or their partners as experts. This also raises as yet unanswered questions about NHS staff perception of safety in relation to the service they and their colleagues provide. It also offers a challenge to the definition of freebirth. If either the person who is giving birth or their partner is currently in clinical practice, can the

[1]From the larger survey, the reserving of pool rooms for women with Covid-19 appears to be a common practice, even though women with Covid-19 are not supported in having a waterbirth in most NHS Trusts.

birth be said to be "without health care professionals (HCPs) present (1)?"

We note that participants within our survey have specifically used the term "freebirth," alongside responses that indicate that they or their partners are healthcare professionals, and we believe it is important that their terminology about their birth choices is respected. The term was also used by most participants in the survey without healthcare training or partners. Using the term "freebirth" is an active, linguistic choice indicating an awareness of it as a social phenomenon. Moreover, those that indicate they or their partners are healthcare professionals, will likely have awareness of the stigma of freebirthing. We do not propose to offer an alternative definition of freebirth here, but instead highlight this as an issue for consideration should further research into health care professionals stepping outside the NHS maternity system be undertaken.

It is well-established that pregnant lesbian and bisexual women face routine heteronormativity, invisibility and invalidation in their encounters with perinatal care (20). Research also shows that LGBTQ+ people may experience fear and discomfort when accessing healthcare services; that fear being based on frequent accounts of other LGBTQ+ people being denied access to healthcare services or discriminated against when they disclose their gender or sexual orientation (21). A small amount of research shows that lesbian and bisexual women may even face hidden physical assault in perinatal care, such as deliberately rough vaginal examinations (22). We do not know whether this community experience of poor care was a factor in LGBTQ+ people choosing to freebirth in this study, but fear of poor care is a motivating factor that has been identified in other freebirth research (see for example 4). Other studies have not identified LGBTQ+ people choosing to freebirth before, and research into LGBTQ+ birth choices have not identified freebirth as a possible decision. Further research in this area is needed to understand whether LGBTQ+ people considering freebirth come from similar or different motivations than cis-heterosexual people.

The Importance of Choice

Anyone can legally choose to give birth at home, regardless of whether this would be medically recommended. This is a well-established right, which has been confirmed under European law (23). Birth centers and MLUs can have their own policies about who is allowed to give birth there. NHS England says that the place of birth should be decided by the person who is pregnant:

> "Women should be able to make decisions about the support they need during birth and where they would prefer to give birth, whether this is at home, in a midwifery unit or in an obstetric unit [(24), p. 9]."

However, in many NHS Trusts there is a policy that only women deemed "low risk" can give birth in birth centers or MLUs. The National Institute of Clinical Excellence (NICE) suggests that only around 45% of pregnancies are considered "low risk" (25). This means that when a homebirth service is withdrawn, many people may only be able to give birth in the hospital labor ward if they want NHS healthcare professionals' support during the birth, even if the birth center or MLU remain open.

Research is shortly due to be published that shows which perinatal choices different NHS Trusts were able to maintain, and which they decided it was necessary to remove. These results are welcome, and important for future emergency planning of perinatal services. As these findings show, removal of choice leads to pregnant people who would rather have an attended birth considering freebirth. However, the stories above also show that personal circumstances can mean that the maintenance of choice in birth is not as simple as which of the four places of birth are open. If a birth center is kept open when a homebirth services is closed but is only available to those who are "low risk", it does not provide choice for most people. If a homebirth service is still running, but children and those from other households are not allowed in the room, it is not a service that can be used by single parents. If a single birth supporter is allowed, but they have to be from the same household, single pregnant women and people face giving birth without support from someone they know. As can be seen in the responses to this survey, it can be the most vulnerable people who are affected by service disruption the most, and who then feel they are left with no choice but to consider freebirth. Choices which are seen as clinically minor choices (such as access to a birth pool on a labor ward) may be of great importance to pregnant people when making decisions about birth. It is therefore important that quantitative research into the choices that NHS Trusts were able to maintain is nuanced to service users' choices and takes into account the ways different personal circumstances may interact with perinatal service availability or restriction.

Although this study of freebirth took place during the Covid-19 pandemic it becomes apparent that pregnant people's motivations reflect those noted by previous scholars. Concern about the safety of hospitals, the reduction of homebirth options, the practicalities of attending hospital and previous birth trauma were all important motivations in this cohort. This demonstrates that the Covid-19 pandemic has placed a spotlight on existing problems in maternity care. Data from this study is clear: when pregnant people are presented with a maternity service they deem unsafe or does not align with their needs, desires or world view, they may step outside of that system. If service providers wish to ensure people have access to perinatal maternity care, they must provide a service that is acceptable to those who are using it.

This study has also exposed how some pregnant people considered maternity policies as coercive. A fear of being coerced into unwanted medical interventions raises serious issues regarding the under-researched area of informed consent and refusal in NHS maternity care. It must be ensured that policies do not inadvertently subvert informed consent as this could result in those giving birth submitting to interventions they may otherwise have refused. As already highlighted above, a desire to avoid such policies was a motivating factor for some people in this cohort.

Freebirth as a subject of academic research has only begun to be studied relatively recently, and the literature pertaining to it is small. The available literature suggests that it is a decision pregnant women make for a variety of reasons, including previous traumatic births (6), a lack of support for birth choices (4) and a belief in the inherent safety of undisturbed physiological birth (3). This research suggests that a global pandemic represents a new factor in such decisions.

Risk

Although the concept of risk typically dominates discussion on pregnancy and childbirth, the Covid-19 pandemic appears to have challenged people's views on where and how it is safest to give birth. Hospitals are generally assumed to be places of safety, however for women who have experienced a traumatic birth, or who are worried about iatrogenic harm in birth, hospitals may feel unsafe (26). During the pandemic, hospitals have become viewed by many people as risky places to be avoided, where the risk of Covid-19 transmission is high (27), and this fear was expressed by participants in this research too. Conversely, freebirth may be assumed to be a risky choice, and those who choose to freebirth are sometimes accused of making choices for their own benefit whilst disregarding the safety of their baby. Participants in this survey who were considering freebirth because they wished to avoid hospitals were clear that they were putting safety first. The vast majority of people within this study had not considered freebirth before the pandemic, but Covid-19, birthing restrictions and rapidly changing policies created competing risks that meant freebirth became an acceptable option. This indicates the complexity of people's decision-making and demonstrates how people's understanding of risks associated with place and manner of birth are not limited to what may be deemed a medical calculation of physical risks.

Strengths and Limitations

This project provided a brief snapshot into the thoughts, feelings, and decisions of expectant parents in the first weeks of the Covid-19 lockdown in the UK. There is an immediacy to these qualitative responses that can provide researchers, policy makers, and practitioners with an insight into lived experiences. The numbers considering freebirth, and the reasons that they were considering this could usefully inform reorganization and prioritization of perinatal services in the event of future lockdowns.

The research was intended to capture experiences from a wide range of expectant parents, and freebirth was not a specific area of investigation within the research. Capturing data from so many people considering freebirth was unexpected. Data capturing the number of freebirths are not routinely collected in the UK, apart from in London, where this information can be volunteered by parents (28). Through Freedom of Information requests to Health Boards some data is available for Wales, but here the numbers also include cases where a baby was born before the arrival of a midwife at home, or the parent at a hospital, MLU or birth center (28). We cannot therefore know if the 72 participants considering freebirth in this research represents a greater than usual proportion. Additionally, as most people who answered the survey had not yet given birth, we can only state how many people *considered* freebirth, and cannot know the numbers of those who eventually decided to do so. A limitation of this real-time survey tool is that the resultant dataset is a convenience sample which may be biased toward those that feel most strongly about their pregnancy experiences. It could therefore be that those expectant parents who were considering freebirth were more likely to complete this questionnaire than parents who felt more sanguine about the available NHS birth choices.

Future Research Directions

Further research into perinatal experiences during the Covid-19 pandemic has already been planned and partially conducted both within the UK and internationally. The results of other studies will fill some of the research gaps within this work. The opportunity to compare these findings on an international level would also create a more nuanced understanding of the circumstances that affect the consideration of freebirth during a pandemic.

As mentioned above, it is not currently known how many participants considering freebirth went on to have a freebirth within this study. Follow-up research to determine the actual circumstances of birth, and participants' satisfaction with their decisions could provide useful information, as no freebirth research to date has focused on consideration of freebirth.

This research suggests for the first time that specific groups of people may be more likely to have considered freebirth during the Covid-19 pandemic. Further research with LGBTQ+ people and HCPs would be useful to establish whether these groups are more likely to consider freebirth outside of a pandemic, and to understand the reasons why this might be.

DATA AVAILABILITY STATEMENT

The data will be made available without undue reservation through the UK Data Service, in accordance with ESRC protocols.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by King's College London, BDM Research Ethics Subcommittee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG: conceptualization, methodology, formal analysis, writing—original draft, and writing—review and editing. SP-G: formal analysis, writing—original draft, and writing—review and editing. GM: writing—original draft and writing—review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2021.603744/full#supplementary-material

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Children's Vulnerability to Sexual Violence During COVID-19 in Kenya: Recommendations for the Future

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This article discusses the latest research that reveals that children seem to be facing new risks of sexual violence in Kenya during the COVID-19 pandemic. The evidence suggests there have been changes in patterns of sexual offenses against children coincident with lockdowns, curfews, and school closures. In particular, emerging evidence from Kenya suggests that child victims are younger, more likely to be victimized by a neighbor in a private residence, and in the daytime, compared to pre-pandemic. We conclude that situational crime prevention strategies that focus on providing alternative safe venues to reduce offending opportunities must be a central part of a public health approach to reduce children's vulnerability during crises such as COVID-19.

Keywords: sexual violence against children, COVID-19, situational crime prevention, public health approach, offender versatility, Kenya

INTRODUCTION

During the COVID-19 pandemic, many countries have implemented emergency measures to reduce the spread of the disease. However, these measures may be intensifying sexual and gender-based violence [SGBV; (1)]. UN Women (2) found that in the last 12 months, 243 million women aged 15–49 had been subjected to SGBV by an intimate partner. The UN Population Fund (3) estimates that, after 6 months of emergency measures, there will be 31 million additional SGBV cases worldwide. SGBV is exacerbated during crisis situations because of heightened gender inequality and financial pressures (4), as well as difficulties in accessing relevant medical and legal services (5). COVID-19 has further intensified SGBV due to lockdown measures, effectively trapping victims in their homes with potential abusers [for a review of GBV during COVID-19, see (4)].

Specific concerns have been highlighted for COVID-19 and sexual and reproductive health. For example, the postponement of programmes designed to protect girls from female genital mutilation (FGM) and child marriage due to COVID-19 is estimated to lead to two million more cases of FGM and 13 million more child marriages over the next 10 years (3). This perspective piece focuses on low- and middle-income countries (LMICs), and specifically Kenya. This is because there is political good will to research and respond to SGBV in Kenya following President Kenyatta's call to action in the wake of increasing SGBV in the country (6). There is also mounting empirical evidence about new patterns of violence against children, owing to the data collection infrastructure established by the Survivors of Sexual Violence in Kenya Network (7). In Kenya, a reported 29% of women are married before the age of 18 (8). This is expected to increase during COVID-19, as financial strain leads families to marry their daughters to reap economic benefits in contexts where bride price is practiced (9, 10). Additionally, the Kenyan Democratic and Health Survey (8) estimates that 21% of Kenyan women aged 15–49 years had experienced female genital mutilation (FGM). During COVID-19, school closures and limited police presence have left young girls increasingly exposed to FGM (11). A report from October 2020 found that 2,800 12 year-old girls were paraded through the Kuria village in Kenya to showcase their initiation, despite legislation prohibiting FGM (11).

In this article, we discuss how the latest research reveals that children in LMICs such as Kenya seem to be facing new risks of sexual violence during the pandemic. In particular, while previous research has highlighted the adverse consequences of suspending programmes designed to prevent SGBV, we will highlight that patterns of offending behavior have potentially changed following the implementation of lockdowns, curfews, and school closures. These new risk factors must be considered in order to protect children from sexual violence.

Child Victims in Low- and- Middle Income Countries During COVID-19

Whilst the impact of COVID-19 on sexual violence and children is a global issue, it is of particular concern in LMICs. For example, South Africa saw a 61.6% increase in child abuse disclosures during COVID-19 in comparison to the previous year, with emotional abuse being the most frequent, followed by physical and sexual abuse (12). Additionally, emerging findings suggest that measures used to control COVID-19 in Kenya have exacerbated sexual violence against children, particularly girls. Kenya had high rates of victimization pre-COVID-19, with the National Violence Against Children Survey (13) finding that 13.5% of girls and 2.4% of boys experience sexual violence by the age of 17. However, this escalated further with the emergency measures introduced to prevent COVID-19 spread, including a nightly dusk-to-dawn curfew, travel restrictions, and school closures (6, 7, 14).

Ongoing evidence collection by the Survivors of Sexual Violence in Kenya Network suggests that COVID-19 has changed patterns of sexual violence against children (7, 15). First, child sexual violence victims are now age 12 on average (7), compared to 16 previously (13). This finding is corroborated by evidence from forensic medical examiners at gender-based violence recovery centers in Kenya who have noted that survivors attending hospitals for SGBV violations during COVID-19 are now younger and mostly below the age of 16 (16).

Second, school closures and reduced parental monitoring have coincided with an increase in offenses perpetrated by individuals known to the survivor. Offenses are more often being perpetrated by neighbors during the pandemic compared to before (42 vs. 16%) (7, 13). There are reported cases wherein neighbors have gained access to children through the ruse of providing educational resources, such as laptops and internet access, during school closures (7, 15). Worryingly, it is increasingly being recommended that neighbors should be utilized during COVID-19 to help identify and protect victims, and to aid in reporting incidences [e.g., (1, 17)]. However, prevention and protection programmes must urgently take heed of emerging evidence that neighbors are frequent perpetrators of violence during the pandemic in Kenya.

Third, the timing and location of sexual violence offenses seem to have changed during the COVID-19 pandemic. Offending during the pandemic in Kenya most often is taking place during the day (76% of all cases) when children would have previously been at school (7). Additionally, most sexual offenses against children during COVID-19 appear to be occurring in private locations (71% of all cases), with most of these offenses occurring in the perpetrator's home (65%), followed by the child's own residence [29%; (7)]. This is in stark contrast to pre-COVID-19, when few offenses against children occurred in private (24.5% of all cases), and few attacks occurred at the perpetrator's home (14.9%) or the child's residence [5.4%; (13)].

DISCUSSION

School closures are associated with many consequences for children, including a lack of access to educational content with 80% of 18 million children not accessing the radio or online content provided by the Government during this time (18). As a result, Kenya's Education Minister has announced that students will be required to repeat this academic year (19). Additionally, the above findings and other previous research highlights that school closures are related to increased sexual violence against children. Whilst boys and girls are both victims of sexual violence, sexual violence disproportionately affects girls with 13.5% of girls experiencing sexual violence by the age of 17 in comparison to 2.4% of boys (13).

Goulds et al. (20) studied school closures during the Ebola epidemic in Sierra Leone in 2014–15, finding that closures left children at greater risk of rape, and led to 65% increase in teenage pregnancies (21). Furthermore, research has found that the financial strain experienced during pandemics increases the number of young girls being forced into child marriage and high-risk work to provide food for their families. Moreover, there is heightened concern that school closures due to COVID-19 will increase children's vulnerability to violence and abuse (22).

Young girls are also at an increased risk of FGM and child marriages whilst they are not able to access the safety of their school networks (23, 24). Schools may offer sanctuary to young girls escaping child marriages and FGM, providing them with shelter, food, education, and the chance of a better future (25). However, school closures during the pandemic may result in young girls being sent home to families which will exploit them, if no one else in the community is able to protect them adequately from COVID-19 or afford to sponsor them (25). Additionally, financial pressures exacerbated by COVID-19 increase the proportion of child marriages, as families require the bridal price paid for their daughters to support their families (23, 25). Child marriages, like rape, lead to teenage pregnancies, with one area in Kenya reporting that 4,000 teenagers have become pregnant during the pandemic (6). Moreover, it is clear that the school closures implemented to reduce the spread of COVID-19 has had far reaching consequences, which disproportionately affect young women and more protective measures need to be endorsed to reduce this (26).

Versatility of Sexual Offending

Sexual offender specialization and versatility have been widely studied to understand how to prevent and protect people from violence. Shifting patterns in the "who, what and where" of sexual violence seen during COVID-19 illustrate the *versatility* of sexual offending, which means that offenders adjust their offending behaviors to correspond with the offending opportunities that arise (27). Most sexual offenders, including child molesters, are versatile (28). Many sexual offenders do not have a predilection toward victims of a specific age range, but rather victimize people across a range of ages [(29); see also (30)]. Most concerning is that versatile offenders pose a higher risk for future sexual and violent recidivism than non-versatile offenders (31). Thus, it is important for policy makers and duty bearers to recognize that sexually violent behavior evolves with the circumstances. The COVID-19 pandemic has resulted in more unsupervised children and offenders being close to home, likely providing increased opportunities for offenders to target and violate especially younger children. Therefore, protection strategies need to be reviewed and adapted to changing risks.

Protecting Children: Situational Crime Prevention

Situational crime prevention strategies can potentially reduce immediate offending opportunities that are arising from school closures (32, 33). Situational crime prevention strategies consider key environmental factors that are associated with offending opportunities, and design prevention measures that restrict opportunities, whilst also increasing the risks of offending and limiting the benefits (33–35). One example of situational crime prevention commonly used to address SGBV is the implementation of safe refuge locations, with these primarily run by community groups (34, 36). These shelters increase the safety of survivors whilst also promoting community participation in their protection (36). The prioritization of refuge centers for SGBV survivors is vital during COVID-19 to prevent survivors being isolated with their abusers, as many perpetrators are family members (1, 7, 16, 37).

In combination with temporary housing for survivors, alternative safe environments for children are required during the day whilst schools are closed. This will limit offenders' opportunities to access children during extreme circumstances such as a pandemic (21). These safe spaces for children should be developed by trusted community groups, as they have advanced knowledge of the local population and their needs (34). Alternative safe environments were used in Sierra Leone during the Ebola pandemic (21). In this context the protective space was used for social support, education on sexual and reproductive health, and vocational training to increase the economic potential of the young girls (21). Programs such as these could be implemented in LMICs during COVID-19 to reduce the sexual exploitation of young girls and prevent school dropouts due to teenage pregnancies [(21); see (7) for further recommendations].

One limitation of the situational crime prevention framework is that by limiting an offender's opportunity to target certain victims, offenders may instead pursue other types of victims [e.g., new age groups or another gender; (35)]. This was found in Sierra Leone, where only younger girls accessed the safe space; thus, offenders began violating older girls instead (21). Moreover, alongside crime prevention methods, long-term holistic societal changes are needed to prevent this displacement, such as by tackling social and economic factors that correlate with crime (35).

Violence against women is a systemic issue. Attitudes towards gender equality license SGBV. Therefore, it is essential a wider public health approach is taken to tackle SGBV (38, 39). A public health approach aims to create an environment where all citizens are safe and healthy (38). Therefore, a public health approach would work to adapt a culture of gender equality, where the human rights of individuals were respected to promote safety. This can be achieved alongside a situational crime prevention framework by the implementation of wider community programs, such as education programmes on gender equality, healthy relationship formation, and bystander intervention, as well as economic strengthening programs, such as cash transfers and micro-finance training (40). These programs would work to implement a culture of zero tolerance toward violence, whereby all are equal and financially viable.

However, one weakness regarding research into crime prevention methods is that there is limited empirical data from low-resource environments. It is imperative to increase the capacity of countries like Kenya and South Africa to document cases and research patterns of violence over time (41). This information can be used to monitor and evaluate crime prevention techniques and suggest how they can be improved in the future.

CONCLUSION

Emerging evidence from Kenya suggests that COVID-19 and the associated curfews and school closures have coincided with children being violated at a younger age, and increasingly in private residences by individuals known to them, namely neighbors. It is critical that crisis management plans for COVID-19 are altered to explicitly provide for the protection of children, such as by providing alternative safe environments during school closures and increasing the provision of refuge centers. Continued surveillance of patterns of sexual violence against children is vital to identify new risk factors and protect children during COVID-19. Whilst the data presented here are specific to the Kenyan context, these patterns and recommendations should be applied to protecting children globally, especially in other LMIC contexts.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LS, HF, and JR drafted the manuscript, which was reviewed by SR, MC, and WK. All authors contributed to the editing of the approved final manuscript.

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Anxiety, Health Self-Perception, and Worry About the Resurgence of COVID-19 Predict Fear Reactions Among Genders in the Cuban Population

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The resurgence of COVID-19 could deepen the psychological impacts of the pandemic which poses new challenges for mental health professionals. Among the actions that should be prioritized is the monitoring of the groups that have shown greater psychological vulnerability during the first stage of the pandemic. The first aim of our study is to explore the fear reactions to COVID-19 between genders during the second wave of the outbreak in Cuba. Second, establish possible predictors of fear of COVID-19 in relation to gender. Specifically, we will evaluate how anxiety related to COVID-19, health self-perception, and worry about the resurgence of COVID-19 predict fear reactions among women and men in the Cuban population. A cross-sectional online study was designed. The research was conducted between August 16 and October 18, 2020. A total of 373 people completed the online survey. A socio-demographic questionnaire, the Fear of COVID-19 Scale and the Coronavirus Anxiety Scale were used. An independent-samples *t*-test was conducted to compare the fear, worry, anxiety and self-perceived health scores, between genders. The relationship between those variables and fear of COVID-19, was investigated using Pearson correlation coefficient. Finally, multiple linear regression was used to evaluate the possible associations (predictors) related to fear of COVID-19. In our study, women, compared to men, presented greater fear reactions, greater concern about resurgence of COVID-19 and poorer self-perceived health. Anxiety reactions in our sample showed no differences between genders. In women, anxiety of COVID-19, worry about resurgence of COVID-19, and self-perceived health are associated with fear reactions to COVID-19. In the case of men, the self-perceived health showed no associations with fear reactions. Our results confirm the results of several related investigations during the first wave of the pandemic where women have shown greater psychological vulnerability compared to men. However, we cannot rule out that the real impact of the pandemic on mental health in men is much greater than that described by the studies conducted to date. Additional studies are needed on the psychological impact of COVID-19 on men.

Keywords: gender, fear of COVID-19, resurgence, anxiety, health self-perception, worry

INTRODUCTION

Since December 2019 the world has faced a common enemy: the new coronavirus disease 2019 (COVID-19). This new disease (caused by the virus designated as SARS-CoV-2), has constituted an extraordinary challenge for global public health (1).

COVID-19 is also characterized by its fast transmission and high mortality (2). To date (11/12/20), 52 million people have fallen ill with COVID-19, with 1.29 million people dying from the disease (3). The presence of non-communicable chronic diseases (hypertension, diabetes, obesity, chronic renal impairment, etc.), age over 60 years, and the existence of respiratory diseases have been associated with higher mortality rates (4, 5).

In the absence of a definitive cure, measures to contain the spread of the disease include restriction of movement, physical distancing, the establishment of quarantines, the closure of public places (bars, schools, gyms, airports, etc.), and the use of face masks (6, 7).

The measures implemented to contain the pandemic have reduced the growth in the number of cases, preventing the collapse of medical services and saving thousands of lives (8). However, these measures have had a considerable impact on the mental health of the population (9, 10).

In this sense, several studies have been carried out to explore the impact of the pandemic on people's mental health. Among the most frequent mental health problems related to COVID-19 outbreak reported to date are anxiety, insomnia, stress, post-traumatic stress symptoms (PTSS) depression, anger, and fear (10–17).

Currently, the resurgence of the disease in several countries around the world indicates the beginning of the second wave of COVID-19 (18). According to some authors, the second wave of COVID-19 constitutes a significant threat at the social level, exacerbating the impact caused by the first wave in sectors such as the economy and public health (19). Additionally, the resurgence of COVID-19 could deepen the psychological impacts of the pandemic (20), which poses new challenges for mental health professionals around the world. In our opinion, among the actions that should be prioritized at this stage is the monitoring of the groups that have shown greater psychological vulnerability during the first stage of the pandemic.

Women are among the most vulnerable groups in terms of mental health during the current pandemic. The greater vulnerability of women, in comparison to men, in terms of mental health during the current pandemic is related to biological, psychological and sociocultural factors (21). For example, from a biological perspective in situations of acute stress, women show a lower adaptation to hypersecretion of the corticotropin-releasing factor (CRF) (2), making them more vulnerable to developing mental disorders involving hyperarousal (22).

This pattern of response to stress has an expression in the prevalence of mental disorders that are diagnosed more frequently in women. Persistent exposure to stressful situations increases the vulnerability to develop posttraumatic stress disorder, panic disorder, and major depression, disorders that are diagnosed more frequently in women (23). These differences between women and men in terms of the psychopathological profile have been previously reported in non-pandemic times. For example, in response to situations of chronic stress, women generally develop phobia, depression, anxiety, and panic disorders more frequently than men (24).

However, the risk that the current pandemic poses to women's mental health cannot be understood solely in biological terms. In addition, there are socio-cultural factors that also create a gap between genders. For example, around 70% of healthcare and social services workforce are women, increasing the risk of infection by the virus (25) unlike men who are generally exposed to the virus in a non-health care setting (26). Additionally, in countries like Singapore and Germany more women than men have lost their jobs during the current pandemic and also a greater number of women have seen their formal work hours reduced and their domestic work hours increased (27).

In the long term, being unemployed has a negative impact on mental health, increased relative-risk of death by suicide, compared with being employed (28). On the other hand, during the current pandemic caregiver responsibilities have increased, especially after the closure of childcare centers (21), potentially increasing stress and negatively impacting psychological well-being, especially in women (29). This scenario places women in a position of increased vulnerability during the current pandemic, having a negative impact on their mental health.

Several studies to date have found that women, compared to men, have experienced higher levels of psychological discomfort, depression, anxiety, psychological distress, insomnia, adjustment disorder, and fear related to COVID-19 (16, 30–33).

Fear has been one of the most studied emotional reactions during the current outbreak. This emotion is defined as an unpleasant state due to the perception of threat (34) acting as an intervening variable between a set of context-dependent stimuli and suites of behavioral response (35). During the pandemic, fear has shown an adaptive function by stimulating self-care behaviors (36, 37). However, high levels of fear increase distress and anxiety, increasing vulnerability to develop mental illness (34).

In this sense, it has been proven that women are more susceptible to developing disorders related to fear responses compared to men (38). A tentative etiological explanation for this phenomenon has been the existence of a longer extinction duration of fear generalization in women (39). These results have also been supported by neuroimaging studies. In the case of women, during the fear conditioning process, greater BOLD-signal changes have been observed the right amygdala, right rostral anterior cingulate (rACC) and dorsal anterior cingulate cortex (dACC) (40). This characteristic would contribute to a greater risk to the mental health of women compared to men when they are exposed to stressful situations that evoke fear responses.

In the literature, different predictors of fear reactions have been described in the general population. For example, it has been shown that anxiety, intolerance of uncertainty, perceived infectability, worry, media exposure, and depression has been associated with fear of COVID-19 in the general population (41–46).

THE CURRENT STUDY

The first case of COVID-19 in Cuba was reported on March 11, 2020. To date (26/01/2021), more than 22 600 cases positive of COVID-19 have been reported in Cuba and 200 people have died from this disease (47).

During the first 4 months of the fight against the pandemic, the measures of the Cuban government and the Ministry of Public Health included the mandatory use of the face mask, the closure of international borders, the closure of schools, and the establishment of quarantines in places with significant outbreaks of the disease (Cuba's COVID-19 strategy, 2020). These measures made it possible to significantly reduce the number of positive cases throughout the country.

However, since August 2020, the country has experienced a sustained increase in the number of positive cases for the disease. In the first 8 days of August alone, 255 cases were confirmed, representing 90% of the confirmed cases in July (Ministry of Public Health, 2020). Although the use of face masks and social distancing remain mandatory, the authorities will no longer isolate those who have been in contact with suspected cases, school activities are restarted, airports are open and economic activity in the country is reactivated.

This scenario constitutes a major challenge for mental health, as people must return to their daily activities even when there is no cure for the disease, potentially increasing fear and anxiety reactions, especially in the most vulnerable groups.

In Cuba, a study conducted by Broche-Pérez et al. (33) during the first wave of the disease found a greater fear response related to COVID-19 in women. However, the authors did not explore predictors of fear reactions in the sample, making it difficult to design interventions that reduce the negative impact of the outbreak on the mental health of women and men. The design of interventions is very important in the Cuban context considering that the country is already facing the resurgence of COVID-19.

In this study we will focus specifically on how anxiety related to COVID-19, health self-perception and worry about the resurgence of the outbreak are related to fear reactions to COVID-19 in the Cuban population. Although the terms fear, anxiety and worry are sometimes used synonymously, they are separate constructs. Both fear and anxiety are the result of adaptive defensive behavior that aims to escape a threat or motivational conflict (48). However, according to Öhman (49) fear reactions denotes dread of impeding, disaster and an intense urge to defend oneself, and anxiety has been described as an ineffable and unpleasant foreboding. On the other hand, worry and anxiety should also be considered as separate constructs (50). While worry is related to problem-focused and adaptive coping strategies, anxiety is associated with negative affect (51).

The first objective of our study is to explore the fear reactions to COVID-19 between genders during the second wave of the outbreak in Cuba. Second, to establish possible predictors of fear of COVID-19 (anxiety related to COVID-19, health self-perception, and worry about the resurgence of COVID-19) among women and men in the Cuban population.

MATERIALS AND METHODS

Study Design and Participants

A cross-sectional online study was designed. To disseminate the survey, the Google Forms® platform was used. The survey was released through social media (Facebook, WhatsApp, and Telegram). An announcement of the study was also published on the website of the Wellbeing Center of the Universidad Central "Marta Abreu" de Las Villas. The research was conducted between August 16 and October 18, 2020. All Cuban citizens over 18 years were eligible. A total of 373 people completed the online survey. For this sample size, a power analysis was running (*post hoc*) using the G*Power software (version 3.1.9.2) (52). Considering the statistical test (multiple linear regression), and the number of predictors (three predictor) the sample showed a power of.99.

Instruments

Background Information

The demographic variables explored included the age, gender and education. To evaluate health self-perception, we use the *ad hoc* question "how do you consider your health is?" [from 1 ("very poor") to 5 ("excellent")]. To explore worry about the resurgence of COVID-19 we used the *ad hoc* question "how concerned are you about the resurgence of COVID-19?" [from 1 ("not at all") to 5 ("very concern")].

The Fear of COVID-19 Scale

The Fear of COVID-19 Scale (FCV-19S) (41) is made up of seven items with a five-item Likert-point response from 1 ("strongly disagree") to 5 ("strongly agree"). The score range of the FCV-19S is 7 to 35. Higher scores indicate greater fear of COVID-19. In this study, the Cuban version of the scale was used (53). For the Cuban population the Cronbach alpha coefficient was 0.80.

The Coronavirus Anxiety Scale

The Coronavirus Anxiety Scale (CAS) (54) was developed to assess the anxiety reactions related to COVID-19 pandemic. The CAS consists of 5 items with a Likert-point response from 0 ("not at all") to 4 ("nearly every day over the last 2 weeks"). The original version of CAS has excellent internal consistency, with a Cronbach alpha coefficient reported of 0.93. For the Cuban population the Cronbach alpha coefficient was 0.88 (33).

Procedure

The study protocol was approved by the ethics committee of the Department of Psychology of the Universidad Central "Marta Abreu" de Las Villas. All procedures performed in this study were in accordance with the ethical standards of the 1964 Helsinki Declaration. Informed consent was obtained from all participants included in the study.

Data Analysis

The data were processed using SPSS/Windows (version 21). Descriptive statistics was used to explore participants' characteristics. An independent-samples t-test was conducted to

TABLE 1 | Characteristics of survey participants ($N = 373$).

Characteristics	Fr (%)
Age [M(SD)]	32.1 (12.9)
Gender	
Female	238(63.8)
Male	135 (36.2)
Education status	
Primary school	6 (1.6)
Secondary school	3 (0.8)
Higher secondary level	78 (20.9)
Tertiary education	286 (76.7)
Self-reported health status	
Very poor	1 (0.3)
Poor	7 (1.9)
Average	86 (23.1)
Very good	214 (57.4)
Excellent	65 (17.4)
Worry about outbreak	
Not at all	8 (2.1)
Not too much	50 (13.4)
I can say	24 (6.4)
Concern	214 (57.4)
Very concern	77 (20.6)

M, mean; SD, standard deviation; fr, frequency.

compare the fear of COVID-19 scores, worry about resurgence of COVID-19, anxiety related to COVID-19 and self-perceived health between genders. Results with p <0.05 were regarded as significant. The Cohen's d were calculated to estimate effect sizes in all comparisons. Values above 0.2, 0.5, and 0.8 were considered as small, medium, and large effect size, respectively (55). The relationship between fear of COVID-19, anxiety related to COVID-19, worry about resurgence of COVID-19 and self-perceived health was investigated using Pearson product-moment correlation coefficient. Finally, multiple linear regression was used to evaluate the effects of worry about resurgence of COVID-19, anxiety related to COVID-19 and self-perceived health over fear of COVID-19 scores.

RESULTS

Characteristics of Participants

Table 1 shows the characteristics of the participants. The mean age of participants ($n = 373$) was 32.1 years, with a range between 18 years to 81 years old. In the study women predominate, representing 63.9% of the participants. Most of the participants (76.7%) finished college. In the sample, 279 participants (74.8%) rated their health as "very good" or "excellent." On the other hand, 291 participants (78%) expressed feeling "concerned" or "very concerned" with the second wave of COVID-19.

Comparisons Between Genders on the Fear of Coronavirus-19 Scale and Related Variables

The results of the comparison of variables between groups are shown in **Table 2**. There are significant differences in fear of COVID-19, worry about resurgence of COVID-19 and self-perceived health between genders. The female participants showed higher levels of fear of COVID-19 and worry about resurgence. Women also perceived their health status as poorer compared to men. No differences between female and male participants were found in anxiety related to COVID-19.

Correlations Between Variables

The relationship between fear of COVID-19, anxiety related to COVID-19, worry about resurgence of COVID-19 and self-perceived health was investigated using Pearson product-moment correlation coefficient (**Table 3**). Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. There was a strong, positive correlation between the fear of COVID-19, anxiety related to COVID-19 and worry about resurgence of COVID-19, with high levels of fear of COVID-19 associated with high levels of anxiety and worry about resurgence of COVID-19. It was also found a negative correlation between the fear of COVID-19 and self-perceived health with high levels of fear associated with lower levels of self-perceived health.

There is a statistically significant difference in the strength of the correlation between fear of COVID-19 and self-perceived health for males and females ($z = -2.90$; $p = 0.003$). The correlation between fear of COVID-19 and anxiety ($z = 0.84$; $p = 0.40$) and between fear of COVID-19 and worry about resurgence of COVID-19 ($z = -1.32$; $p = 0.18$) did not show significant differences in the strength of the correlations between the groups.

Regression Analysis

A multiple regression analysis was run to predict fear of COVID-19 levels between genders from anxiety related to COVID-19, worry about resurgence of COVID-19 and self-perceived health. The **Table 4** shows that the independent variables statistically significantly predict the dependent variable (for both groups) (male: $F_{(3, 131)} = 54.766$, $p < 0.0001$, $R^2 = 0.55$; female: $F_{(3, 234)} = 74.928$, $p < 0.0001$, $R^2 = 0.49$). In the case of women, the three variables included in the analysis made it possible to predict fear reactions in this group (p <0.05). In the case of men, the variables anxiety related to COVID-19 and worry about resurgence of COVID-19 showed associations with fear reactions in this group (p <0.001). However, self-perceived health was not a predictor of fear reactions to COVID-19 in the case of men ($p = 0.30$).

DISCUSSION

The first objective of our study was to explore the fear reactions to COVID-19 between genders during the second wave of the outbreak in Cuba. Second, to establish possible predictors of fear of COVID-19 in relation to gender. In our study, women, compared to men, presented

TABLE 2 | Comparisons between genders on the Fear of Coronavirus-19 Scale and related variables.

	Female ($n = 238$)	Male ($n = 135$)			
Variables	**M (SD)**	**M (SD)**	***t***	***p***	***d***
Fear of COVID-19	19.02 (5.93)	17.34 (6.29)	2.566	0.01	0.27
Anxiety related to COVID-19	8 (3.51)	7.24 (3.89)	1.905	0.058	0.20
Worry about resurgence of COVID-19	3.97 (0.85)	3.52 (1.12)	4.413	<0.001	0.47
Self-perceived health	3.81 (0.67)	4.05 (0.72)	3.218	0.001	0.35

M, mean; SD, standard deviation.

TABLE 3 | Correlations between gender on the Fear of Coronavirus-19 Scale and related variables.

Gender	**1**	**2**	**3**	**4**	
Male	1.Fear of COVID-19	-			
	2.Anxiety related to COVID-19	684**	-		
	3.Worry about resurgence of COVID-19	365**	0.110	-	
	4.Self-perceived health	-428**	-459**	-261**	-
Female	1.Fear of COVID-19	-			
	2.Anxiety related to COVID-19	632**	-		
	3.Worry about resurgence of COVID-19	482**	349**	-	
	4.Self-perceived health	-141*	−0.033	−0.038	-

***Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed).*

TABLE 4 | Predictors of Fear of COVID-19.

Gender		**B**	**SE**	**β**	***t***	**Sig.**
Male	(Constant)	7.086	3.269		2.168	0.032
	Anxiety related to COVID-19	1.003	0.106	0.621	9.487	0.000
	Worry about resurgence of COVID-19	1.551	0.336	0.278	4.610	0.000
	Self-perceived health	−0.607	0.583	−0.070	−1.040	0.300
Female	(Constant)	7.551	2.097		3.602	0.000
	Anxiety related to COVID-19	0.888	0.084	0.526	10.555	0.000
	Worry about resurgence of COVID-19	2.047	0.348	0.294	5.890	0.000
	Self-perceived health	−0.988	0.410	−0.113	−2.410	0.017

Dependent Variable: Fear total score; SE, standard error.

greater fear reactions, greater concern about resurgence of COVID-19 and poorer self-perceived health. The anxiety reactions between men and women did not show significant differences.

Additionally, we verified that *anxiety related to COVID-19*, *concern about the resurgence of COVID-19* and *self-perceived health* showed associations with the fear response in the case of women. In the case of men, the *self-perceived health* variable does not predict fear reactions.

Several studies conducted during the pandemic have confirmed a greater psychological vulnerability in women compared to men. For example, research has confirmed in women a greater experience of fear, post-traumatic stress symptoms (PTSS), adjustment disorder anxiety, depression and anxiety (9, 16, 32, 33, 56–59).

In the specific case of fear, our study supports the results reported by Broche-Pérez et al. (33) during the first wave of the disease in Cuba. In our study, women also showed a greater fear reaction compared to men. The mean reported by Broche-Pérez et al. (33) in the first study was 17.9 (SD ± 8.05) for men and 21.9 (SD ± 6.9) for women. In our study, the mean for men was 17.34 (SD ± 6.29) and 19.02 (SD ± 5.93) for women. We also found that women showed poorer self-perceived health compared to men, and that self-perceived health values have an inverse relationship with fear reactions (better self-perceived health is related to less fear reaction). This result is consistent with studies showing that, around the world, women tend to rate their self-perceived health as weaker compared to men (60). This result is important because it has been proven that poorer self-perceived health is related to poorer mental health. For example, more self-perceived health has been associated with a greater experience of depression, anxiety and psychological distress in various populations (61–65).

During the pandemic, it has been reported that the lowest levels of self-perceived health reported by women have been related to residing in places with a high prevalence of the disease (66), however, more studies are needed to explore the relationship between self-perceived health and mental health outcomes during the current pandemic. The gap between women and men in relation to self-perception of health has been attributed in part to social factors (gender inequality index, education or employment) rather than to behavioral factors (67).

On the other hand, worry about resurgence was also higher in women compared to men. In the past, worry have been related to depressive rumination (31) generalized anxiety (6), panic disorder, and obsessive-compulsive disorder (30). During the pandemic, elevated levels of worry have been related to higher levels of anxiety, stress, intrusive thoughts, avoidance and fear of mental health (1, 68). However, greater worry in women can also have a positive effect by stimulating safety behaviors, such as the use of personal protective equipment (68). In the Cuban context, the concerns related to COVID-19 during the second wave could be closely related to the return to daily life, the opening of schools, airports, and the increase in the number of infections compared to the first wave.

These results show a greater vulnerability in women compared to men. This results may have several tentative explanations, both from a biological, and sociocultural perspective. For example, there is evidence on the differences between women and men in relation to reactivity to stress, which is related to the prevalence and presentation of many psychiatric disorders (2, 22, 69). For example, women more frequently develop mental disorders in response to situations involving hyperarousal (22), closely related to fear responses. This vulnerability in women could be related, among other factors, to a lower adaptation of women to hypersecretion of the orticotropin-releasing factor (CRF) (2).

On the other hand, there are also sociocultural factors that increase the vulnerability of women during the current pandemic. For example, gender roles (70, 71), long-existing inequalities, and social disparities (72) are among the factors that exacerbate the impact on mental health in women during the current pandemic.

However, in our opinion the fact that most of the studies conducted during the pandemic report a greater psychological impact of the outbreak on women does not mean that men are exempt from risk. In fact, we cannot rule out that the real impact of the pandemic on mental health in men is much greater than that described by the studies conducted to date. This is especially important in countries where the social construction of gender is structured around a "hegemonic masculinity." For example, in Latin America the term "machismo" refers a set of attitudes and identities associated with the concept of masculinity (73). This implies that men to be "really men" must suppress their emotions, they must not worry about their health, they must show great inner strength and they must have self-control (74). This social construction of masculinity has a negative impact on the general health and mental health of men (73, 75, 76), even when the results of most research during the pandemic place greater emphasis on the vulnerability of women.

The results obtained must be considered when designing interventions to reduce the impact of the current pandemic on the mental health of Cuban women. Interventions should be implemented as soon as possible, because evidence suggests that delays in receiving psychological treatment result in higher rates of baseline negative psychological symptoms (77). To date, in Cuba, psychological intervention actions have been carried out using telepesychology, both in its synchronous mode (telephone counseling, and support groups through WhatsApp) and asynchronous (design of mobile applications and self-help bulletins) (78, 79). For example, from the Community Mental Health Centers and the Women and Family Orientation Houses, support groups could be implemented where women receive training in stress and anxiety management.

However, to date we are not aware of other studies carried out in Cuba during the current pandemic in which other types of interventions such as cognitive behavioral therapy (CBT) were implemented. The use of brief cognitive behavioral interventions is of great importance, above all because of its proven effectiveness in disorders related to anxiety and fear responses (80). There are international experiences that have implemented CBT during the current outbreak, demonstrated effectiveness in reducing psychological distress in vulnerable populations, including women (77).

Our study presents some limitations that must be discussed. First, the study sample is relatively small. The size of our sample is fundamentally due to the difficulties in internet connectivity that still exist in the country and to the prices of the service. This causes that many potential participants who receive the survey do not complete it. It is possible that participants with a medium or high socioeconomic status predominate in our sample, however this variable was not explored. In this sense, in future studies it would be convenient to explore the socioeconomic status of the participants included in the study. In future studies, other variables related to the family should also be explored in greater depth, such as the quality of the health of close relatives (children, grandparents, etc.). This variable would allow a better understanding of fear reactions in the Cuban population. On the other hand, the presence of psychiatric antecedents in the participants must also be studied in depth, which may explain the variability in fear reactions among Cubans. It would also be interesting to stratify the sample by educational levels, considering that in our study most of the participants have tertiary education, which has been related to better general health (81). Despite these limitations, we consider that our study offers a first approach to the mental health of the Cuban population with an emphasis on gender differences.

CONCLUSIONS

In conclusion, during the second wave of COVD-19 in Cuba, women show greater psychological vulnerability compared to men. The women reported greater experiences of fear, greater concern about the resurgence of COVID-19 and worse self-perceived health. The anxiety reactions between genders did not show significant differences in our sample. Additionally, we found that the variables anxiety, concern for the resurgence and self-perceived health allow predicting the response to fear in the case of women. In the case of men, the self-perceived health variable did not constitute a statistical predictor of the level of fear. It is important to delve into the psychological impact of the pandemic on men, considering that some characteristics related to the social construction of gender could mask the reality of mental health in this gender. Our results will allow the design of interventions in the Cuban context considering that the country is already facing the resurgence of COVID-19.

Interventions must be designed and implemented briefly and must also use evidence-based techniques that are culturally adapted to the Cuban context.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: http://dx.doi.org/10.17632/srtb8gnrkp.1.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universidad Central Marta Abreu de Las Villas, Department of Psychology. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YB-P analyzed the data, and was responsible for preparing the first draft of the article. All authors contributed to the study design. All authors contributed to the article and approved the submitted version.

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Laboratory Effects of COVID-19 Infection in Pregnant Women and Their Newborns: A Systematic Review and Meta-Analysis

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Amidst the COVID-19 pandemic, there is a need for further research on its manifestation in pregnant women, since they are particularly prone to respiratory pathogens, like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), due to physiological changes during pregnancy. Its effects on infants born to mothers with COVID-19 are also not well-studied, and more evidence is needed on vertical transmission of the disease from mother to infant and on the transmission of IgG/IgM antibodies between mother and infant. We aim to systematically review and evaluate the effects of COVID-19 among SARS-CoV-2-positive pregnant women in late pregnancy and neonates with SARS-CoV-2-positive pregnant mothers using blood assays to find indicators of maternal and neonatal complications. We searched for original published articles in Google Scholar, Medline (PubMed), and Embase databases to identify articles in the English language from December 2019 to July 20, 2020. Duplicate entries were searched by their titles, authors, date of publication, and Digital Object Identifier. The selected studies were included based on patient pregnancy on admission, pregnant mothers with laboratory-confirmed COVID-19 virus, maternal/neonatal complications, and blood test results. We excluded duplicate studies, articles where full text was not available, other languages than English, opinions, and perspectives. The meta-analysis using the Generalized Linear Mixed model was conducted using the "meta" and "metaprop" packages in R code. Of the 1,642 studies assessed for eligibility, 29 studies (375 mothers and neonates) were included. Preterm birth rate was 34.2%, and cesarean section rate was 82.7%. Maternal laboratory findings found elevated neutrophils (71.4%; 95% CI: 38.5–90.9), elevated CRP (67.7%; 95%: 50.6–81.1), and low hemoglobin (57.3%; 95% CI: 26.0–87.8). We found platelet count, lactate dehydrogenase, and procalcitonin to be less strongly correlated with preterm birth than between high neutrophil counts ($P = 0.0007$), low hemoglobin ($P = 0.0188$), and risk of preterm birth. There is little evidence for vertical transmission. Elevated procalcitonin levels (23.2%; 95%

CI: 8.4–49.8) are observed in infants born to mothers with COVID-19, which could indicate risk for neonatal sepsis. These infants may gain passive immunity to COVID-19 through antibody transfer via placenta. These results can guide current obstetrical care during the current SARS-CoV-2 pandemic.

Keywords: COVID-19, preterm birth, neonatal sepsis, meta-analysis, blood assay, vertical transmission, passive immunity

INTRODUCTION

A global pandemic due to the outbreak of a novel coronavirus was first reported in Wuhan, China in December 2019. This novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes the disease COVID-19. While the name of SARS-CoV-2 suggests that COVID-19 is primarily a respiratory illness presenting with symptoms including fever, cough, and shortness of breath, which may progress to respiratory failure, COVID-19 can present with a wide spectrum of symptoms including sore throat, headache, loss of taste or smell, nausea, vomiting, and diarrhea (1).

Pregnant women are particularly prone to respiratory pathogens, like SARS-CoV-2, due to physiological changes during pregnancy; increased oxygen intake and diaphragm elevation make pregnant women susceptible to hypoxia (2, 3). There is accumulating evidence on pregnant women with COVID-19. However, early data do not indicate that pregnant women are at increased risk of morbidity, but do indicate increased risk for ICU admission and ventilation (4). Furthermore, because of increased concentration of ACE2 receptors in the placenta, there is concern about the possibility of vertical transmission from mother to infant (5). In fact, case studies have shown that SARS-CoV-2 can infect the placenta (6, 7); this study investigated whether or not this risk of vertical transmission is significant.

Reported laboratory abnormalities seen in pregnant patients with COVID-19 include lower white blood cell counts (lymphopenia and thrombocytopenia) and increased C-reactive (CRP) protein levels, elevated lactate dehydrogenase, and prolonged prothrombin time (8, 9). To investigate these abnormalities, we systematically reviewed the blood assays among SARS-CoV-2-positive pregnant women in late pregnancy and among neonates with SARS-CoV-2-positive pregnant mother to find indicators of maternal and neonatal complications. We compared these laboratory values to those of non-COVID-19-infected pregnant women and to those of non-pregnant women to provide more accurate diagnosis. By identifying laboratory indicators and trends in preterm birth, neonatal sepsis, and other complications, clinicians are better prepared for treating those complications before they manifest.

METHODS

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reviews of analytical observational studies.

Search Strategy and Eligibility Criteria

We searched for original published articles in Google Scholar, Medline (PubMed), and Embase databases to identify articles reporting maternal and neonatal complications in pregnant women with COVID-19 in accordance with the PRISMA guidelines (**Figure 1**). The authors also searched through the references listed within those published articles. The search was conducted using combinations of the terms "Novel coronavirus," "COVID-19," "SARS-CoV-2," "Maternal," "Neonatal," "Mother," "Pregnancy," "Newborn," "Infant," "Antibody," and "Laboratory" in the English language on July 20, 2020. Duplicate entries were searched by their titles, authors, date of publication, and Digital Object Identifier.

Study Selection and Data Extraction

Two authors (C.Z. and J.Z.) searched the literature, compiled all articles identified through the literature search, and extracted the data. The primary eligibility for inclusion of studies were published studies, with patient pregnancy on admission and COVID-19 infection confirmed by laboratory diagnosis, which investigated maternal/neonatal complications, and recorded blood assay results. The following information was extracted from each eligible study: authors, publication date, type of study, study size, maternal characteristics (age, gestation, preterm birth, vaginal/cesarean birth, symptom severity, and maternal death), infant characteristics (birth weight, Apgar score, and neonatal death), maternal and neonatal blood assays, and laboratory-confirmed vertical transmission of COVID-19. We excluded duplicate studies, articles where full text was not available, other languages than English, opinions, and perspectives. After assessment for duplicates, titles, and abstracts, and full texts of articles, the individual patient characteristics and summary estimates from each selected article were extracted to an Excel spreadsheet (see section Data Availability Statement).

Data Synthesis

The meta-analysis included all studies. Pooled means on age, gestational age, blood assay values, antibody levels, and pooled prevalence on preterm birth, C-section delivery, vertical transmission, abnormal blood assay values, and elevated antibody levels were assessed using the Generalized Linear Mixed model; the meta-analysis was performed using the "meta" (10) and "metaprop" (11) packages in the R statistical software (12). The random effects model was applied to calculate the pooled

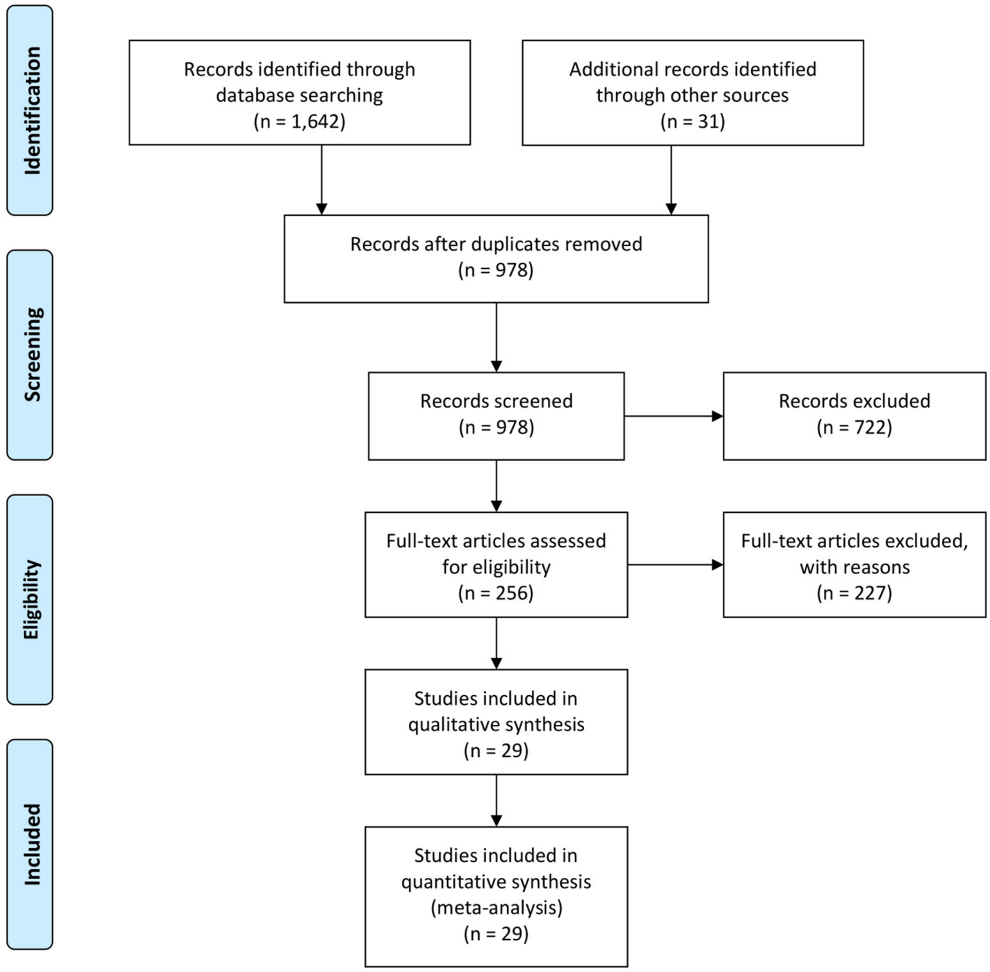

FIGURE 1 | PRISMA flow diagram.

prevalence and single means with a 95% confidence interval (95% CI). Heterogeneity was assessed using Cochran Q test and Higgins' I^2 statistic (represented as a percentage, using the Restricted Maximum Likelihood method). Begg's Test, Egger's test, and a new publication bias statistic, Lin and Chu (13), which generally performs better than Egger's test (14), were used for testing publication bias. Statistical significance was considered with a $P < 0.05$. For studies without reported standard deviations (SD), their SD was replaced with the average of the studies whose SD were calculated or reported (15).

RESULTS

Study Characteristics

A total of 1,673 literatures were initially retrieved from searching online databases and citations. Among these, 695 duplicate literatures were identified and removed. Remaining literatures were screened according to their titles and abstracts. Twenty-nine articles were selected to be analyzed (**Table 1**). A total of 375 SARS-CoV-2-positive pregnant women in late pregnancy and neonates born to these infected mothers were evaluated in 4 cohort studies, 7 case series, 11 retrospectives, and 2 observational studies, which were all conducted between December 2019 and July 2020. Three studies provided antibody (IgG/IgM) test results.

Quantitative Analysis

Characteristics and Blood Assay of Pregnant Women With COVID-19

The general characteristics of pregnant patients with COVID-19 are summarized in **Table 2**, and the prevalence of maternal and neonatal abnormalities are summarized in **Figure 2**, and their meta-regression results are summarized in **Table 3**. The pooled mean maternal age was estimated at 30.86 years (95% CI: 30.16–31.55). The pooled mean of gestational age was estimated as 37.20 weeks (95% CI: 36.52–37.88) and was not significantly different from the normal gestational age of 37 weeks (45). The global proportion of preterm birth was estimated at 11% before the pandemic (46). This study found the proportion to be 34.19% (95% CI: 28.29–40.61%), suggesting a trend for higher risk of

TABLE 1 | Baseline characteristics of included studies.

Study	Study period	Study type	Study size	Mean age	Mean gestational age at birth
Zeng et al. (16)	January to February 2020	Cohort	3	NA	37
Dong et al. (17)	February 2020	Case Study	1	29	34
Chen et al. (18)	January 2020	Retrospective	9	29.89	37.11
Zhu et al. (19)	January to February 2020	Retrospective	9	30.89	35.11
Khan et al. (20)	January to February 2020	Case Series	17	29.29	37.82
Yin et al. (21)	January to February 2020	Cohort	17	31	37
Liu et al. (22)	January to February 2020	Retrospective	18	31	38.6
Chen et al. (23)	March 2020	Case Series	4	29	37.75
Alzamora et al. (24)	March 2020	Case Study	1	41	33
Xiong et al. (25)	January 2020	Case Study	1	25	33
Yang et al. (26)	January to March 2020	Cohort	13	30.2	38.2
Hantouchzadeh et al. (27)	March 2020	Retrospective	9	34.86	30
Qiancheng et al. (28)	January to March 2020	Cohort	22	30	38
Hu et al. (29)	January to February 2020	Case Series	7	32.71	38.71
Lu et al. (30)	February 2020	Case Study	1	22	38
Yan et al. (31)	January to March 2020	Retrospective	99	30.8	38
Ferrazzi et al. (32)	March 2020	Retrospective	24	30.9	NA
Zeng et al. (33)	March 2020	Retrospective	6	NA	NA
Iqbal et al. (34)	April 2020	Case Study	1	34	NA
Yang et al. (35)	January 2020	Case Series	7	NA	36.71
Wu et al. (36)	December 2019 to March 2020	Retrospective	20	33.35	31.87
Zhang et al. (37)	January to March 2020	Observational	18	29.11	38.4
Liu et al. (38)	March 2020	Retrospective	21	31	NA
Lee et al. (39)	January 2020	Case Study	1	28	37
Li et al. (40)	January to February 2020	Retrospective	16	30.9	38
Ibrahim (41)	February 2020	Retrospective	6	NA	NA
Semeshkin et al. (42)	May 2020	Observational	20	NA	NA
Liu et al. (43)	January to February 2020	Case Series	3	32.67	39
Adhdam et al. (44)	March 2020	Case Study	1	NA	NA

TABLE 2 | Meta-analysis of general maternal and neonatal characteristics.

Statistic	No. of studies	Reference range	Mean/prevalence (%)	95% CI LB	95% CI UB	I^2 (%)	*Q* test *P*-value	Begg's test	Egger's test	Lin and Chu
Maternal Age (years)	23		30.86	30.16	31.55	66.3	<0.01	0.63	0.76	0.68
Gestational Age (weeks)	22	38–42	37.20	36.52	37.88	77.8	<0.01	0.09	0.02	0.03
Preterm Birth	21	10%	34.19%	28.29%	40.61%	6.3	0.06	0.30	0.95	0.68
Vaginal Birth	20	68.1%	15.33%	8.49%	26.11%	60.9	<0.01	0.21	0.31	0.02
Cesarean Birth	20	31.9%	82.69%	70.48%	90.53%	66.5	<0.01	0.36	0.41	0.07
Severe Symptoms	11		9.28%	2.83%	26.44%	75.0	<0.01	0.37	0.99	0.14
Maternal Death	26		0%	0%	100%	98.9%	0.01	0.00	0.01	0.00
Birth Weight (g)	23	2,500–4,000	3,040	2,910	3,170	74.8	<0.01	0.26	0.43	0.00
Low Birth Weight	18	8.2%	13.32%	5.92%	27.31%	57.4	<0.01	0.29	0.32	0.02

preterm birth in pregnant patients with COVID-19. The results of the meta-regression did not show any correlation between the means of gestational age and maternal age ($P = 0.1542$).

Frequency of severe symptoms/admission to intensive care units (ICUs) was estimated at 9.28% (95% CI: 2.83–26.44%), which is not significantly different from the normal. There were seven cases of maternal death in this review; the prevalence of maternal death was not significantly different from zero (95% CI: 0.0–100.0%) and had significant publication bias (Begg's Test $P < 0.01$; Egger's Test $P = 0.01$; Lin and Chu $P < 0.01$).

The maternal laboratory findings are summarized in **Table 4**. The most common laboratory findings were high neutrophil

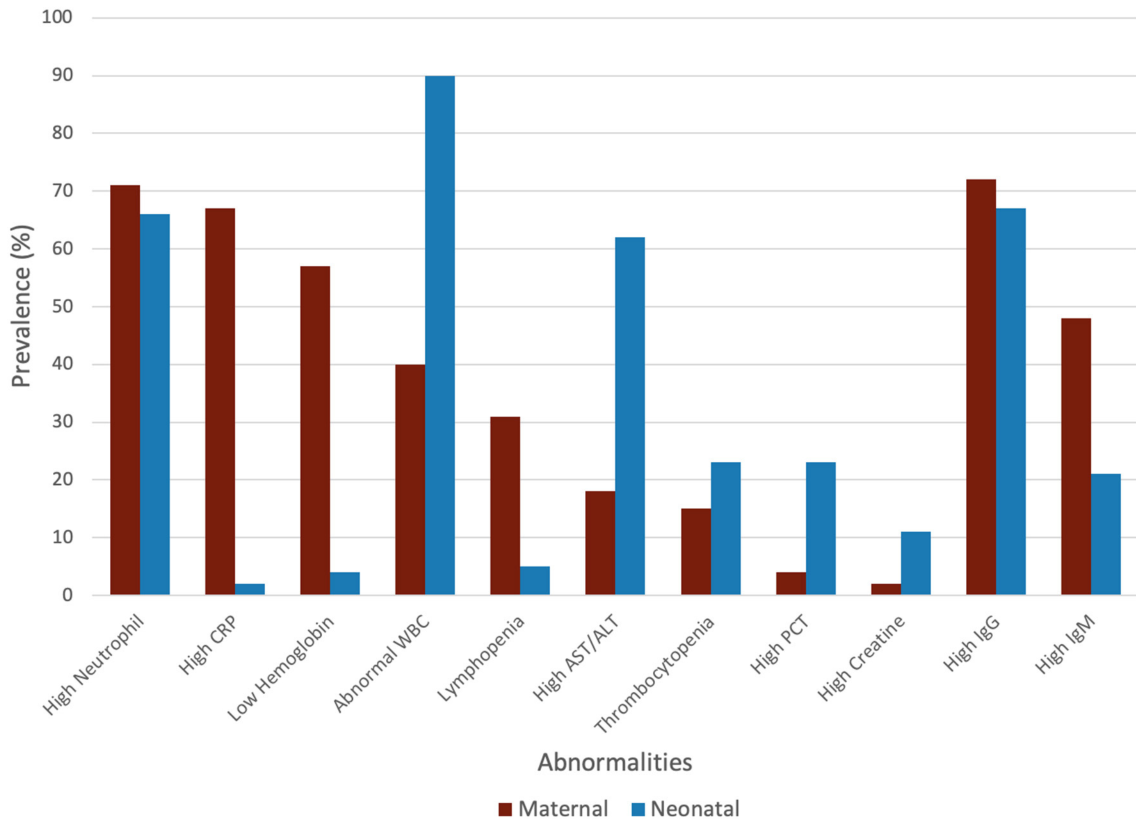

FIGURE 2 | Prevalence of maternal and neonatal abnormalities.

count, which was present in 71.9% of patients (95% CI: 38.49–90.87%) followed by CRP [67.7% (95% CI: 50.59–81.0)] and low hemoglobin [57.3% (95% CI: 26.0–86.76%)]. The pooled mean of neutrophils was estimated as 7.08 10^9/L (95% CI: 5.07–9.10), CRP was estimated as 24.88 mg/L (95% CI: 13.80–35.96), and hemoglobin was estimated as 112.41 g/L (95% CI: 13.70–121.13). The results of the meta-regression showed that neutrophil levels have a significant relationship with gestational age (coefficient: −1.18, $P < 0.01$, 95% CI: −1.84–0.49; intercept = 50.48) and that hemoglobin levels have a relationship with gestational age (coefficient: 3.25, $P = 0.02$, 95% CI: 0.54–5.97; intercept = −5.35). Less commonly encountered abnormalities were lymphopenia, which was found in 31.99% of patients (95% CI: 21.64–44.49%), thrombocytopenia [15.07% (95% CI: 3.95–43.37%)], and elevated procalcitonin (PCT). The pooled prevalence of elevated PCT was estimated at 3.76% (95% CI: 0.06–72.79%) and had significant publication bias (Lin and Chu $P = 0.01$).

The following outcomes were from a meta-analysis with <10 studies. The pooled mean of lactate dehydrogenase has been estimated as 236.91 U/L (95% CI: 148.28–325.54), which is not significantly different from the normal. The results of the meta-regression showed that blood urea nitrogen (BUN) levels have a significant relationship with gestational age (coefficient: 0.26, $P = 0.04$, 95% CI: 0.01–0.51). The pooled mean of prothrombin time (PT) was estimated as 12.11 s (95% CI: 11.7175–12.4990), which is significantly higher from the normal (8.7–11.5). The pooled mean of D-dimer has been estimated as 2.2651 mg/L (95% CI: 1.2956–3.2346), which is significantly higher than the normal range (<0.5).

Characteristics and Blood Assay of Infants Born to Pregnant Women With COVID-19

The general characteristics of infants born to mothers with COVID-19 are summarized in **Table 2**, and their meta-regression results are summarized in **Table 3**. The pooled mean of birth weight has been estimated as 3,040 g (95% CI: 2,910–3,170). The pooled prevalence of low birth weight has been estimated as 13.2% (95% CI: 5.92–27.31%), which is not significantly different from the estimated worldwide prevalence of low birth weight in 2015 of 14.5% (47). The results of the meta-regression showed that the means of birth weight have a relationship with gestational age with a correlation of 111 g/week ($P < 0.01$, 95% CI: 56.04–166.48; intercept = −1,106.99). This is not significantly from previous studies (48).

The neonatal laboratory findings are summarized in **Table 5**. The most common laboratory findings were elevated IL-6, which was present in 91.1% of the neonates (95% CI: 32.38–99.97%), abnormal white blood cell count (WBC), elevated neutrophil count [66.67% (95% CI: 47.33–81.66%)], and elevated AST/ALT

TABLE 3 | Meta-analysis of correlations between maternal and neonatal characteristics.

Moderator	Response variable	No. of studies	Correlation	95% CI LB	95% CI UB	Correlation *P*-value	I^2	*Q* test *P*-value	Begg's test	Egger's test	Lin and Chu
Mat. IgG	Neo. IgG	3	0.85	0.67	0.93	<0.01	0%	0.41	0.16	0.00	0.00
Mat. IgM	Neo. IgM	3	0.43	0.06	0.70	0.03	0%	0.97	0.22	0.03	0.02
Maternal age	Gestation	20	0.15	−0.50	0.08	0.15	95%	<0.01	0.02	0.00	0.00
	Weight	20	−33.71	−87.24	19.82	0.22	80%	<0.01	0.30	0.54	0.27
	WBC	16	−0.12	−0.55	0.31	0.58	73%	0.00	0.65	0.43	0.76
	Neutrophil	11	0.55	−0.08	1.18	0.08	98%	<0.01	0.04	0.11	0.09
	Lymphocytes	13	0.05	−0.11	0.10	0.96	69%	0.00	0.67	0.56	0.90
	Platelets	9	−2.57	−9.66	4.53	0.48	79%	<0.01	0.75	0.04	0.24
	Hemoglobin	9	−0.18	−2.17	1.81	0.86	82%	0.00	0.02	0.00	0.05
	C-reactive	17	−1.22	−4.20	1.77	0.42	99%	<0.01	0.58	0.04	0.00
	Creatine-Kin.	6	−0.98	−5.64	3.69	0.68	99%	<0.01	0.70	0.05	0.23
	PCT	8	0.01	−0.08	0.11	0.26	96%	<0.01	0.70	0.57	0.12
	AST	14	0.51	−5.18	6.21	0.86	99%	<0.01	0.54	0.77	0.00
	ALT	15	0.09	−7.83	8.02	0.98	100%	<0.01	0.27	0.74	0.00
	Bilirubin	4	−1.01	−4.03	2.00	0.51	83%	0.00	0.72	0.63	0.62
	Lact Dehydro	4	10.82	47.63	69.26	0.72	98%	<0.01	0.75	0.83	0.96
	Albumin	6	−1.02	−3.48	1.43	0.41	100%	<0.01	0.42	0.46	0.51
	BUN	7	−0.03	0.23	0.17	0.78	97%	<0.01	1.00	0.43	0.68
	D-dimer	7	−0.08	−0.38	0.23	0.63	95%	<0.01	0.36	0.66	0.59
Gestational age	Weight	21	111.26	56.04	166.4	<0.01	56%	0.00	0.18	0.09	0.14
	WBC	15	−0.26	−0.81	0.30	0.37	75%	0.00	0.52	0.51	0.60
	Neutrophil	10	−1.17	−1.84	-0.49	0.00	95%	<0.01	0.05	0.03	0.14
	Lymphocytes	12	0.06	−0.14	0.26	0.58	73%	0.00	0.54	0.11	0.81
	Platelets	8	−1.04	−12.80	10.73	0.86	83%	<0.01	0.71	0.00	0.24
	Hemoglobin	8	3.25	0.54	5.97	0.02	58%	0.04	0.03	0.09	0.10
	C-reactive	16	−1.30	−6.02	3.43	0.59	99%	<0.01	0.52	0.03	0.00
	Creatine-Kin.	6	7.56	−4.63	19.74	0.22	99%	<0.01	0.70	0.14	0.23
	PCT	8	0.02	−0.15	0.18	0.83	98%	<0.01	0.70	0.03	0.12
	AST	13	−1.56	−11.27	8.15	0.75	99%	<0.01	0.39	0.77	0.01
	ALT	14	−0.82	−14.29	12.66	0.91	100%	<0.01	0.18	0.58	0.00
	Albumin	5	0.87	−0.33	2.08	0.16	92%	<0.01	0.80	0.45	0.67
	BUN	6	0.26	0.01	0.51	0.04	67%	0.03	0.44	0.68	0.90
	D-dimer	6	−0.18	−0.61	0.25	0.41	95%	<0.01	0.72	0.38	0.66
Gestational age**	WBC	9	0.48	−0.35	1.31	0.26	14%	0.35	0.75	0.05	0.46
	Neutrophil	5	−0.44	−1.75	0.87	0.51	26%	0.21	0.48	0.35	0.50
	Lymphocytes	6	−0.03	−0.91	0.85	0.95	92%	<0.01	1.00	0.07	0.81
	Platelets	6	3.71	−19.28	26.70	0.75	79%	0.01	1.00	0.19	0.69
	Hemoglobin	4	3.20	−5.40	11.81	4.66	42%	0.19	0.75	0.56	0.65
	C-reactive	8	−0.33	−1.00	0.35	0.34	98%	<0.01	105.00	0.79	0.60
	Creatine-Kin.	5	−139.9	−277.3	-2.48	0.05	100%	<0.01	0.48	0.36	0.70
	PCT	6	−0.16	−1.31	0.99	0.79	100%	<0.01	0.44	0.06	0.54
	AST	9	3.75	−2.21	9.70	0.22	0%	0.68	0.75	0.80	0.91
	ALT	9	2.03	−0.83	4.89	0.16	0%	0.93	0.46	0.22	0.29
	Apgar 1 min	17	0.24	−0.09	0.57	0.15	99%	<0.01	0.45	0.43	0.10
	Apgar 5 min	17	0.17	−0.15	0.49	0.31	99%	<0.01	0.41	0.87	0.00
	Vertical	22	1.06	2.95	0.82	0.26	96%	1.00	0.72	0.30	0.31
Birth weight**	WBC	10	0.00	0.00	0.01	0.12	11%	0.14	0.86	0.94	0.59
	Neutrophil	5	−0.01	−0.03	0.01	0.27	0%	0.03	0.46	0.45	0.50
	Lymphocytes	6	0.00	−0.01	0.01	0.82	92%	<0.01	1.00	0.30	0.81
	Platelets	7	0.03	−0.05	0.12	0.44	81%	0.00	0.77	0.65	0.73

(Continued)

TABLE 3 | Continued

Moderator	Response variable	No. of studies	Correlation	95% CI LB	95% CI UB	Correlation *P*-value	I^2	*Q* test *P*-value	Begg's test	Egger's test	Lin and Chu
	Hemoglobin	5	0.02	−0.01	0.04	0.30	23%	0.21	0.23	0.14	0.20
	C-reactive	9	0.00	−0.01	0.00	0.15	97%	<0.01	0.11	0.90	0.46
	Creatine-Kin.	5	0.15	−0.95	1.26	0.78	100%	<0.01	0.48	0.04	0.70
	PCT	6	−0.01	−0.01	−0.01	<0.01	90%	<0.01	0.44	0.06	0.53
	AST	9	0.02	0.00	0.05	0.09	0%	0.83	0.75	0.84	0.91
	ALT	9	0.01	−0.01	0.03	0.21	0%	0.90	0.46	0.31	0.29
	Apgar 1 min	17	0.00	0.00	0.00	0.04	98%	<0.01	0.45	0.10	0.10
	Apgar 5 min	17	0.00	0.00	0.00	0.05	99%	<0.01	0.41	0.58	0.00
	Vertical	23	0.00	−0.01	0.00	0.25	89%	0.00	0.56	0.87	0.47

***Indicates that the corresponding response variable is a neonatal characteristic; unless specified, the corresponding response variable is a maternal characteristic.*

[62.0% (95% CI: 47.96–74.28%)]. The pooled prevalence of normal WBC has been estimated as 9.85% (95% CI: 3.13–26.96%), indicating that over 90% of all patients had abnormal white blood cell counts. This can be attributed to the high neutrophil counts in neonates, which was estimated at 10.18 $\times$ 10^9/L (95% CI: 8.90–11.46). The pooled mean of IL-6 levels was estimated at 23.22 pg/ml (95% CI: 16.94–29.49), which is significantly higher than the normal. AST levels were estimated at 59.34 U/L (95% CI: 49.81–68.86), which is also significantly higher than the normal.

Frequency of high PCT was less common and has been estimated as 23.17% (95% CI: 8.4–49.785%). The results of the meta-regression showed that PCT levels have a relationship with birth weight (coefficient: −0.01, $P < 0.01$, 95% CI: −0.01 to 0.01; intercept = 16.66).

The pooled mean of 1-min Apgar has been estimated as 7.94 (95% CI: 7.26–8.62). The results of the meta-regression showed that 1-min Apgar scores have a relationship with birth weight (coefficient: 0.002, $P = 0.04$, 95% CI: 0.00–0.01; intercept = 1.26). The pooled mean of 5 min Apgar has been estimated as 8.97 (95% CI: 8.34–9.61). The results of the meta-regression showed that 5 min Apgar scores have a relationship with birth weight (coefficient: 0.002, $P = 0.04$, 95% CI: 0.00–0.004; intercept = 2.49).

The pooled prevalence of vertical transmission has been estimated as 0.18%, but it was not significantly different from zero (95% CI: 0.0%−8.95%; I^2 = 88.6%, $P < 0.01$), and had significant publication bias (Begg's Test $P < 0.01$; Lin and Chu $P < 0.01$).

Antibodies of Infants and Pregnant Women With COVID-19

High IgG in mothers was highly prevalent and has been estimated as 72.73% (95% CI: 55.35–85.16%). The pooled mean of maternal IgG was estimated as 76.90 AU/ml (95% CI: 43.02–110.79), which is significantly higher than the normal. The pooled prevalence of high IgM in mothers was less than high IgG and was estimated as 48.94% (95% CI: 14.35–84.58). The pooled mean of maternal IgM was estimated as 96.89 AU/ml (95% CI: 0.00–212.81).

High IgG in neonates born to mother with COVID-19 was highly prevalent and was estimated as 67.16% (95% CI: 37.87–87.27%). The pooled mean of neonatal IgG was estimated as 72.47 AU/ml (95% CI: 26.41–118.54). The pooled prevalence of high IgM in neonates was estimated as 20.65% (95% CI: 2.75–70.54%). The pooled mean of neonatal IgM was estimated as 15.86 AU/ml (95% CI: 0.00–34.65).

The results of the meta-regression showed that infant IgG levels have a relationship with their mother's IgG level (coefficient: 0.85, $P < 0.01$, 95% CI: 0.67–0.93) and that infant IgM levels have a relationship with their mother's IgM level (coefficient: 0.43, $P = 0.03$, 95% CI: 0.06–0.70).

DISCUSSION

Characteristics and Blood Assay of Pregnant Women With COVID-19

The global proportion of cesarean section was ∼21.1% in 2017 (49). The present study found the overall proportion of cesarean section to be 82.7%, much higher than the global prevalence. While the decision to undergo C-section can vary due to differences in clinical practice and accepted standards of care, reasons found in studies selected in this review suggest that COVID-19 patients are more likely to have a C-section because they had underlying disease and intolerance against respiratory dysfunction. Given this is a novel disease, there is a general tendency for clinicians to avoid more complicated deliveries by undergoing C-section.

Results from our study suggest that severe symptoms or the need for intensive care appeared to be higher than that that for non-pregnant women of similar age (30.56 years). We found the proportion to be 9.3%, which was higher than previous estimates of 4.2–7.0% (50, 51); however, severe symptom criteria and ICU admission criteria were not well defined and varied between studies. Furthermore, this study's prevalence of severe symptoms is not significantly different from previous estimates, or from the general prevalence of severe COVID-19. Therefore, there is not enough evidence to suggest pregnant women are at increased risk of ICU admission or more severe symptoms. Prevalence

TABLE 4 | Meta-analysis of maternal laboratory tests and antibodies.

Statistic	No. of studies	Reference range	Mean/prevalence (%)	95% CI LB	95% CI UB	I^2 (%)	*Q* test *P*-value	Begg's test	Egger's test	Lin and Chu
WBC (10^9/L)	15	4.5–11	8.50	7.60	9.43	61.2	<0.01	0.63	0.76	0.68
Normal WBC	16		60.32%	47.28%	72.04%	59.2	<0.01	0.09	0.02	0.03
Neutrophil (10^9/L)	11	1.5–8.0	7.08	5.07	9.10	99.7	0.00	0.30	0.95	0.68
High neutrophil	6		71.39%	38.49%	90.87%	60.9	0.02	0.21	0.31	0.02
Neutrophil percent	5	45–75%	78.47	71.69	85.24	90.0	<0.01	0.36	0.41	0.07
Lymphocytes (10^9/L)	13	1.0–5.0	1.26	1.14	1.39	62.7	<0.01	0.37	0.99	0.14
Low lymphocytes	15		31.99%	21.64%	44.49%	59.4	<0.01	0.00	0.01	0.00
Lymphocytes percent	6	18%−45%	25.55	4.67	46.43	100	0.00	0.65	0.51	0.18
Platelets (10^3/μl)	9	150–450	177.92	151.02	204.82	77.3	<0.01	0.85	0.05	0.09
Low platelets	8		15.07%	3.95%	43.37%	68.1	<0.01	0.04	0.01	0.15
Hemoglobin (g/L)	9	120–155	112.4	13.70	121.1	70.2	<0.01	0.44	0.21	0.68
Low hemoglobin	7		57.30%	26.00%	86.76%	57.3	<0.01	0.41	0.99	0.91
CRP (mg/L)	17	<10	24.88	13.80	35.96	97.1	<0.01	0.67	0.49	0.06
Elevated CRP	13		67.70%	50.59%	81.09%	70.0	<0.01	0.58	0.26	0.93
Creatine-kinase (U/L)	6	22–198	49.56	26.34	72.79	99.2	<0.01	1.00	0.26	0.46
High creatine-kinase	5		2.17%	0.31%	13.88%	0.0	0.8267	0.75	0.12	0.40
PCT (ng/ml)	8	<0.5	0.27	0.00	0.59	80.3	<0.01	0.88	0.59	0.53
High PCT	8		3.76%	0.06%	72.79%	70.5	0.04	0.02	0.02	0.94
AST (U/L)	14	<36	41.11	18.24	63.98	96.6	<0.01	0.19	0.10	0.09
ALT (U/L)	15	<36	40.39	9.00	71.78	98.9	<0.01	0.58	0.01	0.01
Elevated AST/ALT	13		18.81%	8.21%	37.49%	68.0	<0.01	0.29	0.04	0.00
Total bilirubin (μmol/L)	4	1–12	14.37	2.98	25.76	77.5	<0.01	0.70	0.09	0.61
Lactate dehydro. (U/L)	4	<225	236.9	148.3	325.5	97.4	<0.01	0.07	0.20	0.02
Albumin (g/L)	6	35–50	26.73	16.85	36.07	99.3	<0.01	0.70	0.19	0.12
BUN (mmol/L)	7	2.5–7.1	3.22	2.28	4.14	88.5	<0.01	1.00	0.31	0.01
PT (s)	3	8.7–11.5	12.11	11.72	12.50	0.0	<0.01	0.54	0.08	<0.01
APTT (s)	3	30–40	3.10	29.93	44.27	90.9	<0.01	0.27	0.10	0.00
D-dimer (mg/L)	7	<0.5	2.27	1.30	3.23	95.5	<0.01	0.62	0.95	0.15
IgG (AU/ml)	15	<10	76.90	43.02	110.79	61.2	<0.01	0.72	0.86	0.50
High IgG	16		72.73%	55.35%	85.16%	59.2	<0.01	0.50	0.52	0.17
IgM (AU/ml)	11	<10	96.89	0.00	212.81	99.7	0.00	0.42	0.34	0.48
High IgM	6		48.94%	14.35%	84.58%	60.9	0.02	1.00	0.85	0.66

of maternal death was not significantly different from zero; all maternal deaths were from a single study (27), so maternal death is much more likely due to the quality of birthing conditions than due to maternal complications caused by COVID-19.

The most common abnormalities found in the pooled blood assay were high neutrophil count, increased C-reactive protein (CRP), and low hemoglobin (71.9, 67.7, and 57.3%, respectively). Compared to abnormalities found in previous reviews, the only abnormalities shared by our review was increased CRPs among mothers with COVID-19 (2, 8, 9, 50). Furthermore, the pooled mean of CRP was significantly higher than the normal range (<10 mg/L) for healthy non-pregnant patients, indicating that elevated CRP is strongly correlated with infection. Our mean CRP level and elevated CRP prevalence is not significantly different from recent meta-analyses on non-pregnant COVID-19-positive patients (52–54). This is expected since COVID-19 can cause an overactive immune response, and CRP is a marker of that increased inflammation throughout the body.

Thrombocytopenia was previously identified as a symptom of infection. In this current study, the prevalence of low platelet counts was estimated at 15.1%, and its pooled mean was not significantly different from the normal range (150–450 10^3/L). Platelet counts generally decrease during pregnancy, particularly during the third trimester, termed "gestational thrombocytopenia." In order to adjust for this, we used a lower limit for platelet count of 115 10^3/μl (55). Using this new parameter, a loose interpretation could be that COVID-19 does not significantly worsen gestational thrombocytopenia since the mean platelet levels is not significantly lower than the normal for pregnant patients. Our platelet results also did not differ significantly from those of a recent meta-analysis on non-pregnant COVID-19-positive patients, so pregnant patients are at no greater risk.

TABLE 5 | Meta-analysis of neonatal laboratory tests and antibodies.

Statistic	No. of studies	Reference range	Mean/prevalence (%)	95% CI LB	95% CI UB	I^2 (%)	*Q* test *P*-value	Begg's test	Egger's test	Lin and Chu
WBC (10^9/L)	10	4.5–11	3,040	2,910	3,170	41.9%	0.08	0.26	0.43	0.00
Normal WBC	10		13.32%	5.92%	27.31%	22.6%	0.17	0.29	0.32	0.02
Neutrophil (10^9/L)	5	1.5–8.0	14.73	13.05	16.42	17.2%	0.31	0.86	0.94	0.60
High neutrophil	5		9.85%	3.13%	26.96%	0.0%	0.21	0.12	0.69	0.02
Neutrophil (%)	3	45%–75%	10.18	8.90	11.46	96.7%	<0.01	0.33	0.32	1.00
Lymphocytes (10^9/L)	6	1.0–5.0	66.67%	47.33%	81.66%	94.5%	<0.01	0.45	0.85	0.93
Low lymphocytes	8		60.09	40.45	79.73	75.9%	<0.01	1.00	0.86	0.98
Lymphocytes (%)	4	18%–45%	2.87	1.57	4.16	89.7%	<0.01	0.85	0.15	0.00
Platelets (10^3/μl)	7	150–450	4.75%	0.35%	41.35%	72.5%	<0.01	1.00	0.03	0.01
Low platelets	7		28.85	15.26	42.45	21.2%	0.22	0.28	0.49	0.96
Hemoglobin (g/L)	5	120–155	250.8	219.4	282.2	34.7%	0.19	0.65	0.84	0.81
Low hemoglobin	5		23.37%	11.27%	42.26%	0.0%	0.73	0.36	0.31	0.66
CRP (mg/L)	9	<10	168.9	158.1	179.7	96.8%	<0.01	0.14	0.14	0.73
Elevated CRP	9		4.17%	0.58%	24.35%	0.0%	0.98	0.14	0.66	0.01
Creatine-kinase (U/L)	5	22–198	1.86	0.56	3.15	99.6%	<0.01	0.11	0.24	0.37
High creatine-kinase	5		1.96%	0.28%	12.65%	69.4%	0.02	0.00	0.04	0.00
PCT (ng/ml)	6	<0.5	64.84	61.03	68.65	50.6%	0.09	0.33	0.27	0.56
High PCT	6		10.65%	1.30%	51.92%	23.0%	0.21	0.62	0.92	0.88
AST (U/L)	9	<36	0.29	0.22	0.35	0.0%	0.60	0.44	0.18	0.14
ALT (U/L)	9	<36	23.17%	8.40%	49.78%	0.0%	0.82	1.00	0.20	0.02
Elevated AST/ALT	8		59.34	49.81	68.86	0.0%	0.80	0.75	0.79	0.05
Albumin (g/L)	3	35–50	14.65	11.93	17.37	44.7%	0.16	0.46	0.16	0.00
IL-6 (pg/ml)	3		62.00%	47.96%	74.28%	35.6%	0.21	0.71	0.72	0.23
High IL-6	3		32.94	28.67	37.21	86.1%	<0.01	0.60	0.71	0.81
IgG (AU/ml)	4	<10	23.22	16.94	29.49	89.2%	<0.01	0.60	0.47	0.33
High IgG	4		91.10%	32.38%	99.97%	2.0%	0.30	0.60	0.27	0.17
IgM (AU/ml)	4	<10	72.47	26.41	118.5	91.6%	<0.01	0.04	0.00	0.99
High IgM	4		67.16%	37.87%	87.27%	72.5%	<0.01	0.70	0.12	0.00
Apgar, 1 min	20	7–10	15.86	0.00	34.65	96.0%	<0.01	0.17	0.16	0.84
Apgar, 5 min	20	7–10	20.65%	2.75%	70.54%	97.6%	<0.01	0.70	0.85	0.83
Vertical transmission	27		7.94	7.26	8.62	88.6%	<0.01	0.87	0.75	0.01

Similarly, while elevated lactate dehydrogenase was identified in COVID-19 patients in previous studies and is associated with worse clinical outcome (53), our results showed that its pooled mean was not significantly different from the normal range (<225 U/L). However, due to the low number of studies that included lactate dehydrogenase in their blood assay, it is not possible to refute if it could also be correlated with infection.

Interestingly, we did not find elevated PCT to be a prevalent symptom of infection. Its prevalence was estimated at 3.8%, and its pooled mean, 0.29 ng/ml, was not significantly different from the normal range (<0.15 ng/ml). Furthermore, there was significant publication bias (Lin and Chu $P < 0.01$) for the pooled prevalence, so it is likely that the true prevalence is lower than the one presented in this study due to the inflation of elevated PCT publications (56). This provides more evidence that suggests that elevated PCT is not a prevalent symptom of COVID-19.

In this study, we present other noteworthy values from the blood assays: neutrophils count, D-dimer, hemoglobin, and BUN. The most prevalent abnormality was high neutrophil count, or neutrophilia, with 71.4% of the women having this condition. Neutrophilia is its associated increased risk of small-for-gestational-age (SGA) birth, which reflects a cycle of inflammation and placental insufficiency (57). The mean neutrophil level was estimated at 7.08×10^9/L, which is over twice as concentrated than in non-pregnant COVID-19-positive patients (53), and the prevalence of neutrophilia is over 10 times greater (52). The results of the meta-regression further show that there is a significant negative correlation ($P < 0.01$) between a mother's neutrophil count and the gestational age at birth, with a gestational age of 32 weeks corresponding to neutrophil count of 13.1×10^9/L. Therefore, excessively high neutrophil counts during mid-to-late pregnancy could be a risk indicator for preterm delivery. This is further supported by the high mean neutrophil–lymphocyte ratio (NLR), which was found to be 5.60. High NLR has been associated with greater risk of preeclampsia (58) and preterm birth (59).

The pooled mean of D-dimer was estimated as 2.27 mg/L, which is much greater than the normal range (<0.5 mg/L) for non-pregnant patients. D-dimer is generally elevated during pregnancy; therefore, using this upper limit of 0.5 mg/L would result in false positives if using an upper limit of 0.5 mg/L. Studies have suggested increasing this threshold to 1.0 or 2.0 mg/L (60, 61). Still, the point estimate and confidence interval (1.30–3.23) are still above these elevated thresholds. Our pooled mean for D-dimer was over twice as concentrated than in non-pregnant COVID-19-positive patients (53). D-dimer is a biomarker for disease severity and blood clotting, so these observations provide evidence that indicate risk of venous thromboembolism and/or pulmonary embolism in mothers with COVID-19.

Low hemoglobin levels were the second most prevalent abnormality in the present study, with 57.3% patients presenting this abnormality. In general, pregnancy-induced anemia is common, so the normal hemoglobin range for pregnant women in the third trimester is 95–150 g/L (62). However, even given this lower threshold, there were many studies that included pregnant women with very low hemoglobin levels. This is concerning since very low hemoglobin levels are associated with increased fetal risk (63). Furthermore, the results from the meta-regression found a significant positive relationship ($P = 0.02$) between hemoglobin levels and gestational age, with the gestational age of 32 weeks corresponding to 98.7 g/L. Very low hemoglobin levels during mid-to-late pregnancy could be a risk indicator for preterm birth, and the infant should be prioritized in consideration for neonatal ICU.

The pooled mean of BUN was estimated as 3.22 mmol/L, which falls within the normal range (2.5–7.1). We found that BUN had a significant positive correlation ($P = 0.04$) with gestational age, with the gestational age of 32 weeks corresponding to 1.44 mmol/L. However, a previous study (whose sampling frame was all pregnant women, not just those infected with COVID-19) found a negative correlation between BUN and gestational age, with a gestational age of 32 weeks corresponding to 17.1 mmol/L (64). Since preliminary studies found that elevated BUN levels increase risk of in-hospital death by 2.51 in COVID-19 patients (65), it is possible that both of these conclusions are true: when BUN levels are abnormally low (<1.5 mmol/L) and are increasing, risk of kidney damage decreases, but the risk increases after BUN levels exceed 4 mmol/L (which is the upper bound for our confidence interval).

Characteristics and Blood Assay of Infants Born to Pregnant Women With COVID-19

The most common abnormality found in the pooled blood assay was elevated IL-6, abnormal white blood cell count (WBC), elevated neutrophil count, and elevated AST/ALT. The pooled mean of IL-6, 23.22 pg/ml, is significantly above the normal range for IL-6 (5–15 pg/ml) (66). Furthermore, the pooled prevalence of elevated IL-6 is 91.1%, which is very frequent. Since elevated IL-6 has been deemed a valid marker for predicting neonatal sepsis (NS) (67), more blood assays for neonates should include IL-6 as a tool for early NS diagnosis. Abnormally elevated IL-6 levels without IL-10 regulation (elevated IL-10 levels) are an essential indicator for further neonatal complications such as necrotizing enterocolitis (NEC) (68). However, only a single study selected for this meta-analysis reported IL-10, and the neonate had elevated IL-10 levels and no NEC, so this study cannot meaningfully comment on the regulation of IL-10. However, given that IL-6 is the main cytokine responsible in the COVID-19-induced cytokine storms, these cytokines could have been shared from the mother to the fetus via the placenta.

Abnormal WBC and elevated neutrophils are well recognized within neonates (69). Hyperleukocytosis (WBC > 100×10^9/L) would be cause for concern, but no cases of hyperleukocytosis were identified in the present study. Similarly, the high prevalence of elevated AST/ALT in neonates has been deemed a benign condition that usually resolves within a year (70).

The pooled mean for PCT has been estimated at 0.23 ng/ml and is significantly higher than the normal value for children older than 72 h (0.15 ng/ml). The results of the meta-regression found a significant negative relationship ($P < 0.01$) between birth weight and PCT levels, corresponding to a birth weight of 2,500 g to 4.4 ng/ml. This is highly concerning because elevated PCT is a biomarker that is much more specific than any other proinflammatory marker in identifying sepsis. Using this relationship, infants with birth weights under 3,000 g could have PCT levels >2 ng/ml, indicating severe sepsis and high risk of developing organ dysfunction.

The pooled 1 and 5 min Apgar scores, 7.94 and 8.97, respectively, were not significantly different from the normal range (7–10). As expected, the 1 and 5 min Apgar scores had significant positive relationships ($P = 0.04$, $P = 0.04$, respectively) with birth weight.

The pooled prevalence of vertical transmission was estimated to be 0.18%, which is not significantly different from 0%. Therefore, we found that the risk of vertical transmission is very low. Due to the significant publication bias, this suggests that the prevalence of vertical transmission is even lower than 0.18%. Recent studies into vertical transmission of SARS-CoV-2 via the placenta have also concluded that the virus very rarely infects the placenta and can only do so with very high maternal viral loads (6). Even after placental infection, the virus may still be blocked from vertically transmitting (7). Furthermore, we found that vertical transmission does not have significant correlations with gestational age and birth weight, so positive vertical transmission is much more likely due to birthing conditions (such as cleanliness and ventilation) than due to maternal or neonatal characteristics.

Antibodies of Infants and Pregnant Women With COVID-19

High levels of IgM antibodies were indicated as the first line of defense to SARS-CoV-2 when the disease is still active, whereas detection of SARS-CoV-2 virus IgG indicates recovery or past exposure to the virus (71). In this study, we used 10 AU/ml as the threshold for IgG/IgM detection (33). As expected, elevated IgG was highly prevalent in pregnant women with COVID-19, estimated as 72.7%; the pooled mean for IgG was significantly different from the normal range, estimated as 76.90 AU/ml.

Interestingly, 67.1% of infants born to mothers with COVID-19 had elevated IgG levels. The pooled mean for neonatal IgG was significantly different from the normal range, estimated at 72.47 AU/ml. This indicates that infants with mothers with COVID-19 may gain natural passive immunity through IgG crossing the placenta during late pregnancy (72). IgM has a larger molecular structure, making it more difficult to cross the placenta (72), though not impossible; this is reflected in the lower prevalence of elevated IgM levels (20.6%). Furthermore, the transfer of antibodies across the placenta is supported by the results of the meta-regression since there are significant positive relationships between maternal IgG and their neonate's IgG, and between maternal IgM and their neonate's IgM ($P < 0.01$, $P = 0.03$ respectively).

Limitations

The major limitations of this systematic review are the retrospective design in almost all of the included studies, the lack of universal testing for COVID-19, the lack of standardized management and timing of women with COVID-19 and the inconsistent treatment and reporting for their newborns, and the lack of standardized blood testing. A significant proportion of the pregnancies were affected by COVID-19 during the third trimester, so we cannot meaningfully comment on early exposure. While common outcomes in blood assay, such as WBC and CRP, are commonly reported, other factors such as lactate dehydrogenase, BUN, D-dimer, and all neonatal outcomes should be tested more often so we can better verify if they are good tools to predicting the symptoms of COVID-19. Lastly, our review did not include studies that were recently published in the literature, particularly in languages other than English.

Conclusions

This systematic review and meta-analysis corroborated with previous studies that pregnant women with COVID-19 are at higher risk of preterm birth, are more likely to undergo cesarean section, and have elevated CRP levels and prolonged PT. In contrast to previously published reviews, we did not find an association between COVID-19 and thrombocytopenia, elevated lactate dehydrogenase, and elevated PCT to be prevalent symptoms for COVID-19. We report additional findings associated with COVID-19-infected mothers, including high neutrophil counts, low hemoglobin, and risk of preterm birth. Consistent with other reports, we found little evidence for vertical transmission. In neonates, we observed that infants born to mothers with COVID-19 are more likely to have elevated PCT levels and NS, but also may gain passive immunity to COVID-19 through antibody transfer via placenta. More testing and laboratory data are needed to clarify the relationships we found between D-dimer and thromboembolism, and between BUN and gestational age. Since the evidence is still increasing, this review provides information that can guide future systematic reviews for more meaningful results and can guide current health care during the current SARS-CoV-2 pandemic.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Mendeley Data: http://dx.doi.org/10.17632/fh557t857g.1.

AUTHOR CONTRIBUTIONS

CZ and HC conceived the study. CZ and JZ searched the literature and extracted the data. CZ performed the statistical analysis and drafted the manuscript. YV and HC helped to edit the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2021.647072/full#supplementary-material

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COVID-19-Related Changes to Pregnant People's Work-Plans Increase Prenatal Depression

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The COVID-19 pandemic has caused unprecedented rates of unemployment in the United States. Pregnant workers may be especially affected as they are over-represented in low-wage service and hospitality industries impacted by the pandemic. We surveyed an online convenience sample of currently working pregnant people living in the U.S. (n = 1,417) to determine whether COVID-19-related changes to how long individuals planned to work during their pregnancy, and uncertainty about these changes, were associated with prenatal depression. As hypothesized, both COVID-19-related work-plan changes (OR = 1.81, 95% CI 1.36–2.42, $p < 0.001$) and uncertainty about the precise nature of these changes (OR = 2.62, 95% CI 1.14–6.0, $p = 0.022$) were associated with significantly higher odds of a clinically-significant depression score. These effects appeared to be even greater among individuals who continued working outside the home during the pandemic. Since the U.S. is one of the few countries in the world that does not guarantee paid parental leave, pregnant people may be forced to choose between keeping their jobs and risking infection during the COVID-19 pandemic. Our results demonstrate a need for immediate suspension of the eligibility requirements for the Family and Medical Leave Act and/or universal access to both paid family leave and prenatal depression screening. This would help to alleviate these concerns and provide pregnant people with more options while preserving their employment status and financial security.

Keywords: Coronavirus, pregnant workers, perinatal depression screening, paid family leave, Family and Medical Leave Act

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INTRODUCTION

The COVID-19 pandemic has drastically affected employment in the U.S., with national unemployment rates hovering around 6.7% as of December 2020 after reaching a high of 14.7% in April 2020 (1, 2). Women, especially those that are pregnant, are over-represented in low-wage industries impacted by the pandemic (e.g., service and hospitality), leaving them vulnerable to changes in their work-plans during their pregnancy (3–5). Moreover, the three most common jobs held by pregnant women (elementary school teachers, nurses, and home health aides) put them at significant risk for infection (3). In the absence of universal paid parental leave and strict eligibility requirements for the federal 1993 Family and Medical Leave Act (FMLA), pregnant persons working outside the home may be forced to choose between keeping their job and risking infection (6–10), leading them to feel like they have little control over their circumstances.

Perceived lack of control over life events can substantially impact mental health, increasing depression risk (11–14). For example, pregnant individuals reporting a low sense of control over triggers such as stressful life events and lower income have been found to have a higher likelihood of perinatal depression (15). It is therefore reasonable to expect that unplanned alterations to work-plans and uncertainty about the nature of these changes due to the COVID-19 pandemic may elevate depression risk among pregnant persons. However, this has yet to be fully explored, despite the fact that pregnant people display elevated depression risk. Depression during and after pregnancy is more common than in the general population, affecting one in seven women in high-income countries (15). This may be due to higher rates of depression in women than men in general, as well as increased life demands and hormonal changes during pregnancy and the postpartum period.

Even still, perinatal depression is often underreported due to stigma (15, 16) and a failure of health care providers to screen pregnant people for depression (17). The CDC reports that about one in five pregnant people are not asked about depression symptoms during a prenatal visit (17). Recent evidence suggests that perinatal depression symptomatology has become even more common during the COVID-19 pandemic (18–20). These changes appear to be linked with factors including disruptions to daily exercise routines, social isolation, financial stress, and fears of COVID-19's impact on mothers and their infants' long-term health, highlighting the need for increased perinatal depression screening and treatment (18–22). Given the high percentage of individuals with prenatal depression who go undiagnosed and untreated, there is a need to improve depression screening and identify risk factors, especially during the COVID-19 pandemic.

Considering this background, the present study assesses whether changes and uncertainty surrounding work-plans during the COVID-19 pandemic significantly predict the likelihood of prenatal depression among pregnant persons living in the U.S. Specifically, we examined whether pandemic-related changes to how long individuals intended to work during their pregnancy were associated with prenatal depression. We also examined whether uncertainty about changes to work-plans was associated with prenatal depression. We hypothesized that currently working individuals reporting changes to how long they planned to work in pregnancy or uncertainty about their work-plans during the COVID-19 pandemic would have significantly higher depression scores. Information on the effects of the COVID-19 pandemic on pregnant people's work-plans and associated depression risk can help guide both the development of comprehensive national policies on paid parental leave, and universal screening and referral protocols for perinatal depression.

MATERIALS AND METHODS

Data come from the COVID-19 and Reproductive Effects (CARE) study, an online survey that was administered to a convenience sample recruited primarily through social media (i.e., Twitter and Facebook) and via dissemination to U.S.-based contacts working in maternal health. Surveys were completed between April 16th—30th 2020. The target population for the CARE study was pregnant people aged 18 years or older living in the United States, while the present analysis focuses specifically on those participants who were working at the time of survey completion. This study received ethical approval from Dartmouth College (STUDY00032045). Informed consent was collected by participants clicking a box saying that they consent to the information provided on the consent form. The survey was administered in REDCap, which automatically captures survey responses.

Completion of the survey was voluntary, and participants were allowed to skip any questions they did not want to answer. Only individuals who completed the survey (went through to the end of the questionnaire, even if they were missing data on individual questions) were included in the analysis. Of 2,467 people who consented to take the survey, 1,970 completed it (80%). Of the complete surveys, 1,600 participants were currently working and therefore eligible for inclusion in these analyses.

COVID-19 Pandemic Effects on Work-Plans

Participants were asked "Has the pandemic changed your plans for how long you plan to work during your pregnancy?" (yes/no).

Work-Plan Uncertainty

If participants reported that COVID-19 had changed their work-plans, they were prompted to qualitatively describe how their work-plans had been affected. A subset of 348 participants provided a qualitative response describing these changes. Given that work-plan uncertainty has been linked with increased emotional distress (23), these 348 qualitative responses were assessed to identify participants who were uncertain about the precise nature of changes to work-plans (e.g., whether or not they would stop working earlier than planned due to fear of getting COVID-19 or an inability to continue working entirely from home).

Work Location

Participants who reported that they were currently working were asked to identify their work location (from home; outside the home; or both).

Depression Symptoms

Depression symptoms were screened for using the Edinburgh Postnatal Depression Survey (EPDS) (24). The EPDS is considered to be the gold standard perinatal depression measure and is the most widely used validated screening tool worldwide [e.g., (25, 26)]. Depression symptoms were analyzed according to clinically significant prenatal depression criteria for pregnant persons (cut point $\geq$ 15) (27).

Age

Participants self-reported their age in years.

Education

Participants selected their highest completed education from the following options: Some high school, no diploma (1) High school graduate, diploma or the equivalent (for example: GED)

(2) Some college credit, no degree (3) Trade/technical/vocational training (4) Associate degree (5) Bachelor's degree (6) Master's degree (7) Professional degree (8) Doctorate degree (9). A composite education variable was created for analysis: less than a bachelor's degree, a bachelor's degree, or a degree beyond a bachelor's degree.

Household Income

Participants indicated their annual household income (USD) from the following options: <\$10,000 (1); \$10,000–19,999 (2); \$20,000–34,999 (3); \$35,000–49,999 (4); \$50,000–74,999 (5); \$75,000–99,999 (6); \$100,000+ (7). A composite household income variable was created for analysis: <\$49,999, \$50,000–99,999, and \$100,000+.

Race/Ethnicity

Race/ethnicity were self-reported and measured according to the Office of Management and Budget Standards (28). Native Hawaiian/Pacific Islander participants were re-classified as "Other" due to a small sample size ($N = 3$).

Current Gestational Week

Participants indicated their current gestational week.

High-Risk Pregnancy

Participants were categorized as high risk if they reported that they had been classified as "high-risk" by their maternity care provider or if they were aged 35 or older.

Self-Reported Health

Participants were asked whether they would describe their health as poor, fair, good, or excellent. This was re-categorized into good/excellent vs. poor/fair.

Statistical Analysis

Data analyses were conducted using Stata 15.1. All continuous variables exhibited normal distributions, with skewness values within $\sim\pm 0.5$ and kurtosis values within $\sim\pm 3$. Multicollinearity was not detected between any variables; all VIF values were in an acceptable range of 1.03–1.75. Sample descriptive statistics were calculated and bivariate analyses were conducted to evaluate significant differences in study covariates according to COVID-19-associated work-plan changes.

A multivariate logistic regression was used to evaluate whether work-plan changes predicted a clinically significant depression score (EPDS $\geq$ 15; yes/no). The model was adjusted for maternal age, education, income, week of pregnancy at time of survey, self-rated health, race/ethnicity, working outside the home, and "high-risk" pregnancy. After analyzing this relationship in the entire sample, we then stratified the analysis according to whether participants were working entirely from home during the pandemic or working outside the home. We then repeated this analysis process (i.e., multivariate logistic regression including the same covariates within the complete sample, and then stratified by work location) to evaluate whether there was an association between depression and work-plan uncertainty.

RESULTS

In total, 1,417 participants were eligible for the study (i.e., reported they were currently working) and were not missing data for study variables and were therefore included in the analysis. Study participants were a mean of 31.7 years old (SD = 4.2) and 25.8 weeks pregnant (SD = 8.8) at the time of survey completion. The study sample was 87.0% White ($N = 1223$), 5.6% Hispanic/Latina ($N = 79$), 1.6% African American ($N = 23$), 3.5% Asian ($N = 49$), 0.6% American Indian/Alaskan Native ($N = 8$), and 1.8% Other ($N = 25$). Over one-third (34.7%, $N = 491$) of the study population had a college education, and nearly one-half (49.4%, $N = 700$) of the study population had a degree beyond a college education. When asked about household income, 8.2% of respondents ($N = 116$) reported earning <\$49,999 annually, 34.7% ($N = 491$) reported earning between \$50–99,000, and 61.6% ($N = 873$) reported earning \$100,000+ (**Table 1**). Moreover, 26.2% of study participants ($N = 372$) reported that they experienced a COVID-19-related work-plan change (**Table 1**). Additionally, among the 348 participants who described how their work-plans had been altered by COVID-19, 30 individuals explicitly stated that they were uncertain how the pandemic would alter their work-plans.

In bivariate analyses, participants who experienced a COVID-19-related work-plan change reported lower household incomes [$\chi^2_{(2)} = 17.70$, $p < 0.001$], were less educated [$\chi^2_{(2)} = 9.62$, $p = 0.008$], were farther along in pregnancy [$t_{(1415)} = -4.57$, $p < 0.001$), and were more likely to continue to work outside the home during COVID-19 [$\chi^2_{(2)} = 52.41$, $p < 0.001$] compared to individuals who did not experience a COVID-19-related work-plan change. There were no statistically significant differences in maternal age [$t_{(1415)} = 1.66$, $p = 0.10$], race/ethnicity $\chi^2_{(5)} = 6.37$, $p = 0.27$], high-risk pregnancy [$\chi^2_{(1)} = 0.36$, $p = 0.55$], previous birth [$\chi^2_{(1)} = 0.002$, $p = 0.96$], self-rated health [$\chi^2_{(1)} = 0.59$, $p = 0.44$] or provider type [$\chi^2_{(2)} = 0.51$, $p = 0.76$] between individuals reporting a work-plan change and those reporting no change (**Table 1**).

Participants who experienced a COVID-19-related work-plan change had a significantly higher mean EPDS score (12.0) compared to individuals who did not report a COVID-19-related work-plan change [EPDS = 9.9; $t_{(1415)} = -6.81$, $p < 0.001$]. In multivariate logistic regression models using an EPDS score $\geq$ 15 as the clinical cutoff for depression and adjusting for covariates, participants reporting a work-plan change were significantly more likely to exhibit a depression score above the clinical cutoff point compared to those reporting no work-plan change (OR = 1.81, 95% CI 1.36–2.42, $p < 0.001$, **Table 2**). When stratifying the sample according to whether participants worked entirely from home or outside the home, work-plan change was significantly associated with an increased likelihood of depression in both models, but the OR appeared larger for those working outside the home (working outside the home: OR = 2.39, 95% CI = 1.42–4.05, $p = 0.001$; working from home only: OR = 1.61, 95% CI 1.13–2.29, $p = 0.007$, **Figure 1**).

Likewise, uncertainty about the nature of the work-plan change was significantly associated with an increased likelihood

TABLE 1 | Descriptive statistics.

	Total sample (*N* = 1,417)	COVID-19 related change in work-plans (*N* = 372)	No COVID-19 related change in work-plans (*N* = 1,045)	*p*-value*
Age	31.7 (4.2)	31.3 (4.1)	31.8 (4.2)	0.10
Weeks pregnant	25.8 (8.8)	27.6 (8.2)	25.2 (9.0)	**<0.001**
Race/ethnicity				0.27
White	1,233 (87.0%)	322 (86.6%)	911 (87.2%)	
Hispanic/Latino	79 (5.6%)	25 (6.7%)	54 (5.2%)	
African American	23 (1.6%)	2 (0.5%)	21 (2.0%)	
Asian	49 (3.5%)	15 (4.0%)	34 (3.3%)	
American Indian/Alaska Native	8 (0.6%)	3 (0.8%)	5 (0.5%)	
Other	25 (1.8%)	5 (1.3%)	20 (1.9%)	
Household Income				**<0.001**
<49,999	116 (8.2%)	48 (12.9%)	68 (6.5%)	
$50–99,000	428 (30.2%)	119 (32.0%)	309 (29.6%)	
$100,000+	873 (61.6%)	205 (55.1%)	668 (63.9%)	
Education				**0.008**
Less than a college education	226 (16.0%)	78 (21.0%)	148 (14.2%)	
College education	491 (34.7%)	124 (33.3%)	367 (35.1%)	
Degree beyond College education	700 (49.4%)	170 (45.7%)	530 (50.7%)	
Self-rated health				0.44
Poor/Fair	91 (6.4%)	27 (7.3%)	64 (6.1%)	
Good/Excellent	1,326 (93.6%)	345 (92.7%)	981 (93.9%)	
High-risk pregnancy	498 (35.1%)	126 (33.9%)	372 (35.6%)	0.55
Previous birth	608 (42.9%)	160 (43.0%)	448 (42.9%)	0.96
Provider type				0.78
Obstetrician	1,148 (81.0%)	306 (82.3%)	842 (80.6%)	
Midwife	244 (17.2%)	60 (16.1%)	184 (17.6%)	
Other	25 (1.8%)	6 (1.6%)	19 (1.8%)	
Current work location				**<0.001**
Home	1,039 (73.3%)	226 (60.8%)	813 (77.8%)	
Outside home	286 (20.2%)	123 (33.0%)	163 (15.6%)	
Both in the home/outside the home	92 (6.5%)	23 (6.2%)	69 (6.6%)	
Depression symptoms (EPDS, 0–30)	10.5 (5.2)	12.0 (5.1)	9.9 (5.1)	**<0.001**

*Values with $p < 0.05$ are shown in bold. *P-value represents significant differences in each variable according to whether or not COVID-19 affected people's work plans. T-tests were used for continuous variables, chi-squared tests for categorical variables.*
Mean (SD) reported for continuous variables, N (%) for categorical variables.

of having a depression score above the clinical cutoff point (OR = 2.62, 95% CI 1.15–6.0, $p = 0.022$, **Table 2**). When stratifying the sample according to whether participants worked entirely from home or outside the home, the coefficients were similar to or greater than that for the total sample but were no long statistically significant (working outside the home: OR = 3.02, 95% CI = 0.73–12.6, $p = 0.13$; working entirely from home: OR = 2.33, 95% CI = 0.78–6.92, $p = 0.13$) (**Figure 2**). This non-significant finding may be due to reduced statistical power resulting from only a subset of the sample reporting on the exact nature of work-plan changes. Self-rated health was the only covariate that was significantly associated with depression in adjusted models; respondents who reported good/excellent health had a lower likelihood of depression regardless of work-plan changes (Model 1: OR = 0.29, 95% CI 0.19–0.47, $p < 0.001$) (**Table 2**).

DISCUSSION

The aim of our study was to examine whether COVID-19-related changes to how long pregnant people intended to work during their pregnancy were associated with prenatal depression. Pregnant people who reported that COVID-19 had affected how long they planned to work during pregnancy

TABLE 2 | Regression results for association between work-plan changes and clinically significant depression (Model 1) and uncertainty about work-plan changes and depression (Model 2).

	Model 1 (*N* = 1,417) OR (95% CI)	Model 2 (*N* = 348) OR (95% CI)
Work-plan change	**1.81 (1.36–2.42)***	–
Uncertainty about work-plan change	–	**2.62 (1.14–6.00)***
Provider type		
Obstetrician	REF	REF
Midwife	0.98 (0.69–1.39)	0.56 (0.27–1.17)
Other	0.77 (0.26–2.29)	1.32 (0.23–7.72)
Race/ethnicity		
White	REF	REF
Hispanic/Latino	1.43 (0.86–2.40)	0.94 (0.35–2.48)
African American	1.14 (0.40–3.20)	Omitted
Asian	**0.27 (0.09–0.79)***	0.59 (0.15–2.31)
American Indian/Alaska Native	1.30 (0.26–6.62)	1.64 (0.13–18.78)
Other	1.66 (0.67–4.10)	2.18 (0.33–14.24)
Income		
<49,999	REF	REF
$50–99,000	0.78 (0.48–1.27)	0.89 (0.39–2.02)
$100,000+	0.72 (0.44–1.17)	1.04 (0.45–2.38)
Education		
Less than a college education	REF	REF
College education	0.82 (0.55–1.21)	0.64 (0.32–1.26)
Degree beyond college education	0.69 (0.46–1.03)	0.59 (0.30–1.16)
No previous birth	0.93 (0.71–1.22)	0.90 (0.53–1.53)
High risk pregnancy	1.05 (0.76–1.46)	1.08 (0.59–7.95)
Weeks pregnant	1.00 (0.98–1.01)	0.99 (0.96–1.02)
Maternal age	0.98 (0.94–1.02)	0.97 (0.90–1.05)
Current health		
Poor/Fair	REF	REF
Good/Excellent	**0.29 (0.19–0.47)***	0.50 (0.22–1.18)
Adjusted model R2	0.05	0.04

Values with $p < 0.05$ are shown in bold. ***$p < 0.05$.**

were significantly more likely to exhibit signs of clinical depression, as were individuals who were unsure how their work-plans would be affected by COVID-19. These effects appeared to be particularly strong among individuals who continued to work outside of the home during the pandemic. Cumulatively, our findings support the study hypotheses and are consistent with earlier work. Previous research conducted among working pregnant people living in the U.S. indicates that maintaining a sense of control bolsters mental health during the transition to parenthood (29). Keeton et al. also found that this protective sense of control includes perceived ability to manage work schedules (29). Likewise, reports of "serious difficulties at work" have been linked with prenatal depression risk (30). These findings and the results of the present study suggest that work disruptions may elevate maternal depression risk.

Pregnant workers are especially vulnerable to COVID-19-related work disruptions. The three most common occupations for pregnant women are elementary school teachers, nurses, and home health aides, all of which have been considered essential during the COVID-19 pandemic and may put individuals at significant risk of contracting disease (3). Additionally, more than one in five pregnant workers are employed in low-wage jobs, which often have inflexible scheduling (impairing ability to attend doctor appointments) and generally lack paid sick leave or work-from-home options (3–5). These factors render pregnant workers in essential and low-wage positions more susceptible to contracting COVID-19 and thus increase their likelihood of having a work-plan change during the pandemic, either because they become sick or fear becoming sick.

Additionally, uncertainty surrounding future work-plans appears to be an important determinant of depression risk among

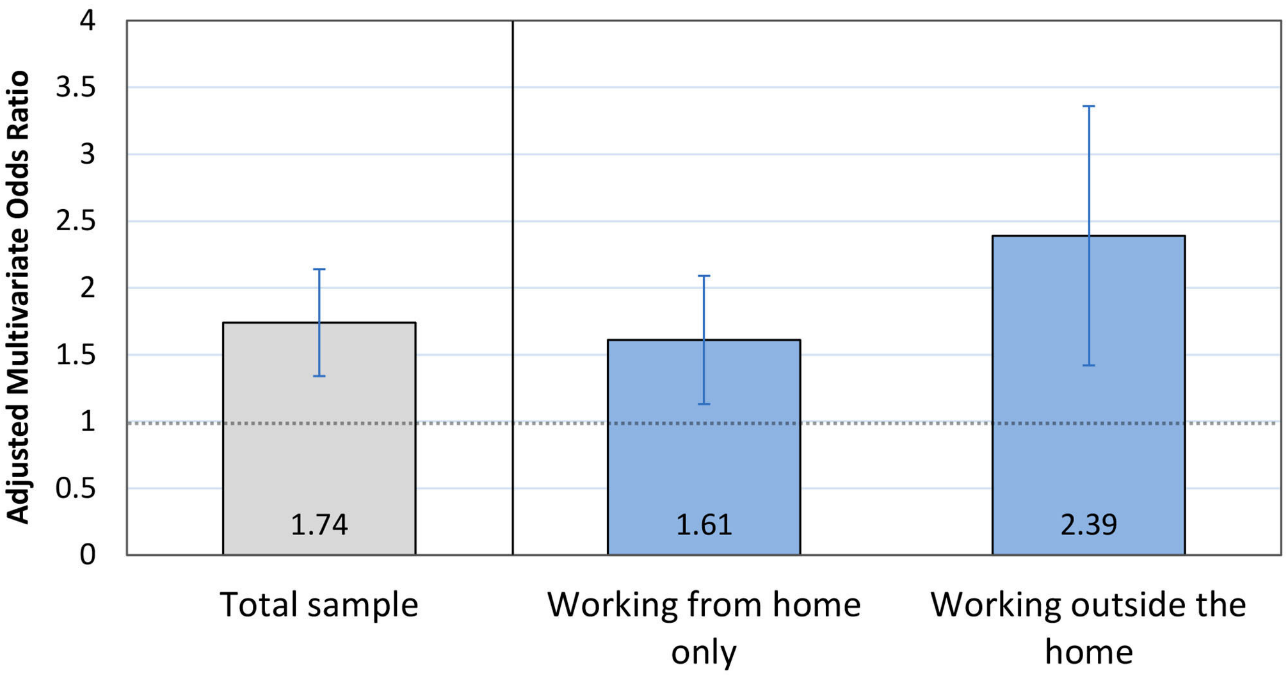

FIGURE 1 | Prenatal depression and COVID-19-related work-plan changes. Odds ratio and 95% confidence interval from multivariate regression model predicting clinically significant depression symptoms in response to experiencing a work-plan change. Results are shown within the total sample (in gray); and then stratified according to whether individuals worked entirely from home or outside of the home during the pandemic (in blue).

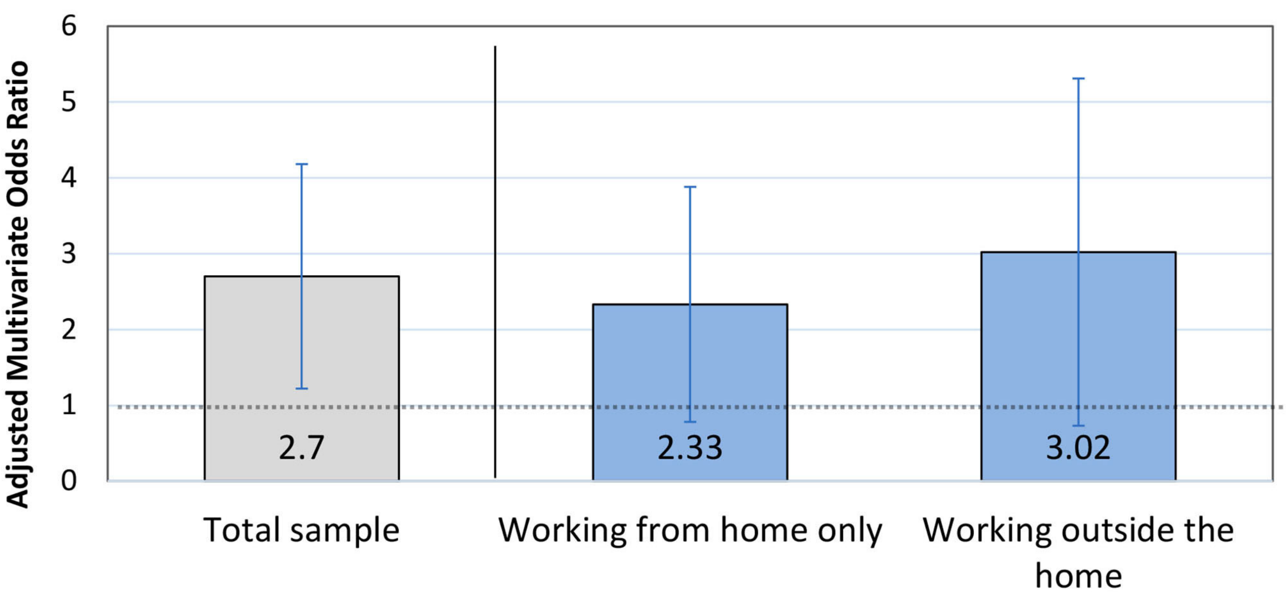

FIGURE 2 | Prenatal depression and uncertainty surrounding COVID-19-related work-plan changes. Odds ratio and 95% confidence interval from multivariate regression model predicting clinically significant depression symptoms among participants in response to being unsure about how the pandemic would affect their work-plans. Results are shown within the total sample (in gray); and then stratified according to whether individuals worked entirely from home or outside of the home during the pandemic (in blue).

pregnant people, which is consistent with previous findings that perceived lack of control over life events is central to the development of depression (12, 14, 15, 31, 32). Therefore, in response to rising perinatal depression rates during the pandemic, obstetric care providers can use the results from this analysis to better identify depression risk factors during COVID-19 and use this information to better screen patients. For instance, the results of our analysis suggest that clinicians should consider adding screening questions related to work-plan disruptions (either resulting from COVID-19 or other factors), as they could signify a risk factor for depression. Moreover, clinicians and medical researchers should consider how uncertainty related to a range of factors—including work-plans, financial situations, and even pregnancy outcomes—may impact maternal mental health. Documenting common sources of uncertainty may help healthcare providers and researchers design more effective interventions to address these underlying issues (e.g., offer targeted information and resources relevant to a particular source of uncertainty, thereby helping the affected individual regain some sense of control).

Unfortunately, even though mental health concerns are increasing during the pandemic, in-person clinical screens for depression have decreased as most prenatal appointments are done remotely by telehealth (4, 18–20, 33). The American College of Obstetricians and Gynecologists recommends that obstetric care providers screen patients for depression and anxiety at least once during the perinatal period using a standardized, validated tool (15). Many studies (4, 34, 35) have argued for obstetricians to go beyond this recommendation and make depression screening a routine part of prenatal care, as screening is critical to avoid adverse outcomes for mother and baby and to reduce postpartum depression risk, a leading cause of maternal mortality (16, 34–37).

One way to mediate the effects of COVID-19-related work-plan changes and prenatal depression would be through universal paid family leave, which could alleviate anxiety caused by choosing to work while risking infection (4). The U.S. is one of the few countries in the world that does not guarantee paid parental leave, despite the benefits associated with leave (e.g., reduced cesarean section rates and lower infant mortality) (6, 9). The FMLA gives workers 12 weeks of *unpaid* time off, but only ∼60% of workers are actually eligible (7, 9, 10). Employer provision of any *paid* family leave (PFL) is voluntary and more common among high-paying occupations; in 2018, only 16% of employees had access to PFL (7, 8, 10). Policy recommendations could therefore include instituting a universal paid family leave policy and/or temporarily suspending FMLA eligibility requirements (5). Future research can also investigate whether states and countries with more favorable parental leave policies have had better mental health outcomes during the COVID-19 pandemic relative to those without such policies.

Despite the strengths of this study, including the large sample size and wide distribution of participants across the U.S., our study was limited by the nature of self-reported data (38). Future work should test these associations using more objective measures designed to explicitly capture types of work-plan changes and the uncertainty surrounding these changes [e.g., providing a list of possible work-plan changes and asking participants to select the response(s) that accurately described their situation]. Additionally, as the survey was distributed through social media, it did not involve random sampling, despite attempts to distribute the survey to a diverse set of maternal-health organizations in various states. Our study population was less diverse than the U.S. birthing population, with study participants more likely to be non-Hispanic White and to report higher education and income levels than national averages (39). Another limitation was that prenatal participant data were not available on social support received or relevant mental health history (e.g., current psychotropic treatment, previous depression diagnoses, or family history of mental illness), variables that have been linked with prenatal depression risk e.g., (30, 40). Finally, individuals with severe depression may have been less likely to complete the study survey.

Our analysis also only included currently working individuals, excluding anyone who stopped working before our study began. We focused on currently working participants to evaluate the relationship between work-plan changes and prenatal depression, since depression risk among individuals who had already stopped working could be impacted by changes in routine, financial stress (21), and other factors not directly related to anticipated work-plan changes. Additionally, while respondents qualitatively described working more or less during pregnancy due to the pandemic, this information was not systematically collected so was not included in the present analysis.

More research is needed to assess the effects of work-plan changes and uncertainty during the COVID-19 pandemic in more diverse study populations, especially as Black and Latinx individuals are more likely to hold low-wage occupations affected by the pandemic (3). Moreover, populations who do not speak English or have reliable internet access may be particularly affected by the absence of in-person perinatal depression screens due to language and technology barriers (4). Longitudinal research is also needed to establish directionality in the relationship between COVID-19-related work-plan changes and depression.

Our study found that COVID-19-related work-plan changes and work-plan uncertainty were associated with depression, independent of risk factors including income and education. These results suggest a need for increased mental health screening during the pandemic by providers. Additionally, increased access to FMLA and universal PFL may help reduce stress both during and after the pandemic.

DATA AVAILABILITY STATEMENT

Study data are available from the corresponding author upon reasonable request. Requests can be made through the CARE study website (https://sites.dartmouth.edu/care2020/).

ETHICS STATEMENT

This study received ethical approval from Dartmouth College (STUDY00032045). Study information (e.g., study summary, purpose, benefits, risks, and privacy protection details) was provided to all participants prior their completion of the survey. Informed consent was collected by asking potential participants to click a box saying that they had read the study information and consented to participating in the study.

AUTHOR CONTRIBUTIONS

MS: conceptualized and wrote the manuscript. TG and ZT: study design, revised, and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Prenatal Care Disruptions and Associations With Maternal Mental Health During the COVID-19 Pandemic

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As the novel coronavirus (COVID-19) spread across Canada in March 2020, provinces imposed restrictions. These changes impacted how pregnant individuals received prenatal care and experienced childbirth. The stress caused by these changes may negatively affect the well-being of pregnant individuals with impacts on the developing child. This study investigated the impact of the pandemic on prenatal care and birth plans of pregnant individuals in Canada and potential associations with maternal mental health. Data from 4,604 participants was collected from English- and French-speaking Canadians between April 5 and June 1, 2020 as part of the Canada-wide Pregnancy During the COVID-19 Pandemic study. Symptoms of maternal depression, general anxiety, and pregnancy-related anxiety were assessed. Participants also answered questions about disruptions and changes to prenatal care and their birth plans due to the COVID-19 pandemic. Logistic regression was used to estimate associations between prenatal care disruptions and maternal mental health. Cancellation of prenatal appointments and birth plan changes (specifically changes to childcare during birth and change of support person attending the birth) were significantly associated with greater odds of experiencing clinically elevated depression, anxiety, and/or pregnancy-related anxiety symptoms. These results highlight the need for reliable and accessible prenatal care during the pandemic, such as the integration of mental health screenings and co-ordination of prenatal care providers.

Keywords: pregnancy, prenatal care, pandemic, depression, anxiety, COVID-19, stress

INTRODUCTION

Proper prenatal care is important for the health of both the pregnant individual and the developing baby. Inadequate prenatal care has been associated with low birth weight, preterm birth, and miscarriage (1–5). The emergence of the novel coronavirus (COVID-19) led to widespread restrictions that disrupted prenatal care for many pregnant individuals around the world. During the COVID-19 pandemic, the Canadian government recommended remote (virtual) appointments with doctors and obstetricians where possible (6), and some hospitals and healthcare providers prevented support persons from prenatal appointments, ultrasounds, or the birthing room, switched to virtual appointments, and/or limited in-person meetings with care teams. Restrictions and changes to prenatal care and birth protocols occurred quickly, adding potential uncertainty and stress for pregnant individuals.

Prior studies show that 10–25% of individuals experience mild to moderate anxiety and/or depression during pregnancy (7). Prenatal depression and anxiety have been linked to a negative perception of the birth experience (8), greater risk of postnatal depression (9–12), and loss of interest in the child (13). Prenatal stress is also related to adverse cognitive and behavioral outcomes in children (14–17). Pregnancy-related anxiety refers to worries or fears in relation to childbirth, the safety and the health of the baby, and future parenting. Higher pregnancy-related anxiety is strongly associated with adverse birth outcomes, including preterm birth and low birth weight, problematic infant temperament, behavioral and emotional problems in the child, and developmental delays (18–20). Recent studies indicate substantially elevated symptoms of anxiety and/or depression in pregnant individuals during the current COVID-19 pandemic compared to pre-pandemic pregnancy cohorts (21–25).

The goal of the present study was to determine the impact of the COVID-19 pandemic on prenatal care and birth plans of pregnant individuals in Canada and how these changes were associated with maternal mental health.

MATERIALS AND METHODS

Participants

The current study reports data collected from the Pregnancy during the COVID-19 Pandemic study (26) between April 5 and June 1, 2020. These dates were chosen to capture the effects of the initial lockdown period. The ongoing Pregnancy during the COVID-19 Pandemic study recruited pregnant individuals across Canada using social media, primarily via Facebook and Instagram ads, to complete an online survey. The inclusion criteria were as follows: living in Canada, able to read and write English and/or French, 17 years of age or older, and having a confirmed pregnancy <35 weeks' gestation. This study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB20-0500).

COVID-19 and Prenatal Care

Participants completed a questionnaire about disruptions and changes to their prenatal care and birth plan due to the current COVID-19 pandemic. Participants were presented with the following questions/statements: "Have you experienced changes in the way that prenatal care is delivered to you during the COVID-19 pandemic?," "Have any of your prenatal care appointments been canceled?," and "Are you able to bring your partner or support person to your appointments?" Participants answered these questions using a binomial scale (yes/no). Participants were also asked "Which changes have you made to your birth plan (check all that apply): Birth Location; Support People; Childcare Arrangements; Other changes".

Anxiety and Depression Symptoms

The Edinburgh Postnatal Depression Scale (EPDS) (27, 28) was used to measure maternal depressive symptoms. Although the EPDS is not diagnostic, scores $\geq$13 have been shown to have maximal consistency with a diagnosis of major depressive disorder and are used to identify individuals with clinically concerning depression symptoms (27). Using a cut-off of 13 for the EPDS, sensitivity ranges from 38 to 43% (trimester dependent) and specificity is 98–99% (29). The PROMIS Anxiety Adult 7-item short form was used to assess general anxiety. Scores $\geq$60 on this measure have been associated with clinically elevated anxiety, possible scores range from 36.3 to 82.7 (30). Data from the EPDS and PROMIS measures were dichotomized at the established cut-off scores, $\geq$13 and $\geq$60 respectively, representing clinically elevated symptoms. Official French translations were used for each measure. Pregnancy-related anxiety, referring to fear and worries surrounding the circumstances of birth and health of baby, was assessed differently in the English and French sample due to availability of measures. Responses to the English survey were assessed using a 10-item questionnaire (PRAQ), in which participants pick from four possible responses. The French survey used a similar, but slightly different, validated 10-item questionnaire (PRAQ-R2), in which participants chose from five responses per question (31). Neither the PRAQ (English) nor the PRAQ-R2 (French) provide cut-off scores for clinically elevated symptoms; previous treatment studies commonly use a median split method to define groups with higher vs. lower pregnancy related symptoms (32). We used a conservative approach and used the upper quartile to define individuals with elevated symptoms (PRAQ $\geq$ 24 and PRAQ_R2 $\geq$ 30).

Statistical Analysis

IBM SPSS Statistics 26 was used for all statistical analysis. Survey responses were manually checked for accuracy before analysis, and invalid records (e.g., implausible due date) were removed. The associations between clinically elevated psychological symptoms and COVID-19 related disruptions to prenatal care and birth plans were estimated using multivariable logistic regression using IBM SPSS. Separate logistic regressions were completed for each measure of mental health in relation to prenatal care disruptions and changes to birth plans. The PROMIS Anxiety and EPDS measures were analyzed from English and French survey responses in combination. Analysis for the PRAQ and PRAQ-R2 were completed separately for participants completing the survey in English or French, as had different score ranges. Logistic regression models were adjusted for age, parity, ethnicity, trimester, maternal education, and household income as covariates. A supplementary analysis was conducted controlling for prior history of anxiety and depression, in addition to other covariates (age, parity, trimester, income, maternal education, ethnicity). Missing data was coded as N/A and those values did not contribute to the statistical model.

TABLE 1 | Demographics, mental health scores, and disruptions to prenatal care.

Measure	*n*	Mean	Standard deviation	Range
Gestation (weeks)	4,604	21.63	8.48	3.7–35
Age (years)	4,604	31.56	4.39	18–49
Mental health scores				
Edinburgh postnatal depression scale (EPDS)	4,491	10.30	5.37	0–30
PROMIS anxiety T-scores	4,477	58.74	8.2	36–82.7
Pregnancy-related anxiety questionnaire (PRAQ)				
English PRAQ measure	3,681	21.23	5.26	8–40
French PRAQ-R2 measure	789	25.71	7.84	10–48
	N	**%**		
Disruptions to prenatal care				
Changes in way prenatal care had been delivered	4,115/4,604	89.4% Yes		
Cancellation of prenatal care appointments	1,644/4,114	40% Yes		
Support person allowed to attend prenatal appointments	4,21/4,604	9.1% Yes		
Changes to birth plan	1,535/4,604	33.3% Yes		
- Birth location	434/4,599	9.4% Yes		
- Support person	1,229/4,599	26.7% Yes		
- Childcare plan	499/4,599	10.8% Yes		
- “Other” changes	204/4,599	4.4% Yes		

RESULTS

Participants

A total of 4,604 records collected between April 5 and June 1, 2020 were included in the current analysis. 3,755 participants completed the survey in English and 849 in French. Participants were aged 31.56 ± 4.39 years (range 18–49 years). The majority of participants were married (67.0%) or living with a partner (28.6%). All participants lived in Canada, with the majority residing in Ontario (28.3%), Alberta (23.2%), and Quebec (21.0%). Most participants self-identified as Caucasian (81.6%), with others identifying as First Nations (1.0%), Metis (1.2%), Black (1.7%), Chinese (1.7%), Filipino (1.4%), Korean (0.2%), West Asian (0.6%), South Asian (3.3%), South-east Asian (0.3%), Hispanic (2.1%), and Mixed (4.9%).

Participants reported their highest level of education, having completed at least a bachelor’s degree (40.3%), a trade or community college diploma (24.0%), or a master’s degree (18.6%). Participants had a median income range of CAD $100,000–124,999 per year (USD $75,000–95,000). 45.6% of participants reported having other children (32.9% had one child, 9.6% had two children, and 3.2% had three or more children). Average gestation of participants when they completed the survey was 21.6 ± 8.5 weeks (range 3.7–35). Prior history of mental health conditions was reported; 39.7% of participants had a history of anxiety and 18.8% had a history of depression.

Prevalence of Mental Health Symptoms

Mean scores on mental health measures can be found in **Table 1**. 34.0% of participants experienced clinically elevated symptoms of depression (EPDS scores ≥13), and 70.9% of participants had clinically elevated symptoms of anxiety (PROMIS scores ≥60) (**Figure 1**).

Disruptions and Changes to Prenatal Care

Eighty-nine percent of participants reported changes in the way that prenatal care was delivered to them during the COVID-19 pandemic (**Table 1**). Forty percent of respondents reported the cancellation of at least one prenatal care appointment and 90.9% of participants were not permitted to bring their partner or support person to prenatal appointments. 33.4% of participants made changes to their birth plan because of the COVID-19 pandemic: 9.4% changed their birth location, 26.7% changed their birth support person(s), and 10.9% changed their childcare plan (some participants made changes to multiple factors and thus numbers do not add to 33.4%).

Associations Between Prenatal Care Disruptions and Mental Health

Cancellation of prenatal appointments was associated with increased odds of experiencing clinically elevated depression symptoms ($OR = 1.36$, 95% CI [1.19, 1.56], $p < 0.001$), and clinically elevated general anxiety ($OR = 1.33$, 95% CI [1.17, 1.52], $p < 0.001$) (see **Table 2**, **Figure 2**). Changes to the planned support person(s) attending the birth increased odds of clinically elevated depressive symptoms ($OR = 1.61$, 95% CI [1.36, 1.91], $p < 0.001$) and general anxiety symptoms ($OR = 1.77$, 95% CI [1.49, 2.09], $p < 0.001$). Changes to planned childcare arrangements during labor also increased the odds of clinically elevated depressive symptoms ($OR = 1.50$, 95% CI [1.18, 1.92], $p = 0.001$) and anxiety symptoms ($OR = 1.48$, 95%

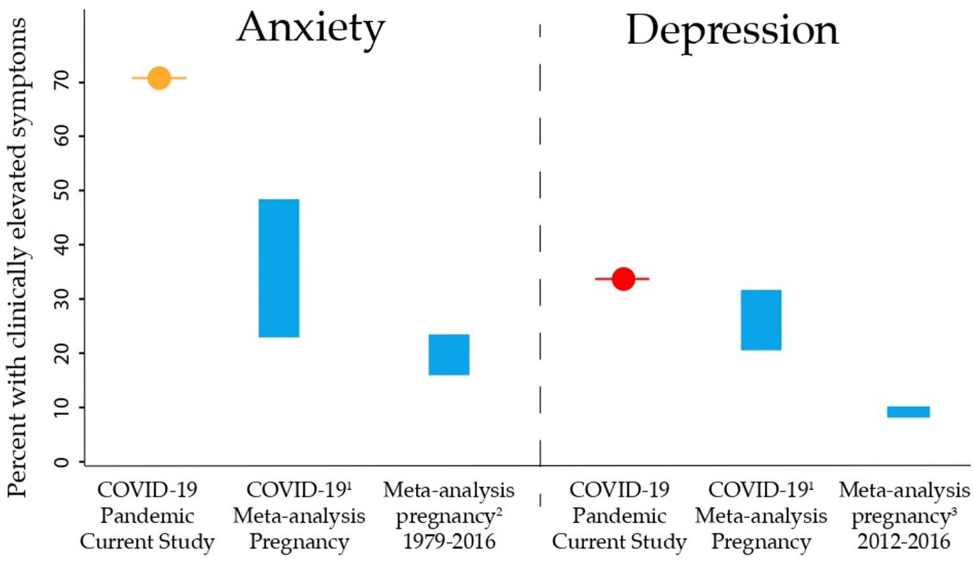

FIGURE 1 | Rates of clinically elevated anxiety and depression symptoms in pregnant individuals in this study were compared to pre-pandemic meta-analysis estimates, and meta-analysis estimates of rates during the COVID-19 pandemic. The prevalence in the current study is given, vs. the estimated ranges in prior studies. The frequency of clinically elevated symptoms of anxiety (orange) and depression (red) in the current study were substantially higher than pre-pandemic and during-pandemic estimates, likely because this data was collected early in the COVID-19 pandemic (April–June 2020) when uncertainty was at its highest. References 1, Tomfohr-Madsen et al. (33); 2, Dennis et al. (34); 3, Gavin et al. (35).

CI [1.16, 1.90], $p = 0.002$). Among English responses, odds of high pregnancy-related anxiety were increased by cancelation of prenatal appointments (OR=1.39, 95% *CI* [1.17, 1.64], $p < 0.001$), changes to planned support person(s) (OR=1.70, 95% *CI* [1.39, 2.08], $p < 0.001$), and changes to childcare during labor ($OR = 1.46$, 95% *CI* [1.08, 2.00], $p = 0.015$). Within French responses, only changes to the planned support person(s) able to attend the birth were associated with increased odds of pregnancy-related anxiety symptoms ($OR = 1.58$, 95% *CI* [1.00, 2.50], $p = 0.049$), though this smaller sample has reduced power.

A supplementary analysis was conducted controlling for prior history of anxiety and depression, in addition to other covariates. All relationships between mental health and changes to prenatal care and birth plans remained significant, except the association between pregnancy related anxiety in the French sample and changes to birth support person ($OR = 1.51$, 95% *CI* [0.93, 2.42], $p = 0.086$).

DISCUSSION

Here, we show that prenatal care disruptions were common during the COVID-19 pandemic, and were associated with clinically elevated depression, anxiety, and pregnancy-related anxiety symptoms. Eighty nine percent of pregnant individuals in this study reported at least one pandemic-related change in their prenatal care. Of these changes, the most common were inability to have support persons attend prenatal appointments (90.6% of participants) and cancellations of prenatal care appointments (40% of participants). COVID-19-related changes in prenatal care may contribute to uncertainty around maternal and fetal health, which may compound the already elevated levels of stress, further increasing the risk of psychological distress. Care providers should work to provide pregnant individuals with consistent and informed prenatal care in an effort to reduce uncertainty and stress. Stress during pregnancy increases the risk of physical and psychological problems in both the pregnant individual and the child (36–38). Thus, these care changes and related increases to anxiety and depression symptoms, have concerning potential long-term implications for children. Given the benefits of support during pregnancy (37, 39), when considered in conjunction with the elevated psychological distress in this population, the need for consistent and supportive care from medical professionals and the prenatal care team should be considered of utmost importance.

Cancellations of prenatal appointment(s), changes to the planned support person(s) attending the birth and changes to childcare plans during labor are all associated with elevated pregnancy-related anxiety in the English respondents, while only a change in support person(s) attending the birth was associated with elevated pregnancy-related anxiety in the French subset. These distinctions between the English and French subsamples potentially reflect the differences in questionnaires used, the smaller sample size of French-speaking participants (which reduces power), and/or differences in how prenatal care was delivered or perceived in Quebec (where most French respondents lived) compared to the rest of the country. Care should be taken to ensure an individualized approach to prenatal care during the COVID-19 pandemic to mitigate pregnancy-related

TABLE 2 | Prenatal care disruptions and symptoms of maternal distress[a].

	Odds ratio	95% CI for odds ratio		*p*-Value
		Lower	Upper	
General anxiety symptoms				
Prenatal appointment canceled	**1.33**	1.17	1.52	**0.000**
Support person(s) not allowed to attend prenatal appointments	0.94	0.74	1.19	0.61
Birth location change	1.11	0.88	1.39	0.38
Birth support person change	**1.77**	1.49	2.09	**0.000**
Birth childcare changes	**1.48**	1.16	1.90	**0.002**
Depression symptoms				
Prenatal appointment canceled	**1.36**	1.19	1.56	**0.000**
Support person(s) not allowed to attend prenatal appointments	0.87	0.67	1.12	0.280
Birth location change	1.23	0.98	1.53	0.080
Birth support person change	**1.61**	1.36	1.91	**0.000**
Birth childcare changes	**1.50**	1.18	1.92	**0.001**
Pregnancy-related anxiety symptoms (english measure)				
Prenatal appointment canceled	**1.39**	1.17	1.64	**0.000**
Support person(s) not allowed to attend prenatal appointments	0.815	0.60	1.11	0.190
Birth location change	1.22	0.94	1.59	0.130
Birth support person change	**1.70**	1.39	2.08	**0.000**
Birth childcare changes	**1.46**	1.08	2.00	**0.015**
Pregnancy-related anxiety symptoms (french measure)				
Prenatal appointment canceled	0.91	0.63	1.32	0.628
Support person(s) not allowed to attend prenatal appointments	1.50	0.73	2.92	0.284
Birth location change	0.74	0.35	1.55	0.422
Birth support person change	**1.58**	1.00	2.50	**0.049**
Birth childcare changes	0.88	0.41	1.90	0.746

[a]*Model adjusted for maternal education, age, ethnicity, household income, parity, and trimester. Bold values indicate significance at* $p < 0.05$.

anxiety in a manner which is specific to the individual in question.

Due to the COVID-19 pandemic, many forms of medical care have transitioned to telehealth (40). Remote delivery of prenatal care without the face-to-face experience has the potential to be perceived as less supportive, despite being an adequate substitute for complete cancellation (40, 41). When prenatal appointments were in person, most participants in this study were not allowed to bring their partner or support person, which may also contribute to a perceived decrease in support. Decreased social support is associated with higher symptoms of anxiety and depression. A result of note was that not being allowed to bring one's support person(s) to prenatal appointments was not associated with maternal psychological distress in this study. With video- or telephone-based remote appointments available for prenatal appointments when they are canceled, individuals can attend these appointments from the comfort of their own home. This may result in an increased level of comfort and perception of support contributing to this result, as compared to when the individual must travel for their appointments. We do not have data regarding the replacement of prenatal appointments with remote appointments, thus this cannot be concluded from these results; further research is needed to expand on this possibility.

Our sample includes pregnant individuals from across Canada. 40.3% of our sample held at least a Bachelor's degree, which is similar to 2016 Canadian Census data showing that 40.7% of women aged 25–34 held at least a Bachelor's degree (42). Statistics Canada reports that 22.3% of Canada's total population is a visible minority, which is slightly higher than the proportion in our sample (18.4%) (42). Clinically elevated symptoms of anxiety were reported by 70.9% of participants, and clinically elevated symptoms of depression by 34% of participants in the current study. These estimates are higher than a recent meta-analysis of rates during the COVID-19 pandemic, and higher than pre-pandemic meta-analyses indicate (see **Figure 1**) (33–35). The higher rate of psychological symptoms reported here may be due to the time period of this study, which collected data early in the pandemic (April–June 2020), when uncertainty was very high, and restrictions were most severe. The proportion of participants in this sample with a prior history of anxiety (39.7%) is higher than would be expected (8.7–11.6%) (43, 44). This could be an attributing factor as to why clinically elevated anxiety symptoms for the sample are much higher (70.9%) than pre-pandemic meta-analysis

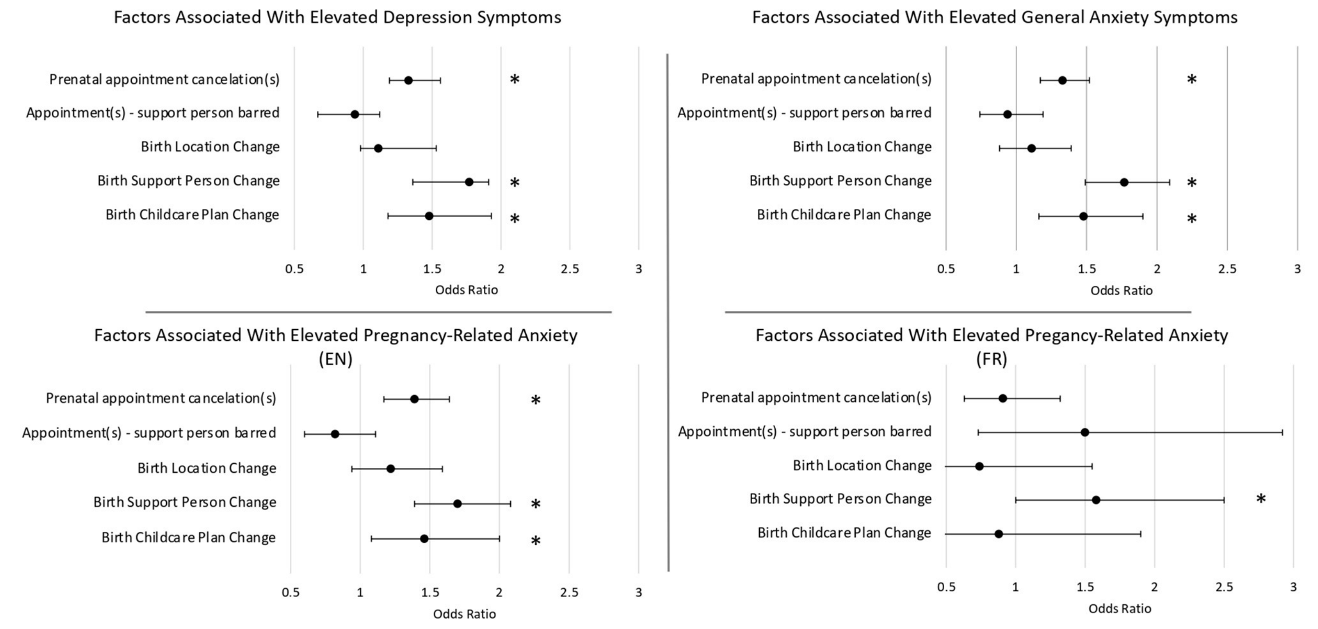

FIGURE 2 | These odds ratios demonstrate how each of the COVID-related disruptions to prenatal care affects the odds of experiencing elevated symptoms of psychological distress. Odds ratios were adjusted for age, parity, ethnicity, trimester, maternal education, and household income. Note that the sample size for the French Pregnancy-Related Anxiety Questionnaire (PRAQ-R2) was smaller than for the English PRAQ. *Indicates statistical significance ($p < 0.05$).

estimates and estimates of rates during the COVID-19 pandemic (see **Figure 1**).

This study has some potential limitations that should be considered when interpreting the results. The primary recruitment method for the Pregnancy During the Pandemic study was advertising on social media, which may have led to a selection bias. Additionally, this study employed the use of screening tools for psychological distress as opposed to diagnostic tools. While these screening tools were previously validated and correlate with diagnostic outcomes (27–31), future studies may look to reinforce these findings with clinical diagnosis. Results may not be generalizable to the entire population, and future studies may consider recruiting participants through alternate methods to capture a different sample.

Pregnant individuals are experiencing significant psychological distress during the COVID-19 pandemic (21–25). Our research provides new insight into the relationship between disruptions to prenatal care and this distress. Prenatal care disruptions were common, and appointment cancellations as well as changes to the birth plan were associated with clinically elevated depression and/or anxiety symptoms. This study illustrates the need for reliable and accessible prenatal care during the current pandemic, including integration of mental health screenings and modified birth plans that create a supportive birthing environment and are person-centered. In order to maintain high quality of care in the face of a public health crisis, prenatal, and medical care professionals should ensure that they are delivering high-quality care in a personal way that maximizes support felt by the individual, which may require additional training in remote methods of care delivery. Care providers should work together to provide pregnant individuals with consistent prenatal care to reduce uncertainty.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by This study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB20-0500). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GG, LT-M, and CL conceptualized the larger Pregnancy during the COVID-19 Pandemic study. TG and MB led statistical analysis and wrote the original manuscript draft. All authors contributed to the article, design of this analysis, critical revisions of the manuscript, and approved the submitted version.

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REVIEW
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Sensitive to Infection but Strong in Defense—Female Sex and the Power of Oestradiol in the COVID-19 Pandemic

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The incidence of SARS-CoV2 infections is around 15% higher in premenopausal women compared to age matched men, yet the fatality rate from COVID-19 is significantly higher in men than women for all age strata. Sex differences have also been observed in recent epidemics including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), with SARS-CoV 2 virus infection sex differences appear more dramatic. The regulation and expression of the angiotensin converting enzyme 2 (ACE2) is the key for this special coronavirus SARS-CoV-2 to enter the cell. 17β-oestradiol increases expression level and activity of angiotensin converting enzyme-2 (ACE2) and the alternative signaling pathway of Ang II via the angiotensin II receptor type II (AT2R) and the Mas receptor is more dominant in female sex than in male sex. Maybe a hint to explain the higher infection risk in women. The same hormonal milieu plays a major role in protecting women where morbidity and mortality are concerned, since the dominant female hormone, oestradiol, has immune-modulatory properties that are likely to be protective against virus infections. It is also known that the X chromosome contains the largest number of immune-related genes, potentially conferring an advantage to women in efficient immune responsiveness. Lifestyle factors are also likely to be contributory. Premenopausal women could possibly face higher exposure to infection (hence higher infection rates) because economic conditions are often less favorable for them with less opportunity for home office work because of jobs requiring mandatory attendance. Due to the additional task of childcare, it is likely that contact times with other people will be longer. Women generally make healthier lifestyle choices, thus reducing the disease burden that confers high risk of mortality in COVID-19 infected men. This narrative review aims to present key concepts and knowledge gaps on the effects of oestrogen associated with SARS-CoV2 infection and COVID-19 disease.

Keywords: COVID-19, hormone therapy, mortality, sex, oestrogen, ACE2, long covid

INTRODUCTION

There are marked and intriguing sex differences in infection rates, morbidity, and mortality from COVID-19. Data from our recent study indicate that premenopausal women are disproportionately (15%) more infected with coronavirus than men in the same age brackets, but they do not become as seriously ill, with 50% more men than women dying from this pandemic. (1) The current epidemiology data from Germany (**Figures 1**, **2**) continue to show these sex differences with more SARS-CoV-2 virus infections in premenopausal women and less COVID-19 deaths compared to men in all age strata. This is an interesting observation for sex and gender medicine experts, raising a number of as yet unanswered questions. For example, do the higher infection rates in premenopausal women reflect socio-cultural conditions such as jobs with fewer home office opportunities and more childcare work with increased contacts with and exposure to other families? Could lifestyle factors, such as higher drinking and smoking rates among men, that increase the disease burden (cardiovascular disease, chronic lung disease) play a significant role in the increased death rates in men? Are biological factors in fact more important? There is a profound difference in the hormonal milieu between men and premenopausal women, the dominant female hormone 17ß-oestradiol apparently playing a central role. Studying women with postmenopausal hormone therapy and COVID-19 disease is an additional approach to gain more data to understand oestradiol effects on disease progression. A study from Wuhan has shown that women with low oestradiol levels had more severe infection with COVID-19 (2). Serum 17ß-oestradiol levels are naturally low in men and postmenopausal women. It is noteworthy that there are a variety of mechanisms by which 17ß-oestradiol could impact on outcomes of SARS-CoV-2 infection. It is a potent immune modulator, with both the innate and adaptive immune systems affected, usually but not always in a favorable manner. Within the whole human genome, the X-chromosome contains the largest number of immune-related genes (3), and women possess two of these chromosomes vs. one in men, giving women a theoretical advantage by the phenomenon of X gene escape of the second X chromosome regularly inhibited in function. There are well-documented sex differences in immune responsiveness (4), with women generally mounting better responses when compared to men. Oestrogen is also known to possess/exert non-immune based antiviral activity. It is also conceivable that 17ß-oestradiol also exerts beneficial effects in women via its protection against coagulopathies (5, 6). Hypercoagulability with fibrin formation and polymerization leads to severe COVID-19 disease with thromboembolism and poorer outcomes, especially in men. Last but by no means least, the cardiovascular beneficial effects of oestradiol could also play a central role. The regulation and expression of the angiotensin converting enzyme 2 (ACE2) is the key for this special coronavirus SARS-CoV-2 to enter the cell. Thus, there are strong indications that the dominant female hormone oestrogen is a key player in the protection of women against COVID-19, which are evident from the epidemiological data. Exploring the potential role of oestradiol when used in postmenopausal hormone therapy with more than 50% reduction in mortality in women 50+ with hormone therapy compared to women 50+ without is an interesting starting point to discuss potential mechanisms.

REVIEW METHODOLOGY

In this narrative review, we aim to present key concepts and knowledge gaps identified by the authors on the effects of oestrogen associated with SARS-CoV2 infection and COVID-19 disease. This review includes a selection of the most recent literature, focused on sex and gender differences of SARS-CoV2 incidence and COVID-19 mortality. Based on the existing knowledge, we present a hypothesis on the biological mechanisms that might explain the sex differences known from epidemiological datasets.

Epidemiology—SARS-COV-2 Infection and COVID-19 Mortality

Epidemiology data on sex differences on severity and mortality in patients with COVID-19 were published by several scientists with almost the same results. For example, Yanez at al. analyzed data for confirmed cases and death from 16 countries and showed drastically increased mortality rates $\geq$65 years of age with 1.77-fold higher mortality rate in men than in women. (7) A meta-analysis of 58 studies showed men with a 1.57-fold higher odds ratio for mortality and a 1.65-fold higher for severe infection than women (8). Recently Sha et al. confirmed again that mortality of women is lower than in men but noticed no-difference in in-hospital mortality in women < 55 years of age compared with the same age men (9). Beside several limitations of this study like retrospective, exploratory, no measurement of oestrogen level and no information of the history of hormone therapy, they opened the discussion whether an association of oestradiol and mortality in COVID-19 disease exists.

Pro arguments for the lower mortality of women are the oestrogen-mediated low inflammatory response and the gender-related arguments which result in a higher mortality rate in older men than in women like lifestyle, dyslipidaemia, more chronic diseases, and lower lymphocytes. Moreover, our group provided a retrospective analysis of a TriNetX Real-World database contributing the hypothesis of a positive effect of oestradiol to the outcome of COVID-19 disease. The analysis of electronic health records of 68,466 COVID-19 positive patients from 17 countries showed, among other results, a significantly decreased fatality rate of postmenopausal women 50+ with regularly taking hormone therapy with 17ß-oestradiol vs. postmenopausal women without therapy. (1) This effect on fatality rate could not be confirmed for premenopausal women with oral contraceptives vs. non-users. The main result in this premenopausal age group was the 15% higher incidence of SARS-Cov2 infection in women than in men. Similar results for the incidence and the fatality rate are shown by the daily updated statistics published by the Robert Koch Institute (RKI) for Germany, the government's central scientific institution in the field of biomedicine (**Figures 1**, **2**).

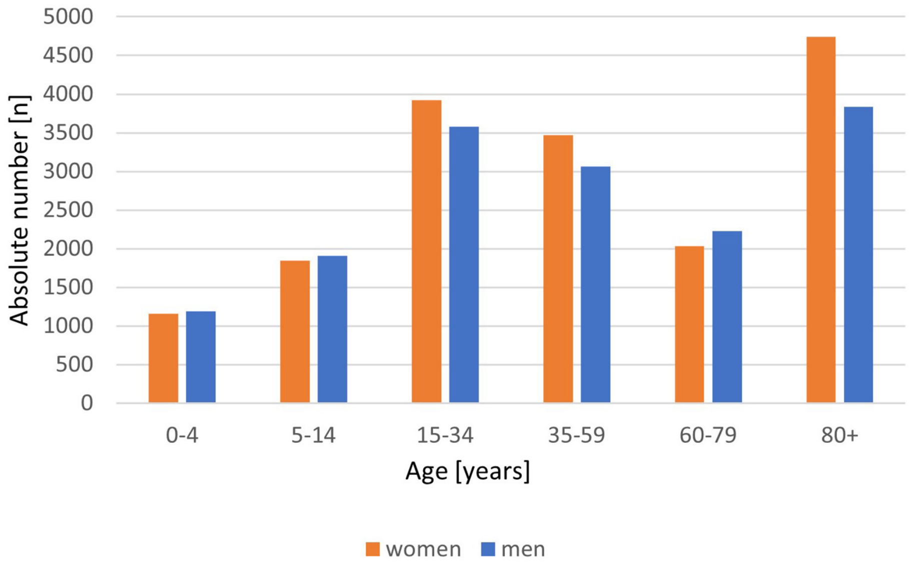

FIGURE 1 | COVID-19 cases by age group and sex/100.000 inhabitants. Absolute number/100.000 inhabitants with COVID-19, disaggregated by women (red) and men (blue). From Robert Koch-Institute/Germany: COVID-19-Dashboard. (retrieved on March 8, 2021).

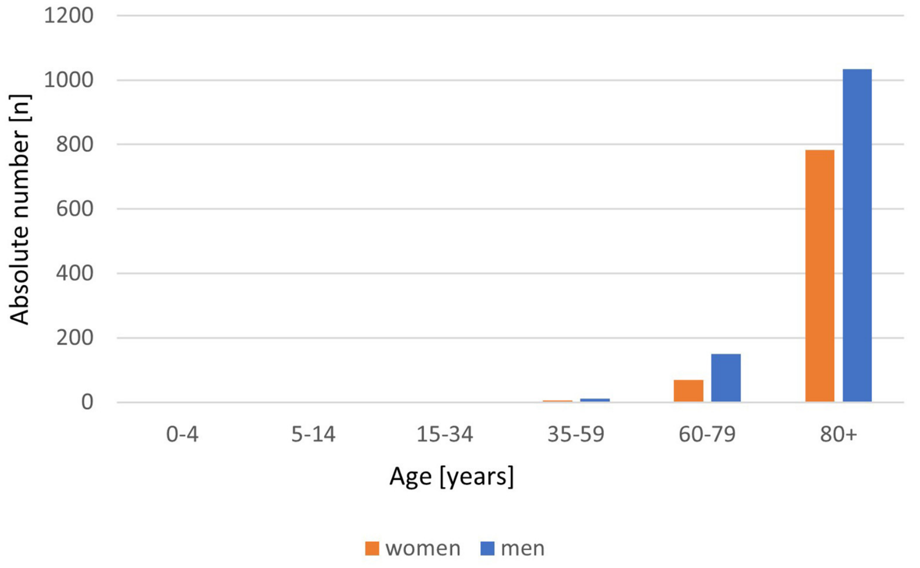

FIGURE 2 | COVID-19 deaths by age group and sex/100.000 inhabitants. Absolute number/100.000 inhabitants of COVID-19 deaths, disaggregated by women (red) and men (blue). From Robert Koch-Institute/Germany: COVID-19-Dashboard. (retrieved on March 8, 2021).

Behavior and Lifestyle—Impact on Gender Differences in COVID-19 Outcomes

For a highly contagious infectious disease such as COVID-19, it is teleologically sound to suppose that behavior and lifestyle could influence outcomes. It has been suggested that male behavior patterns with a tendency to go out into more crowded places such as pubs, a higher use of public transport to access workplaces, and the fact that men tend to wash their hands less frequently than women following high risk exposure (10) would increase their exposure and therefore the incidence of infection. However, evidence shows that women have a 15% higher infection rate than men (1). More studies are needed because possible explanations/mechanisms to explain the different risk profiles between men and women are not fully understood or generalisable. We speculate, admittedly without rigorous research evidence, that during lockdown there might be gender differences in employment patterns that result in more men than women being able to work from home rather than having to go into the office.

It is generally the case that men have jobs that are better paid and have greater flexibility to allow working from home. The burden of parenting responsibilities often falls to women, increasing their exposure if they have to bring their children to the kindergarten and school and then use public transport to attend their places of work. Exposure to infection does not explain the sex differences in morbidity and mortality. However, generally women tend to make healthier lifestyle choices than men: women tend to smoke and drink less than men (11, 12), and consequently often have a lower burden of chronic lung disease or are later in life exposed to cardiovascular disease—that appear to increase mortality risk in COVID-19 patients (13). The challenge is in determining the relative contributions of lifestyle vs. biological factors, and the likelihood is that there is an interplay between the two. This information will only be available if it is possible to use both methodical instruments to collect the facts in parallel in a study, both the measurement of the sex differences due to biological factors and the measurement of the sociocultural influencing gender factors at the same time.

Physiology—Why Oestrogen Matters

Oestradiol and ACE activity—a possible mechanism for increased COVID-19 infection in women vs. men.

Both the circulating and the tissue renin angiotensin aldosterone system (RAAS) play a crucial role in the regulation of kidney, cardiac and vascular physiology. Activation of angiotensin II (Ang II) by angiotensin converting enzyme (ACE) activity and binding to the angiotensin II receptor type I (AT1R) leads to harmful effects such as tissue remodeling, endothelial dysfunction and fibrosis in target organs. Cardiovascular diseases such as hypertension and heart failure are associated with an activated RAAS.

Due to higher 17ß-oestradiol levels another signaling pathway of Ang II via the angiotensin II receptor type II (AT2R) and the Mas receptor is more dominant in women. 17β-oestradiol increases expression level and activity of angiotensin converting enzyme-2 (ACE2) (14). ACE2 cleaves Ang II to Ang 1-7, the substrate for AT2- and Mas receptor. This pathway leads to protective effects on the heart, lung, kidneys, central nervous system and gut (14) (**Figure 3**). The classical ACE–Ang II–AT1R regulatory axis and the ACE2–Ang 1-7–MasR/AT2R signaling pathway counter-regulate one another. These organ-protective effects of 17β-oestradiol are anti-fibrotic, antioxidant, anti-hypertrophic and vascular dilation effects (14).

ACE2 and the transmembrane protease, serine 2 (TMPRSS2) enzyme, play an essential role in viral entry into host cells and serve as the principal entry receptor for SARS-CoV-2 (15). The membrane-tethered ACE2 protein has an amino-2 terminal catalytic domain (a peptidase) that faces the extracellular space. This protein is expressed in numerous tissues, including the nasal-, respiratory-, intestine-, vascular epithelial cells, kidneys and ovaries. This broad tissue expression of ACE2 enables SARS-CoV-2 to infect nasal endothelial cells and spread to all tissues with ACE2 expression, especially the pharynx and the lung. Cells in the neighborhood of infected cell zones try to protect themselves by changes of intracellular protein expression. However often not for the advantage of the cell in terms of its actual function. Moreover, oestrogens binding to the oestrogen receptor alpha (ERalpha) increase TMPRSS2 expression. In men expression of TMPRSS2 would be associated with the activity of the androgen receptor, which may lead to high expression of TMPRSS2 (16). Another reason for sex differences in addition to the positive effect of 17ß-oestradiol on ACE2 protein expression is the fact that ACE2 and AT2R both being located on the X-chromosome. This results in women to be heterozygous which is clearly different to men, who are hemizygous (17). The second X-chromosome is not inactivated in approximately 15% of genes and another 15% of genes vary in whether they are subject to, or escape from, inactivation (18). This may account for some of the differences that are seen between men and women (sexual dimorphism) and could be a reason for higher expression levels of ACE2- and AT2R proteins in women (i.e., a gene dosage effect).

However, our understanding of the sex-related differences in ACE2 expression in tissues and its levels in plasma is limited, and most of it is based on animal models. Recently, it has been shown that the oestrogen-mediated up-regulation of the Mas-receptor contributes to the prevention of acute lung injury and also improves endothelial barrier stabilization (19). In experimental animal models of acute lung injury from SARS-CoV-2, females have been shown to have some protection compared to males which is likely to be due to the beneficial effects of oestradiol (20); Interestingly, this protection was lost in ovariectomized mice and restored upon oestrogen replacement (21). The 17β-oestradiol molecule has been shown to attenuate lung vascular permeability and oedema, and oestrogen has been shown to reduce the pulmonary vasoconstriction during hypoxia by increasing levels of both prostacyclin and nitric oxide (NO) (22).

Taking all facts presented, the levels of cell-surface–exposed ACE2 generally will be higher in premenopausal women than age matched men and postmenopausal women. Conflicting results were published as well, however, not in cardiovascular health conditions but in animal models or human studies with cardiovascular disease cohorts like higher level of cardiac ACE2 activity in male spontaneously hypertensive rats (SHR) than in female SHR (23).

Oestrogen and Direct Antiviral Effects

There is accumulating evidence that oestrogen exhibits antiviral activity that is out-with the innate and adaptive immune systems. In an elegant study of transvaginal infection of the simian immunodeficiency virus using ovariectomised macaques, Smith et al. (24) compared the influence of oestrogen vs. progesterone vs. no treatment. None of the oestrogen-treated macaques became infected, while 100% of the untreated and 85% of the progesterone treated became infected following transvaginal inoculation of virus. The researchers were further able to demonstrate that the oestrogen exerted its blocking effect at the level of the vaginal epithelium and/or lumen, since oestrogen-treated macaques became infected following subepithelial inoculation of virus. Johansen et al. have sought to establish if other oestrogen-related drugs could exhibit antiviral activity. Using molecular probes, the team identified a set of selective oestrogen receptor modulators (SERMS)—including clomiphene and toremifene—which acted as potent inhibitors of infection with the Zaire ebolavirus in an *in-vivo* mouse infection model (25). These two SERMS do not appear to

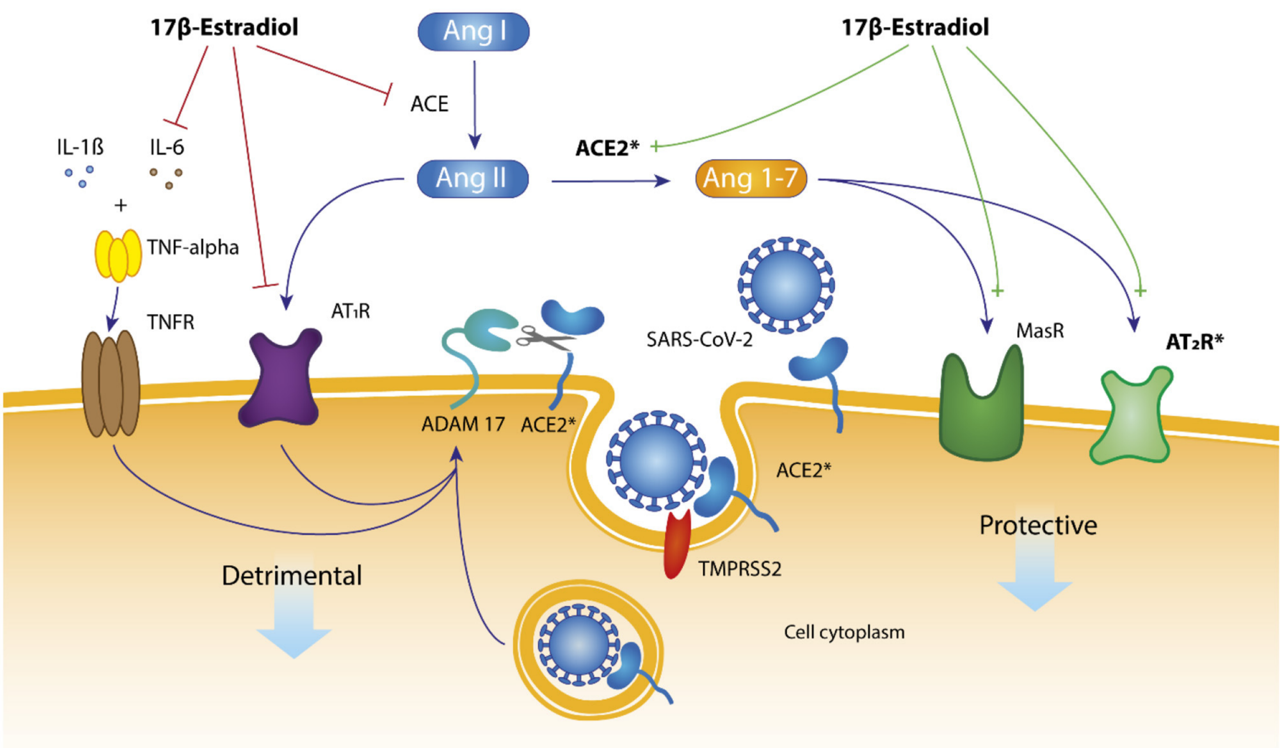

FIGURE 3 | RAAS—Effects of oestradiol on renin-angiotensin-aldosterone system. Hypothesis: mechanistic pathways for the presumably role of 17β-oestradiol for SARS-CoV-2 infection in women. 17ß-oestradiol enhances ACE2 activity. ACE2 cleaves Ang II to Ang1-7 binding to Mas- and AT2 receptor with downstream protective effects for the cell. The membrane-tethered ACE2 protein has an amino- terminal catalytic domain that faces the extracellular space. In case of SARS-CoV-2 infection and endocytosis of ACE2/SARSCoV-2, the metalloproteinase ADAM-17 cleaves membrane bound ACE2 protein followed by downregulation of ACE2 expression at the surface of the cell. The cell thus protects itself against the penetration of further virus particles. Another effect of 17β-oestradiol is the inhibition of IL-6 (interleukin-6) and tumor necrosis factor-α (TNF-alpha) activity followed by less detrimental effects to the cell. *ACE2 and AT2R are located on the X chromosome.

inhibit infection through classical pathways associated with the oestrogen receptor, since inhibition occurred even in the absence of detectable oestrogen receptor expression, and both inhibited virus entry after internalization. Instead, the response appeared to be an off-target effect where the compounds interfered with a step late in viral entry and triggering of fusion. In further studies of the mechanism underpinning the antiviral actions of the SERMS, one team of researchers established that the same dosages of SERMs which induced cholesterol accumulation (an incidental biological activity of SERMS) also inhibited Ebola infection. The hypothesis is that SERMs reduced the cellular sphingosine and subsequently caused endolysosomal calcium accumulation, which in turn led to blocking the Ebola virus entry (26). It is a fascinating concept that the simple and innocuous hormone oestrogen could exhibit direct vital antiviral actions that could impact on outcomes in pandemic-prone viruses. This area should be one of intense research activity.

Oestradiol Effect on Innate and Adaptive Immunity

It is well-established that there are differences between sexes in immune responses to infection, with females having better innate and adaptive immune response than males. Sex specific differences are resulting from genetic differences and changing sex steroid hormone levels especially during the menopause transition. Oestrogens regulate both the innate and adaptive response. It can modulate the differentiation, genetic programming and lifespan of all immune cells including neutrophils, macrophages, dendritic cells, and natural killer cells as there are oestrogen receptors (ER) on all these cells (27). The effects of oestrogens on the innate immune responses that are mediated by monocytes and macrophages are largely repressive (28). 17β-oestradiol and its effect on immunocompetence shown **Figure 4** (29).

Thinking about sex differences in mortality between women and men with COVID-19, it is important to know, that symptoms will be more severe when the innate and adaptive immune response are strong. That means, for optimal immunological homeostasis to be achieved, the pathogen needs to be removed with high efficiency whilst avoiding collateral tissue damage in the host (30). This immunological balance is known to be different between women and men. Once the immune system is unbalanced in men, it is much harder to return immune response to normal compared to women. We know this phenomenon from other diseases as well, such as glomerulonephritis. Women are known to be able to mount stronger immune responses against viruses and against vaccines. However, they also can exhibit adequate immune-mediated tissue repair capacities (31).

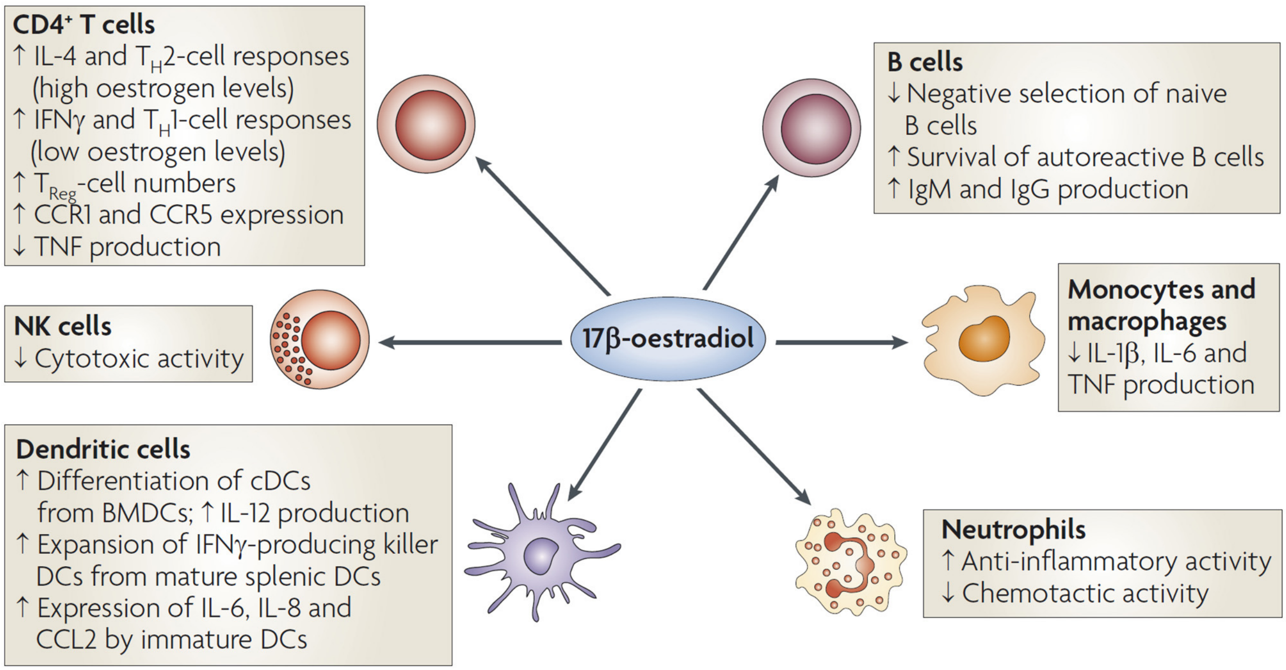

FIGURE 4 | Oestradiol and its effect on immune cells. The activation of oestrogen receptors expressed by T cells, B cells, dendritic cells (DCs), macrophages, neutrophils, and natural killer (NK) cells influences immunocompetence. Low levels of 17β-oestradiol promote TH1-cell differentiation and higher levels promote TH2-cell polarization, with consequent effects on the production of cytokines. Oestrogen decreases tumor-necrosis factor (TNF) production by CD4+ T cells. Oestrogen enhances polyclonal B-cell activation and immunoglobulin production. The inhibition of CD16 expression by oestrogen in monocytes and macrophages leads to the reduced production of the pro-inflammatory cytokines interleukin-1 (IL-1β), IL-6 and TNF. Oestrogen also reduces the cytotoxicity of NK cells (29).

To understand the epidemiological data regarding the discrepancy between the higher incidence of SARS-CoV-2 infections in premenopausal women, and the high fatality rate of men of all ages compared to women, it is important to understand the immune response. Oestradiol has a key role here because it has the ability to reduce the cytokine storm required at the beginning of the infection and to inhibit the cytotoxic NK cells. 17β-oestradiol regulates the production of numerous cytokines and inhibits interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha production. Therefore, 17ß-oestradiol has the potential to attenuate this strong cytokine release which underlies much of the cellular and organ/tissue damage by COVID-19 infection (32).

Past studies have demonstrated that sex has a significant impact on the outcome of infections and has been associated with underlying differences in immune response to infection (33, 34). Previous coronavirus studies (SARS-coronavirus infection) in mice have shown that the female sex hormone oestrogen protected against fatality and lung inflammation. Mice who underwent oophorectomies had more severe disease with more lung inflammation and increased mortality (35). A recent study has linked higher mortality among men to a "cytokine storm," which in turn closely relates to the severity of symptoms such as pulmonary oedema, fibrosis and other deleterious downstream effects associated with acute lung injury (36). An individual's immune response to viral infections can vary with fluctuations in sex hormone concentrations—oestrogens, progesterone, and testosterone.

Oestrogens at levels of ovulatory phase or pregnancy suppress cytotoxicity of NK cells (37). Notably, macrophages treated *in vitro* with oestradiol showed decreased secretion of the proinflammatory cytokines IL-1β, IL-6, and tumor necrosis factor (TNF)-α (38).

This protective effect, mediated primarily by oestrogen, is attenuated in postmenopausal women. The menopause has a distinct impact on the immune system in women. Postmenopausal women exhibit a reduced number of total lymphocytes, mainly B and CD4+ T lymphocytes (39). Low levels of 17ß-oestradiol can augment inflammatory mediators which could explain the proinflammatory states that most postmenopausal women suffer from (e.g., atherosclerosis) (40). Post-menopausal women are reported to have higher levels of proinflammatory cytokines, such as IL-1β, IL-6, IL-10 and TNF-α (41–44).

However, these levels are reduced with the use of menopause hormone therapy which leads to pre-menopausal levels of oestradiol (45).

Oestradiol and Long Covid

In women who develop COVID-19, being post-menopausal has been independently associated with more severe infection (46, 47). These effects may be more profound/common in women who are reaching the end of their reproductive life when ovarian function may be more susceptible to viral insult, that is, during the perimenopause and menopause.

The largest group of patients with Long Covid is women in their early 50s. Considering the mounting evidence of interaction between reproductive hormones and COVID-19, the symptoms of Long Covid may be due to the disturbance of physiological ovarian steroid hormone production following COVID-19 and/or an altered chronic inflammatory response due to sex-based immunomodulation during and after the acute infection.

There is evidence that the RAAS is involved in female reproductive processes such as folliculogenesis, steroidogenesis, oocyte maturation and ovulation. Research has confirmed the existence of an Ang-(1–7)–Mas receptor–ACE2 axis and ACE2 markers in all stages of follicle maturation in the human ovary (48).

ACE2 is widely expressed in the ovary and so many patients with Long Covid are experiencing changes in their periods or even their periods stopping is likely to be related. Many of the symptoms such as fatigue, headaches, dizziness, poor concentration, brain fog and memory problems are likely to be a direct consequence of low hormone (oestrogen and testosterone) levels in women.

An online survey of 793 women with Long Covid found that 74% of women reported that their periods have changed since having symptoms of COVID-19. Furthermore, 80% of women reported that their symptoms of Long Covid changed in relation to their menstrual cycle with 78% of women reporting their symptoms being worse prior to or during their periods, when hormone levels are at their lowest (data not published yet).

It is important that there should be greater inclusion of people with Long Covid in clinical trials for potential COVID-19 treatments, including early interventions in the acute phase to prevent long-term complications, and there is a need for more long-term cohort studies of Long Covid (49).

These symptoms are likely to be related to low female hormone levels so consideration should be given as a priority to replacing these low hormone levels with the right dose and type of MHT.

Treatment Option With Menopause Hormone Therapy in COVID-19 Infection

The menopausal transition provides a unique natural experimental model where the impact of oestrogen on outcomes of COVID-19 infection can be studied, since there is a profound change in the hormonal milieu from the reproductive phase to the menopause. Oestrogen being the dominant hormone that diminishes in the menopause, the experimental design is obvious as this hormone can be administered as HT and its impact on COVID-19 infections studies. With all the evidence presented above pointing to a central role for oestrogen in immune and non-immune response to viral infections, it should not surprise that in women who develop COVID-19, being post-menopausal has been independently associated with more severe infection (46, 47). The largest group of patients with Long Covid (fatigue as the main symptom and physical exhaustion after short period of physical activity) is women in their early 50s, and the symptom profile in these women strongly points to a profound disturbance of physiological ovarian steroid hormone function. Our retrospective analysis of electronic health records of 68,466 COVID-19 positive patients has shown that women taking menopause hormone therapy (MHT) were more than 50% less likely to die from COVID-19 compared to women not taking MHT. This was statistically significant with a Hazard Ratio of 0.29 (95%CI 0.11; 0.76) (1).

A recent UK retrospective cohort study used women with COVID-19 from primary care records found that MHT was associated with a significantly lower likelihood of all-cause mortality in COVID-19 (adjusted OR 0.22, 95%CI 0.05 to 0.94) (50). In addition, there were no reported events for all-cause mortality in women prescribed a combined oral contraceptive pill. The researchers ran multivariable models adjusting for age, ethnicity, index of multiple deprivation, household size, BMI, and comorbidities. They also observed that all-cause mortality risk was higher in COVID-19 amongst women who were older, underweight, from larger households, with hypertension, or on immunosuppressants which is compatible with other studies (50).

We have clear, evidence-based guidelines including from NICE—Menopause: diagnosis and management and from International Menopause Society. Women should be given MHT in the appropriate dose, duration, regimen, and route of administration to improve their symptoms and their future health (51). There is now robust evidence demonstrating that transdermal oestrogen (17-β oestradiol) in association with natural micronized progesterone represents the optimal MHT regimen (52). Transdermal oestrogen is the preferred route of administration because, in contrast with oral oestrogen, oestrogen as a patch, gel or spray is not associated with an increased risk of venous thromboembolism (53). The optimal progestogen is micronized progesterone which is body identical. There is no clot risk with this compared with the older progestogens. In addition, there is no increased risk of breast cancer for at least the first 5 years of taking 17-β oestradiol with micronized progesterone (54, 55).

CONCLUDING REMARKS

The sex and gender differences in favor of women in the morbidity and mortality from COVID-19 infection is well-established, while the underlying mechanisms are open to speculation. The challenge is in determining the relative contributions of lifestyle vs. biological factors, and the likelihood is that there is an interplay between the two. However, the fundamental difference between the two sexes is the hormonal milieu, with oestradiol being the dominant discriminating factor in this regard. This hormone is known to modulate a variety of body functions such as the immune system, viral entry receptors, as well as exhibiting direct antiviral activity, all additively pointing to a crucial role for oestrogen conferring advantages to women in the COVID-19 pandemic. Prospective studies are needed to confirm the positive effect of sex hormone therapy on mortality in postmenopausal women.

AUTHOR CONTRIBUTIONS

US wrote the manuscript and designed the figure about mechanistic pathways. LN, IM, RL, RP, and SP helped write the manuscript and added references. All authors read and approved the final version of the manuscript.

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Opinion Review of Socioeconomic Impact of COVID-2019 on Women's Health

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The global battle to survive the onslaughts of the Coronavirus Disease 2019 (COVID-19) started in December 2019 and continues today. Women and girls have borne the brunt of the hardship resulting from the health crises. This paper examined the effects of COVID-19 on women. Socioeconomic factors resulting from the pandemic, especially in relation to women's health, were discussed after studying published articles. They include gender specificity and COVID-19, the economic toll of COVID-19 on women, pregnancy and COVID-19, gender-based violence due to COVID-19, and health-care impacts of COVID-19. Making up the majority in the healthcare workforce, women were at higher risk of infection with COVID-19 due to their exposure as caregivers to infected patients. The pandemic took its toll on them as part of the greater population in the informal sector of the economy due to the lockdown directive, as many experienced severe monetary shortages and job losses. Pregnant women infected with COVID-19 were prone to severe diseases, maternal complications, and death due to their weakened immunity and exposure during clinical procedures. Gender-based violence was observed to have increased across the globe for women. The results of this review strongly indicate that women are disproportionately affected by the ongoing COVID-19 health crisis. This review will help health-care professionals and policymakers arrive at properly-thought-through decisions to better manage health crises. Governments and all key players should address the challenge by devising effective policies with a gendered view.

Keywords: SARS-CoV2, COVID-19, women's health, socio-economic status, coronavirus

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2), also called COVID-19, is a new coronavirus infection identified in December 2019 originating from Wuhan, China (1). Since its outbreak, it has spread to more than 220 countries in the world with rising cases of fatality. Some regions have overcome the third wave of the crisis and are facing the start of a fourth (2). As of February 1, 2021, 13:00 GMT, the weekly update of the World Health Organization reports that there have been over 100 million confirmed cases with more than two million confirmed deaths globally (3). This disease has initiated a fast-growing global crisis that has taken researchers and policymakers without notice, thus leaving them scrambling to collect and analyze data so that its true impact on affected countries can be grasped (4).

As the world begins vaccination to manage the COVID-19 pandemic, preventive measures have been advocated, including physical distancing. The current pandemic and the imposed physical/social distancing policy are emphasizing health inequalities based on gender, socioeconomic status, and race (5–9), thereby highlighting the discrimination of other marginalized groups, such as internally displaced people, those in extreme poverty, people with disabilities, migrants, and the refugees whose majority are women and children (10). The gendered effect of COVID-19 on women presents a huge challenge that cannot be ignored. Deliberations about the health effects of COVID-19 should include unique conditions that make women more at risk (11).

In this review, research findings from publications retrieved online were used to highlight some health and socioeconomic challenges due to the COVID-19 pandemic that are particular to women. The discussion was based on COVID-19 in relation to five key factors: (1) gender specificity (is COVID-19 neutral to men and women?), (2) economic toll (has COVID-19 affected the economic life of women?), (3) pregnancy (does COVID-19 affect pregnant women more than non-pregnant women?), (4) gender-based violence (has COVID-19 affected the rate of gender-based violence?), and (5) health care (how have women fared in accessing sexual and reproductive health care during the COVID-19 pandemic?). If the items discussed in this paper are properly taken into consideration, the likelihood of future health crises would be better managed.

METHODS

The study employed a literature search of majorly published journal articles written in English from electronic databases such as ScienceDirect, PubMed, and Google Scholar. Information from the World Health Organization and the United Nations Women databases was also accessed. The literature search was performed by all authors listed on the paper between July 15, 2020, and February 3, 2021. Articles were searched using the following keywords: women; COVID-19; impacts of COVID-19 or effects of COVID-19; economic impacts of COVID-19; social effects of COVID-19; health impacts of COVID-19; COVID-19 pandemic; SARS Cov-2; and Coronavirus.

Population

Females in this article refer to women and girls. The ages of the females who participated in the studies included in this review ranged from 13 years old and above.

Selection Criteria

Reports and full-text articles related to the health, social, and economic impacts of COVID-19 on women were selected. The study excluded reports and articles that excluded the impacts/effects of COVID-19 on women, articles not written in English, as well as information derived from blogs and other unverifiable sources.

RESULT AND DISCUSSION

A total of 1,518 records were identified based on selection criteria of key search words: 1,006 from the databases searched and 512 from other sources. After screening to remove articles that did not capture the context of interest, duplicates, and articles not written in the English Language, a total of 291 articles were selected. Of the 291 selected articles, 266 were not suitable because they were misleading in context and were thus excluded. The remaining 25 selected articles were then included for analysis.

Gender Specificity and COVID-19

Gender is a path upon which the COVID-19 pandemic is widening health inequalities (11). Years before this pandemic, women typically reported more physically unhealthy days than men even though they used more preventive care services (12). Women have poorer results for widespread diseases such as myocardial infarction (13), asthma (12), and diabetes (14). This health discrimination is aggravated for women of low socioeconomic status, older age, physical disability, lower education, residence in rural geographic locations, and those who are not white (11). In a recent web-based survey of 780,961 participants from 183 countries, a major risk association for infection with COVID-19 was observed for people who were of the female gender, aged above 60 years, and those who had preexisting disease conditions, such as heart disease, kidney disease, diabetes, and liver disease (15). Women are at greater risk of mental health challenges and exhibit more psychological distress than men (16). Based on the available literature, COVID-19 health crises will likely distress women mentally to a higher degree (16). In a study on mood, empathy, and sleep quality during the isolation period due to COVID-19 in Canada, the authors discovered that women suffered more due to trauma symptoms, depression, and increased anxiety (17). Many health-care staff members could develop posttraumatic stress disorder due to burnout, depression, and anxiety during and after the pandemic, and this is another factor supporting the weightier impact of the pandemic on women (18).

COVID-19 does not discriminate against gender (male or female), health status (healthy or immuno-compromised), or age (although infection in children is less common, most affected adults are between 25 and 89 years old) (19, 20). Initial reports indicated that men were at greater risk of severe disease and death from COVID-19 infection compared with women (7, 21, 22). Researchers warned that those early investigations were to be treated with caution because they are incomplete and inconsistent across countries (23, 24). Current statistics of sex-disintegrated data (which is presently incomplete) show that more women test positive for COVID-19 compared to men (25). Recognizing the direct and indirect effects of the disease on women will assist in providing effective responses for similar health crises in the future (26).

Across the globe, about 70% of health-care workers (doctors, nurses, midwives, community health workers, cleaners, caterers, and launderers) are women, of which 80% are nurses in most countries. These women are particularly at risk of infection through contact with sick patients (23). Factors associated with fatalities of patients with COVID-19 include older age, obesity, diabetes mellitus, hypertension, and cardiovascular diseases (27).

The Economic Toll of COVID-19 on Women

Although physical distancing slows down the transmission of COVID-19, the advantage of this measure needs to be balanced with its effects on the informal sector of the economy (8). The implementation of the lockdown measure in developing countries (particularly in Africa where poverty, weak health-care systems, and overcrowding exists) has taken its toll on all (especially women) (8). Many women in the non-formal sector have limited access to social security, and, as such, widespread job losses will have a long-term impact on their economic independence and security (4).

An estimated 740 million women are employed in the informal sector of the economy, which includes tourism, hospitality, and retail. In developing countries, this workforce constitutes more than two-thirds of women. To make a living, they rely on open public space, which is at present being limited to curb the spread of the virus. Therefore, severe monetary shortfalls are very much felt by these women who earn less, save less, and hold more insecure jobs compared to their male counterparts (7, 28).

COVID-19 and the restrictions put in place to curtail its spread have interrupted markets and businesses and many have lost their means of living (29). In April 2020, The International Labour Organization (ILO) projected that lockdown will distress about 3 billion employees (81% of the global labor force) and that the COVID-19 pandemic could cost between 5 million and 25 million jobs (7). Recently, the ILO posits that estimations of revenue losses from labor show a global decline of 10.7% during the first three quarters of 2020 compared with the corresponding period in 2019, which amounts to 3.5 trillion United States dollars (5.5% global gross domestic product) (30). The International Monetary Fund projected a major shrinkage of global output in 2020 (31).

According to Clare Wenham, assistant professor of Global Health Policy, London School of Economics and Political Science, the economic toll the COVID-19 pandemic has on women is an indirect consequence, coming not from being infected but from being affected (28). Despite a major limitation from the fact that not all countries provide sex-disaggregated data, a clear trend of the pandemic's indirect effect on women has appeared (28). Women have less access to social protection, and most single-parent households are women. The capability of women to absorb economic shocks is less than that of men (28). The Institute for Fiscal Studies found that women in the United Kingdom were 1.5 times more likely than men to have either quit their job or lost it during the lockdown (28). As countries experienced lockdown, jobs were lost with disastrous consequences on the holders.

The care burden on women has increased due to the imposed lockdown—care for the sick and elderly, care for children forced to stay at home because their schools have been ordered to stop, and care for other family members who are all locked down at home. Consequently, during the pandemic, women are the leading participators in an unnoticed economy as unpaid caregivers in the family. This unnoticed economy has actual consequences on the economy and lives of women. It is strongly recommended that governments offer inclusive social security for all caregivers to lessen the burden on unpaid care workers (7, 32).

Pregnancy and COVID-19

Several studies have been conducted, and they unanimously agree that pregnant women could be more prone to contracting COVID-19 due to their weakened immune systems (33–35). Pregnant women who are infected with the COVID-19 virus are at more risk of serious diseases and greater risk of being hospitalized, subjected to mechanical ventilation, and being admitted to the intensive care unit compared with non-pregnant women with COVID-19 (36). This observed susceptibility in pregnant women is probably partly due to exposure risk from clinical settings and practices as well as the physiological changes that occur in pregnancy (11). In infected pregnant women, there is no proof of vertical transmission of the virus to the unborn child; however, there are higher incidences of preterm deliveries (37, 38). Furthermore, several authors reported severe maternal complications related to pregnant women with COVID-19 (39–41) and even deaths (42, 43). After systematically reviewing 19 studies of pregnant women with severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), or COVID-19, Di-Mascio and his fellow researchers revealed that infected pregnant women had more cases of Cesarean delivery, preeclampsia, preterm birth, and maternal death (34, 35, 44, 45).

Data on COVID-19 infections in pregnancy have been mainly from North America and Europe. Early confirmation from low and middle-income countries such as Nepal and Uganda shows that though the rate of infection is not high among the population, imposed restrictions due to the pandemic are distressing maternal-child outcomes, showing a severe drop in maternal facility births (up to 50% in Nepal) and amplified neonatal and maternal morbidity (46, 47).

Gender-Based Violence Due to COVID-19

Crises (natural disasters, war, or epidemics) accentuate incidences of gender-based violence against women (48, 49). This was the trend during the Ebola (2014) and Zika (2016) outbreaks (50). The existing challenge of physical abuse against women will expectedly worsen with COVID-19. Developing data indicate that since the pandemic broke out, domestic and sexual violence have risen in many regions and will likely escalate (51–53). As health, security, and financial challenges cause tension and strain in families, confinement because of the lockdown directive intensifies this pressure and makes people (particularly men, angered and frustrated by their lack of money) more prone to domestic violence toward their female partners (54–56). Some of the risk factors underlying gender-based violence include the narrowness of accommodation due to overcrowding, social isolation, fear of dying, low income, reduced access to services, decreased peer support, increased consumption of addictive substances, and male aggression (7, 51, 57–60). Since the implementation of the lockdown by governments around the world, many countries have observed an upsurge in cases of gender-based violence. Government authorities, civil society groups, and women's rights activists have indicated rising cases of gender-based violence across the globe (51, 52). The Refuge website has equally reported that calls about gender-based violence have increased by 150% (61). Intimate partner violence was reported to have increased by 30% in France and Cyprus, 33% in Singapore, and 25% in Argentina (53). Different states in the US also reported an intimate partner violence increase of 21–35% (62). Increased gender-based violence and demand for emergency shelter were also reported in Spain, Canada, Germany, and UK (53). In Nigeria, with the initial lockdown of three major states—Lagos, Ogun, and the Federal Capital Territory—throughout April 2020, gender-based violence significantly increased by 56% (49). During the first 2 weeks of lockdown, gender-based violence cases rose from 346 to 794 (40).

Health-care services are currently inundated with COVID-19 cases. In places where basic vital services are sustained, a breakdown in harmonized response from important sectors such as health, justice, police, and social services coupled with the physical/social distancing measure implies that sectors will be limited to provide satisfactory care to women who are suffering violence (7). That is to say, though shelters are available for women experiencing violence to take refuge, the lockdown order has compelled bodies such as judicial courts (in which the legal advocacy work for these victims are to be conducted) to close (11). Health-care services and police that are first-line responders are hardly available as they are overwhelmed too (48).

Due to the existing gender digital divide (62, 63), women in several nations, particularly those facing many forms of inequity, might be unable to access help services by cell phone or internet (owing to the lack of it). Even if these women have access to these means, they might be unable to use them because they are being closely watched by their perpetrators of violence. A Delhi-based NGO in India witnessed a 50% drop in calls on its helplines despite increased incidences of gender-based violence. This may have been due to the fear of getting discovered by their offenders (63, 64). As the use of online platforms has increased, women's rights experts and other bodies have reported an increase in varied forms of online violence against women, including bullying, stalking, sex-trolling, and sexual harassment (51, 53, 65).

The Ebola crisis with its resultant school closures showed that several forms of violence had worsened during the national health emergency, such as sexual exploitation and abuse of girls of reproductive age, child marriage, and trafficking (66, 67), and COVID-19 is following a comparable trend (68). The global cost of violence against women is bound to increase as gender-based violence increases during the pandemic and will sadly keep rising in the aftermath (7, 51).

Health-Care Impacts of COVID-19

Epidemics limit access to the healthcare system particularly preventive and reproductive health care (11). Evidence from previous health crises reveals that obstetric care is particularly compromised (11). During a widespread health crisis, such as COVID-19, the unique health needs of women are more unlikely to be met as access to satisfactory health services, reproductive and maternal health care, essential medicines, and vaccines are undermined. The availability of maternal health care with sexual and reproductive health services and gender-based violence-linked services is crucial to the health, welfare, and rights of women. When resources are diverted from these provisions/services, increased maternal mortality and morbidity are the result (7).

The upsurge in cases of COVID-19 is seriously hurting both the wealthiest and most sophisticated health systems. With the ongoing pandemic, honest fears arise about the survival capability of less-developed countries (with frail health systems) (7). From previous national health crises, the diversion of funds from important but less urgent health services, such as maternal care and gender-based violence response, to focus on the health emergency at hand is the advantageous approach, yet important services need not be completely abandoned even at such critical times (8, 11). Conceding the reproductive and sexual health of girls and women during the ongoing pandemic implies many will likely experience pregnancy. According to Guttmacher Institute modeling estimates, a reduction by 10% in short- and long-term use of contraceptives could result in more than 15 million unintended pregnancies across 132 low- and middle-income countries (69).

Limitations of the Study

The study was primarily based on published literature obtained from only three major databases. However, the non-systematic nature of the review represents a limitation in terms of the validity of the findings. Reports from unverifiable sources such as blog sites that were not documented in a verifiable source were not analyzed. The limited evidence for undeveloped/developing regions, or the general unawareness and even blackout regarding gender disparities and inequalities in COVID-19 crises were limitation factors in this study. Nevertheless, the strength of the study lies on the review of parameters that relate to women in the current COVID-19 health crisis. These included gender specificity, economic toll, pregnancy, gender-based violence, and the health-care impacts of COVID-19 on the health status of women around the globe.

CONCLUSION

This article has reviewed some parameters as it relates to women in the current COVID-19 health crisis. Women are at a higher risk of infection with the COVID-19 virus due to their exposure as caregivers. COVID-19-infected pregnant women are at greater risk of other severe diseases including hospitalizations. This is most likely due to the physiological changes and exposure risks during antenatal care and childbirth. More women than men work in the informal sector of the economy, which was the worst hit by the lockdown directive that followed the outbreak of the pandemic. Many women became pregnant during the lockdown as a result of not being able to go to their places of work. Couples spent more time together, and this led to pregnancies for even some who did not plan on getting pregnant (9). The unpaid care burden for the sick, elderly, children, and adults locked down at home fell disproportionately on women. The gender-based violence increased across the globe as physical distancing measures were taken to limit the spread of COVID-19. The unique healthcare needs of women, which include sexual and reproductive health care, maternal health care (antenatal and postnatal care), essential medicines, immunization, and gender-based violence-linked services should not be downplayed during health emergencies. The approach by key players to tackle the impacts of the COVID-19 pandemic will be inefficient if it does not have a gendered stance considering the peculiar needs of women. Governments should therefore provide social security to ease their burden.

Recommendations

Further research in the future is recommended to provide insight on how cultural and racial differences as well as other determinants of health (such as community, education, and the neighborhood) are impacting women during the COVID-19 pandemic. As useful data emerges with time, more investigations to understand the impact of COVID-19 pandemic on women's health across a broader geographic area (especially comparing more developed countries with those of the less developed countries) is imperative. Additional systematic studies to comprehend the overall effect of the COVID-19 pandemic on women's health is important to improve the wealth of scientific knowledge.

AUTHOR CONTRIBUTIONS

SO carried out the concept, design, and main interpretation of the study. VS, AC, SA, and UO conducted the electronic searches. VS drafted the manuscript and participated in the literature search and paper analysis. SO and VS critically reviewed and revised the manuscript for important intellectual content. UO participated in the proof editing. All authors made substantial, direct, and intellectual contributions to the work. The final version of the manuscript was read by all authors before giving their consent for its publication.

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Sleep Disruption and Depression, Stress and Anxiety Levels in Women With Polycystic Ovary Syndrome (PCOS) During the Lockdown Measures for COVID-19 in the UK

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Background: Lockdown measures have been enforced globally in response to the COVID-19 pandemic. Given the comorbidity burden in women with polycystic ovary syndrome (PCOS), these lockdown measures may have a particularly negative impact on sleep health, quality of life (QoL), and depression/stress levels in this population. The aim of this study was to explore whether such potential problems were present in women with PCOS during the COVID-19 lockdown in the UK.

Methods: UK women with PCOS were recruited through social media into a cross-sectional study during the COVID-19 lockdown. The study survey was delivered online, and included demographic and COVID-19 relevant questions, as well as validated questionnaires/scales, namely the Insomnia Severity Index (ISI), Depression Anxiety and Stress Scale (DASS-21), and PCOSQOL questionnaire.

Results: Three hundred and thirty-three women with PCOS [median age: 30.0 (9.0) years] were recruited. Participants were dichotomized based on responses regarding the impact of COVID-19 restrictions on their sleep [negative ($N = 242$) vs. no/positive ($N = 91$) impact]. No differences were noted between groups regarding age, time since PCOS diagnosis, body mass index, or number of comorbidities. Based on the ISI, 44.2% of participants reporting a negative impact on sleep exhibited at least moderately severe clinical insomnia. Compared to those who reported no/positive effect on sleep, the participants reporting a negative impact on sleep also reported poorer QoL, based on the total PCOSQOL score, with a greater impact of PCOS and poorer mood in the corresponding PCOSQOL domains. Based on the DASS-21, the latter also had statistically higher depression and stress levels compared to the former. Finally, for this cohort significant inverse correlations were noted between the ISI and PCOSQOL scores (total and domain scores), whilst the DASS-21 and ISI scores were positively correlated (all p-values <0.001).

Conclusion: The majority of recruited UK women with PCOS reported that the COVID-19 lockdown had a negative impact on their sleep, which was also associated with impaired QoL and higher depression/stress levels. Whilst further research is required, women with PCOS should be considered a vulnerable population that may experience an adverse impact on sleep, QoL and mental health well-being due to lockdown measures during the COVID-19 pandemic.

Keywords: polycystic ovary syndrome, COVID-19, lockdown, sleep, anxiety, depression, stress, quality of life

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), usually manifests as a respiratory tract infection with mild symptomatology (asymptomatic in many cases) (1–3). However, COVID-19 can also lead to severe manifestations in a proportion of high-risk individuals with respiratory and/or extra-pulmonary symptoms/complications requiring hospitalization (1–3). As the latter may require intensive care unit (ICU) support and may even be fatal, the COVID-19 pandemic has resulted in enforcement of varying degrees of nationwide lockdown, quarantine and self-isolation measures in many countries worldwide (4, 5). These measures aim to reduce SARS-CoV-2 transmission in the general population, and thus the risk of severe COVID-19 in vulnerable groups (e.g., older individuals and patients with certain respiratory and cardio-metabolic diseases) (6–12). Indeed, compelling evidence strongly indicates that certain chronic cardio-metabolic diseases, including diabetes and obesity, constitute key risk factors predisposing to severe COVID-19 (6–12). Notably, although severe COVID-19 is more common in men (13, 14), the aforementioned cardio-metabolic comorbidities, which significantly increase the risk of adverse COVID-19 related clinical outcomes, are also markedly prevalent in women with polycystic ovary syndrome (PCOS) (15–17).

PCOS is the most common endocrine disorder in reproductive-aged women, affecting up to 15–20% of this female population depending on the studied population and the applied diagnostic definition (18, 19). After excluding other endocrinopathies with similar symptomatology (19, 20), PCOS is typically diagnosed based on the presence of at least two out of three diagnostic criteria, namely ovulatory dysfunction, hyperandrogenism (clinical and/or biochemical) and polycystic ovaries (PCO) as identified by ultrasound (21). In addition, women with PCOS are also at a high risk of cardio-metabolic complications, particularly obesity, insulin resistance, type 2 diabetes (T2DM), hypertension, non-alcoholic fatty liver disease (NAFLD), and obstructive sleep apnoea (OSA) (22–27). Furthermore, women with PCOS often exhibit psychological comorbidity, with higher prevalence of coexisting anxiety and/or depression (28–31), which also tends to impair their overall quality of life (QoL) compared to women without PCOS (32, 33). Given this increased comorbidity burden, women with PCOS may experience a particularly negative impact from the lockdown/quarantine and self-isolation measures imposed against the transmission of SARS-CoV-2 and may also be at increased risk of severe COVID-19 (16).

Overall, global measures to control the COVID-19 pandemic are expected to inevitably have a negative psychological effect upon the general population (34) due to various factors, including the enforced quarantine measures (35) and their socio-economic impact (36), as well as the concern about COVID-19 (34). This has been previously reported in relation to SARS, which was shown to promote increased stress, anxiety and depression in the general population (37). Such findings are increasingly reported during the current COVID-19 pandemic, with an observed increase in self-reported symptoms of anxiety, depression, and stress (38). Moreover, these negative psychological effects are likely linked to disrupted sleep quality (39). In previous longitudinal studies, new onset mental health issues have been linked to increased sleep disruption (40–42), whilst disturbed sleep is also considered to be a contributing factor to the development of new mental health disorders (43). Of note, irrespective of the COVID-19 pandemic, sleep disturbances are more prevalent in women with PCOS than in the general population (44, 45), potentially due to coexisting OSA, particularly in women with poorer metabolic profiles (26), and/or depression which is also a major predictor of poor sleep quality (46). Furthermore, reduced self-esteem and body satisfaction, which are both frequently associated with PCOS, have also been demonstrated to contribute toward disrupted sleep (44).

In this context, it is likely that a 2-fold effect of increased psychological distress due to the COVID-19 pandemic alongside the established disease-related burden of PCOS may further contribute to impaired sleep quality and QoL, linked also to increased anxiety, depression, and stress levels (47). To date, there have been no published studies exploring these issues in women with PCOS during the COVID-19 pandemic. Therefore, the aim of the current study was to determine whether the COVID-19 pandemic has had a negative effect upon the sleep quality of women with PCOS in the United Kingdom (UK), and whether any such impairment was associated with reduced QoL and increased stress, anxiety, or depression in this female population.

METHODS

For the purposes of this study, we conducted a cross-sectional study based on a web-based survey between 2nd June and 17th August 2020. Ethical approval was granted by the ethics committee of Coventry University (application number: P106195) in May 2020. Recruitment was conducted through social media and with the support of Verity (the UK PCOS charity) and PCOS support groups on Facebook. Participant eligibility criteria included female sex with a previous medical diagnosis of PCOS, age from 18 to 45 years, and UK residency.

A range of structured and validated questionnaires were used to collect the study data; questionnaires were completed online using the survey software, Qualtrics© XM (Qualtrics XM, Provo, Utah, USA). Where participants expressed an interest in participation, a study URL link to the survey was emailed to them directly. Alternatively, participants could access the questionnaires directly *via* the same study URL posted on social media channels. The study URL link contained an initial participant information sheet, as well as provision of informed consent. Where participants failed to complete the provided online survey, this was translated as withdrawal from the study and all data for these participants were excluded from the final analyses.

To capture relevant participant characteristics, a demographics questionnaire was created for this survey. This included self-reported information about time since PCOS diagnosis and diagnosed PCOS phenotype, height, weight, age, questions relating to sleep affected by COVID-19 restrictions (i.e., "*to what extent do you believe that quarantine measures due to COVID-19 have affected your sleep pattern?*"), presence of comorbidities and typical sociodemographic questions. In the context of this study, the PCOSQOL was utilized as a validated measure of QoL (48). The PCOSQOL is a disease-specific questionnaire which was developed and validated to measure QoL in UK women with PCOS, and is also the first PCOS-specific measurement tool to encompass all phenotypic subgroups according to the most recent diagnostic criteria (48). Briefly, this questionnaire incorporates 35 Likert-based questions allowing participants to report the impact of various PCOS-related symptoms upon their day-to-day life, with subscales which allow reporting of the impact of PCOS, infertility, hirsutism, and mood upon QoL (49–51). Total scores are summated with lower scores indicative of poorer QoL.

Information about the mental health well-being of each participant was also captured using the Depression, Anxiety and Stress Scale (DASS-21) (52). The DASS-21 includes 21 questions, seven relating to each domain for depression, anxiety and stress, and requires respondents to rate their level of agreement (0–3) to a series of statements. Each domain score is calculated by summing the responses and multiplying by two, whilst normative and cut-points for depression, anxiety, and stress are provided. Finally, the Insomnia Severity Index (ISI) was applied to measure participants' self-perceived insomnia (53), as a validated and reliable tool for the assessment of insomnia severity (54, 55). The ISI targets the subjective symptoms and consequences of insomnia, as well as the degree of concerns or distress caused by those difficulties. The ISI is composed of seven items that, respectively, evaluate the severity of sleep-onset (initial), sleep maintenance (middle), early morning awakening problems (terminal), satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and level of distress caused by the sleep problem. Each of these items is rated on a five-point Likert scale and the time interval is "*in the last 2 weeks*." Total ISI scores range from 0 to 28, with higher scores indicating greater insomnia severity.

Statistical Analysis

Statistical analysis was completed in IBM SPSS Statistics for Windows (Version 26.0, IBM Corp; Armonk, NY) and in R statistical software [(56), using the *car:* and *MASS:* packages] (57, 58), and statistical significance was set at $p < 0.05$. Descriptive characteristic reports were generated and Shapiro-Wilk tests of normality were completed. Accordingly, a non-parametric approach was adopted for subsequent analysis, as appropriate. Responses to the question "*to what extent do you believe that quarantine measures due to COVID-19 have affected your sleep pattern?*" were split into a dichotomous response—namely, into negative effects or no effect/positive effects—which was used as a categorical variable. Independent samples Mann-Whitney *U*-tests were completed to evaluate the between group differences. Spearman's correlations between the ISI and other questionnaires (i.e., PCOSQOL total and domain scores, and the DASS-21) were also completed for the entire study cohort and also within each group.

Given the Likert scale nature of the data in this study, where Likert scales are a special case of ordinal data, we utilized an ordinal logistic regression (OLR) approach. The OLR approach is comparable to a conventional multiple regression approach, where there may be one dependent variable and one or more independent variables. It does however differ from ordinary least squares multiple regression, by treating the dependent variable as an ordered categorical variable, based upon the principle of cumulative-odds (59). The coefficient of determination, R^2, summarizes the proportion of variance in the dependent variable associated with the independent variables, with larger R^2 values indicating that more of the variation is explained by the model, to a maximum of 1. However, in non-parametric regression, it is not possible to compute a traditional R^2, and a pseudo R^2 is computed instead. In this study, we opted to report Nagelkerke's R^2 (R^2_N), which is an adjusted version of the Cox & Snell R^2 that adjusts the scale of the statistic to cover the full range from 0 to 1 (60, 61). To test the statistical significance of each model coefficient (β), we used the Wald test to compute a Wald statistic with a chi-square distribution. All participant background characteristics were adjusted for in the OLR.

RESULTS

In total, 333 participants met the eligibility criteria and consented to participate in the present study, completing the online survey. Pertinent demographics/characteristics for the recruited study cohort are presented in **Table 1**. The vast majority of the study participants (92.5%) were of White ethnic background. Of the recruited cohort, 40% were married and a further 40% were single, with the remaining 20% being in other non-married relationships, divorced, separated or widowed. Approximately 73% of participants stated that they have no children. Moreover, the majority (63.1%) of the study participants were in full-time employment, 40.2% were educated to at least degree level, and 51.1% had the lowest household income (≤ £39,999). Finally, participants were asked to self-report their diagnosed PCOS phenotype; 46.5% indicated that they had all three PCOS diagnostic characteristics (i.e., hyperandrogenism, menstrual disruption, and PCO), 13.5% PCO and menstrual disruption, 9.6% PCO and hyperandrogenism, 6.9% hyperandrogenism and menstrual disruption, and the remaining 23.1% were unsure of the PCOS phenotype with which they had been diagnosed.

When participants' responses to the question about the impact of COVID-19 restrictions on their sleep were dichotomized into negative and no/positive responses, 242 participants reported that they had experienced either a significant or small negative effect upon their sleep, whilst the remaining 91 reported either no such effect, or at least a small positive effect upon their sleep. Using the ISI scoring guidelines, 44.2% of those reporting negative effects met the scoring threshold (>14) for a diagnosis of at least moderately severe clinical insomnia. Key outcomes of interest were compared between these two study groups and these findings are summarized in **Table 2**.

Overall, there were no differences between the study groups regarding age, weight, body mass index (BMI), time since PCOS diagnosis, or number of comorbidities. As expected, the self-reported insomnia severity assessed by the ISI was significantly higher in those who reported a negative effect of COVID-19 on their sleep quality compared to those who reported no such effect or a relevant positive effect (**Table 2**). Furthermore, the former also reported poorer QoL, as measured by the total PCOSQOL score, whilst they also reported a greater impact of PCOS and poorer mood in the corresponding PCOSQOL domains. Finally, based on the corresponding DASS-21 scale scores, those reporting a negative effect of COVID-19 on their sleep quality also had statistically higher depression and stress levels, but not anxiety, compared to those who reported no such effect (**Table 2**).

For the entire study cohort, Spearman's correlation tests showed an inverse correlation between the ISI and PCOSQOL total score ($r_s = -0.384$, $p < 0.001$), and domain scores for Impact of PCOS ($r_s = -0.379$, $p < 0.001$), Infertility ($r_s = -0.225$, $p < 0.001$), Hirsutism ($r_s = -0.205$, $p < 0.001$), and Mood ($r_s = -0.405$, $p < 0.001$). Furthermore, significant positive correlations were also noted between the ISI and the DASS-21 Depression ($r_s = 0.377$, $p < 0.001$), Anxiety ($r_s = 0.410$, $p < 0.001$), and Stress ($r_s = 0.467$, $p < 0.001$) scores. These correlations between the ISI and the total PCOSQOL score, all PCOSQOL domains apart from Hirsutism, and DASS-21 scores also remained statistically significant within each of the two groups (data not shown).

Results of the OLR indicated that Stress, Anxiety, and Depression, as measured by the DASS-21, alongside PCOSQOL domain scores for Mood, Hirsutism, Infertility, and Impact of PCOS were significant predictors of ISI score (all p-values < 0.01; **Table 3**). Furthermore, we found that the DASS-21 variables were the greatest predictors of ISI score, accounting for the largest proportion of variance in the dependent variable [Stress: Wald χ^2: 87.23, OR: 1.23 (1.18, 1.29), R^2_N: 0.05, $p < 0.0001$; Anxiety: Wald χ^2: 64.06, OR: 1.19 (1.14, 1.25), R^2_N: 0.03, $p < 0.0001$; Depression: Wald χ^2: 55.5, OR: 1.15 (1.11, 1.20), R^2_N: 0.03, $p < 0.0001$]. Finally, no participant characteristic

TABLE 1 | Breakdown of socioeconomic and ethnicity characteristics of interest for the study cohort of UK women with polycystic ovary syndrome [PCOS; $N = 333$; median age (interquartile range) = 30.0 (9.0) years].

Variable	*N* (%)
Ethnicity	
White	308 (92.5)
Mixed background	9 (2.7)
Asian or Asian British	8 (2.4)
Black or Black British	4 (1.2)
Other ethnic background	3 (0.9)
Declined to indicate	1 (0.3)
Relationship status	
Single	134 (40.2)
Married	132 (39.6)
Co-habiting	22 (6.6)
Long-term relationship	19 (5.7)
Civil-partnership	12 (3.6)
Engaged	8 (2.4)
Divorced	3 (0.9)
Separated	2 (0.6)
Widowed	1 (0.3)
Children	
No	242 (72.7)
Yes	91 (27.3)
Education	
Undergraduate	135 (40.2)
College	107 (32.1)
Postgraduate	60 (18.0)
Secondary	26 (7.8)
Doctorate	5 (1.5)
Employment	
Full-time employment	210 (63.1)
Part-time employment	47 (14.1)
Student	27 (8.1)
House person	19 (5.7)
Unemployed	21 (6.3)
Self-employed	9 (2.7)
Household income	
≤ £39,999	170 (51.1)
£40,000–£79,999	137 (41.1)
≥ £80,000	26 (7.8)

All percentage data has been rounded to one decimal place.

significantly influenced the direction or magnitude of the OLR (all p-values > 0.2).

DISCUSSION

To our knowledge, this is the first study to assess the self-reported sleep quality of women with PCOS in the UK during the lockdown/quarantine measures imposed in response to the COVID-19 pandemic, and explore potential corresponding associations with QoL and depression, anxiety, and stress levels in this female population. Of note, according to the findings of the present study ∼73% of the study participants reported that their sleep quality had worsened since COVID-19 restrictions were imposed. Interestingly, when compared to data from a study in the general population during COVID-19 lockdown measures (62), the prevalence of clinical insomnia based upon the ISI among the women with PCOS of the present study was markedly greater (∼35 vs. ∼10%). Our findings are in accord with data reported from a web-based study in the Greek general population during the national lockdown due to COVID-19, where 37.6% of participants (particularly women) scored above the threshold for insomnia based on a relevant validated questionnaire (63). Prior to the COVID-19 pandemic, global estimates for the prevalence of insomnia ranged between 3.9 and 22% (64), thus these findings suggest that there has been an exacerbation of sleep disturbances (e.g., insomnia) during this pandemic.

The present findings showing that the majority of women with PCOS self-report negative effects upon their sleep during the COVID-19 restrictions highlight insomnia and poor sleep health as a significant problem in this female population. However, it should be noted that it is difficult to determine the magnitude of this problem/change without having relevant baseline assessments before this pandemic. Indeed, due to practical difficulties in studying women with PCOS in representative population-based samples, there is an overall paucity of data on the prevalence of sleep disturbances in this population to allow precise comparisons (65). Notably, one common known sleep disorder in women with PCOS is OSA, with a recent meta-analysis reporting that OSA prevalence in women with PCOS is 35% (95% confidence interval: 22.2–48.9%) which is further increased in the presence of overweight/obesity (45). Nevertheless, OSA does not appear to be a defining factor for the findings of the present study, since only 1.2% of participants indicated that they had received a medical diagnosis of OSA, and there were no between group differences for BMI or additional comorbidities (e.g., T2DM) that are often associated with PCOS and OSA (26). Undiagnosed OSA is common in this female population (26), and may also be present among the participants

TABLE 2 | Key outcomes of interest for the study cohort of UK women with polycystic ovary syndrome (PCOS) when split into a dichotomous response regarding the impact of the lockdown measures due to COVID-19 on sleep (reported negative effects vs. no or positive effect).

Study variables/ outcomes	Full study cohort of women with PCOS (N = 333)	Negative impact on sleep (N = 242)	No/positive impact on sleep (N = 91)	P
Age (years)	30.0 (9.0)	29.0 (9.0)	30.0 (10.3)	0.426
Years Since PCOS Diagnosis	8.0 (9.9)	7.3 (9.8)	8.2 (12.0)	0.336
Weight (kg)	93.9 (37.9)	93.9 (37.2)	91.2 (37.5)	0.290
BMI (kg/m^2)	34.8 (13.6)	35.0 (13.1)	34.0 (14.7)	0.322
PCOSQOL				
Total Score	101.0 (60.5)	97.0 (59.0)	114.0 (65.8)	**0.003**
Impact of PCOS	40.0 (28.5)	38.0 (26.0)	50.5 (30.5)	**0.001**
Infertility	24.0 (27.0)	23.0 (27.0)	30.5 (26.5)	0.077
Hirsutism	16.0 (18.0)	16.0 (17.0)	17.5 (20.3)	0.348
Mood	17.0 (10.0)	16.0 (9.0)	21.0 (11.0)	**0.001**
DASS-21				
Depression	18.0 (17.0)	18.0 (16.0)	13.0 (16.0)	**0.014**
Anxiety	10.0 (12.0)	12.0 (12.0)	10.0 (11.0)	0.094
Stress	18.0 (14.0)	18.0 (12.0)	15.0 (14.5)	**0.007**
Insomnia Severity	12.0 (9.5)	14.0 (8.0)	7.0 (8.0)	**<0.001**
Comorbidities	1.0 (2.0)	1.0 (2.0)	1.0 (3.0)	0.737

Data are presented as median (interquartile range). Between group comparisons performed by independent samples Mann-Whitney U-tests. Insomnia severity as assessed by the validated Insomnia Severity Index (ISI). Significance was set at $p < 0.05$. BMI, body mass index; PCOSQOL, Polycystic ovary syndrome quality of life questionnaire; DASS-21, Depression, Anxiety, and Stress Scale; P, asymptotic two-sided significance. Values in a bold font correspond to $P < 0.05$.

TABLE 3 | Results from the ordinal logistic regression (OLR) for the study cohort of UK women with polycystic ovary syndrome (PCOS).

		95% CI					95% CI				
Predictor	β	Lower	Upper	SE	Z	OR	Lower	Upper	Wald χ^2	R^2_N	p
DASS-21 stress	0.21	0.17	0.25	0.02	9.055	1.23	1.18	1.29	87.23	0.05	**< 0.0001**
DASS-21 anxiety	0.17	0.13	0.22	0.02	7.793	1.19	1.14	1.25	64.06	0.03	**< 0.0001**
DASS-21 depression	0.14	0.11	0.18	0.01	7.314	1.15	1.11	1.20	55.5	0.03	**< 0.0001**
PCOSQOL mood	−0.12	−0.1	−0.08	0.01	−7.692	0.88	0.86	0.91	62.49	0.02	**< 0.0001**
PCOSQOL hirsutism	−0.03	−0.05	−0.01	0.008	−3.288	0.97	0.95	0.99	10.98	0.005	**0.001**
PCOSQOL infertility	−0.03	−0.04	−0.01	0.006	−3.942	0.97	0.96	0.98	15.79	0.008	**< 0.0001**
PCOSQOL impact of PCOS	−0.03	−0.04	−0.02	0.005	−6.771	0.96	0.95	0.97	48.01	0.02	**< 0.0001**

CI, Confidence Interval; β, beta-coefficient; SE, Standard Error; OR, Odds ratio; R^2_N, Nagelkerke's pseudo-R²; PCOSQOL, Polycystic ovary syndrome quality of life questionnaire; DASS-21, Depression, Anxiety, and Stress Scale (21 item). Values in a bold font correspond to $P < 0.05$.

of this cohort, but whether this could be an underlying factor contributing to the present findings requires further and more targeted research.

Another mechanism contributing to sleep disturbances in this study may relate to increased depression, anxiety, and stress levels. Indeed, depression, anxiety and stress yield the largest beta coefficients and account for the largest amount of variance to ISI scores in the results of the ordinal logistic regression in the present study. Of interest, when the whole study cohort was considered, 51.5% reported that they had previously received a medical diagnosis of anxiety and/or stress. Whilst it was unclear whether these diagnoses were made prior to, or during the COVID-19 pandemic, additional insight can be gained from the self-reported DASS-21 scores. Based on this validated questionnaire, the prevalence rates of at least mild depression, anxiety, and stress in the study cohort were 80.5, 70.6, and 64.6%, respectively, which are higher than the reported corresponding medical diagnoses. Notably, these are also higher than those reported by a meta-analysis for depression (33.7%; 95% CI: 27.5–40.6), anxiety (31.9%; 95% CI: 27.5–36.7), and stress (29.6%; 95% CI: 24.3–35.4) in the general population during the COVID-19 pandemic (66). Collectively, these data suggest that during the current pandemic, women with PCOS are experiencing a greater psychological burden than the general population, with a markedly higher prevalence. This is in accord with the latest international evidence-based guidance on PCOS, which highlights that, irrespective of a global pandemic, women with PCOS are more likely to experience depression and anxiety (67).

Other reported risk factors for decreased sleep quality during the COVID-19 pandemic are changes to sleep patterns (62), worries about health (68), financial consequences (69), social interactions (70), reduced physical activity (63), and gender with women being reportedly 56% more likely than men to experience sleep disruption during this pandemic (71). As such, it is plausible that such factors further contribute to a potential multifactorial effect upon an already "at risk" population (72), which clearly exacerbates sleep disruption and may result in reduced QoL. Indeed, the results of the present study support this notion, since women with PCOS who reported negative sleep effects during the COVID-19 pandemic also exhibited reduced QoL (as measured by the PCOSQOL) compared to those without any, or with positive effects on sleep. Based on the corresponding PCOSQOL domains, this association was apparently burdened by the impact of PCOS and affected mood in the study participants. However, what cannot be determined by the present findings is the directional role of sleep disruption in the aforementioned milieu for which further studies are clearly needed.

Interestingly, longitudinal studies have previously reported associations between sleep disorders, anxiety, and depression (73, 74), which are known to independently impair QoL (75). Moreover, it has been purported that there is a bidirectional relationship between sleep quality and mental well-being (76), with sleep quality independently predicting the prevalence of anxiety and/or depression, whilst anxiety and depression are also predictors for reduced sleep quality (42, 77). Due to the nature of our analysis, the current study is unable to determine the causal direction between sleep and mental well-being. However, it is likely that the COVID-19 pandemic has created an overarching environment which further exacerbates this relationship with the net result being further impairments of mental health and sleep quality leading to reduced QoL. As prior to the COVID-19 pandemic, women with PCOS were already recognized as a patient population at an increased risk of anxiety/stress, depression, sleep disorders, and impaired QoL (18, 19); the disrupting circumstances of this pandemic mean then that there should be a renewed and heightened focus from healthcare professionals to ensure that adequate support and treatment provision is available to reduce and, where possible, prevent further comorbidity and impaired QoL in these women (16).

Study Limitations

There are certain limitations which should be acknowledged in the present study. This study relied upon participant self-report which can lead to a degree of decreased clarity/accuracy in the provided answers, thus inevitably introducing a degree of information bias to the study findings. For example, it is known that individuals tend to over-report their height and under-report their weight (78), an effect which appears to be further exaggerated in individuals with overweight/obesity (79). This may lead to discrepancies in self-reported anthropometric data which, given the key role of metabolic health in PCOS severity/comorbidity (80) and sleep quality (26) may impact to some degree on the study findings. However, this methodology is frequently employed in studies of this nature, whilst validated instruments/questionnaires were utilized to capture key study data of interest. Another study limitation is the lack of comparative baseline data for the study cohort for a period prior to the COVID-19 pandemic. The study survey questions asked about changes in sleep quality due to COVID-19 restriction measures, but without validated baseline measurements, it is not possible to quantify the exact extent to which the corresponding outcomes have been affected. This issue could be addressed to some degree at a follow-up time point when current restrictions have been eased/lifted. To this aim, the relevant prospective follow-up of this study cohort has been planned. Furthermore, although the large sample size in the present study is a distinct strength, it is accompanied by some inherent limitations. For instance, OLR yielded significant R^2_N for all variables, yet most were of little practical significance; thus, in interpreting these results, the potential fallacy of large sample sizes must be considered (81). Finally, as this is a cross-sectional study, the present findings cannot be used to infer conclusions regarding the temporal/causal relationship between the noted negative impact on sleep and reported levels of depression/stress.

CONCLUSION

The present study offers a novel insight regarding the self-reported sleep quality of women with PCOS during the COVID-19 pandemic lockdown, and how this is associated with QoL and depression, anxiety, and stress levels in this population. Based on our present findings, it is evident that the majority of UK women with PCOS in this study cohort feel that the applied measures imposed in response to the COVID-19 pandemic had a negative impact on the quality of their sleep, with high prevalence of insomnia. There is also evidence that those women with PCOS and impaired sleep have greater levels of psychological morbidity (e.g., depression/stress) and reduced QoL. Whilst it appears that the restrictive measures due to COVID-19 have increased this comorbidity burden in these women with PCOS, the exact magnitude of the impact of this global pandemic upon these parameters and the underlying temporal/causal relationship is less clear. Nevertheless, it has previously been reported that during such disease outbreaks, the number of individuals whose mental health is negatively affected can be greater than the number affected by the infection (82), and that the mental health implications and their prevalence can be even more significant than the epidemic itself (83). Another key message to consider based on the present study is that there are certain groups that may remain relatively overlooked despite being particularly vulnerable during this pandemic. Women with PCOS should be considered within these parameters, since they are at increased risk of cardio-metabolic complications which, in turn, may increase the risk of severe COVID-19, whilst they are also susceptible to significant psychological comorbidity which, regardless of COVID-19, may impair their overall well-being.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available, without undue reservation, by the authors upon reasonable request and where it is ethically acceptable to do so, and does not violate the protection of participants, or other valid ethical, privacy, or security concerns.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Coventry University. The patients/participants provided their online written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CK, LA, GM, JB, IK, and HR developed the study protocol. CK drafted the initial manuscript. CK and CCTC performed the statistical analyses. CK, CCTC, LA, GM, JB, IK, and HR contributed to the literature search, drafted, and/or revised sections of this manuscript. IK and HR supervised the study, combined, edited, and revised all drafts of this manuscript. All authors approved the final manuscript.

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REVIEW
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SARS-CoV-2 in Pregnancy: Fitting Into the Existing Viral Repertoire

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The risk of viral infection during pregnancy is well-documented; however, the intervention modalities that in practice enable maternal-fetal protection are restricted by limited understanding. This becomes all the more challenging during pandemics. During many different epidemic and pandemic viral outbreaks, worse outcomes (fetal abnormalities, mortality, preterm labor, etc.) seem to affect pregnant women than what has been evident when compared to non-pregnant women. The condition of pregnancy, which is widely understood as "immunosuppressed," needs to be re-understood in terms of the way the immune system works during such a state. The immune system gets transformed to accommodate and facilitate fetal growth. The interference of such supportive conversion by viral infection and the risk of co-infection lead to adverse fetal outcomes. Hence, it is crucial to understand the risk and impact of potent viral infections likely to be encountered during pregnancy. In the present article, we review the effects imposed by previously established and recently emerging/re-emerging viral infections on maternal and fetal health. Such understanding is important in devising strategies for better preparedness and knowing the treatment options available to mitigate the relevant adverse outcomes.

Keywords: pregnancy, SARS-CoV-2, maternal fetal health, COVID-19, vertical transmission, neonatal infection

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INTRODUCTION

Pregnancy leads to numerous physiological changes. Specifically, the immune system undergoes extensive transformation, often termed as becoming "immunocompromised," but it is nevertheless essential to support the growth of the developing fetus. However, this state is also one where the body is prone to various infections. Moreover, the probable transmission of virus infections from mother to fetus further complicates and aggravates the disease outcome. Such "vertical transmission" may be defined as the spread of any pathogen from a mother to her fetus (antepartum and intrapartum periods) or to a neonate (postpartum period) via the placenta *in utero* through contact with body fluid during delivery or via breastfeeding post-birth (1). It has been evident in several virus infections, such as HIV (2, 3), the Ebola virus (4), the Zika virus (5), etc. Until now, the only antenatal management for viral infections comprises the diagnosis of TORCH (toxoplasmosis, other, rubella, CMV, and HSV type-1 and -2) infections. This panel is now expanded to include: syphilis, listeriosis, parvovirus, coxsackie virus, *Trypanosoma cruzi,* and others (6). However, no specific therapeutic or preventive approach is employed to address the adverse outcomes that may arise from such viral infections. The recent emergence of the potent novel SARS-CoV-2 has further contributed to this fear of vertical transmission and the unknown infection outcomes during pregnancy. The present review is focused on enumerating various viral infections prevalent during pregnancy and the associated risks to maternal and fetal health (**Table 1**) with special reference to the SARS-CoV-2 infection.

LONG-ESTABLISHED VIRAL INFECTIONS DURING PREGNANCY

Over the years, the risk of viral pandemics has grown with evolving human activities. The first two trimesters of pregnancy exhibit increased inflammatory responses, but the third trimester is a phase of lower immunological activity (36, 37). Encountering any infectious pathogen makes things difficult for both the mother-to-be as well as the to-be-born baby. Progressing time demands a precise understanding of the viral diseases that may hold the potential for major outbreaks. The past pandemics caused by the influenza, Ebola, and Lassa viruses (38, 39) have shown pregnant women to be vulnerable targets with high incidences of fatality and disease severity (40, 41).

Influenza Viruses

Of the four (A, B, C, and D) types of influenza viruses, types A and B are known to cause mild to severe disease in humans. While, both A and B influenza viruses cause seasonal epidemics, pandemics are caused by only the influenza A viruses (IAVs) that are further classified into subtypes on the basis of two viral surface proteins, i.e., hemagglutinin (H) and neuraminidase (N) (42). At present, 18 different H subtypes (designated as H1-H18) and 11 different N subtypes (designated as N1-N11) have been identified. Given these many subtypes of H and N, there can be a total of 198 combinations for possible influenza A virus variants, however, till now only 131 IAV subtypes have been identified (42). IAV (H1N1) and IAV (H3N2) are the most commonly circulating seasonal subtypes. Since the 2009 swine flu pandemic, the pH1N1 strain has undergone mutations and adapted itself as a seasonal IAV(H1N1) strain (42).

Risk to the Mother

Nevertheless, for pregnant women, the risk of severe illness or death from seasonal or pandemic strains of influenza viruses remains high (43). As evident during the 1918 and 1957 flu pandemics, pregnant women exhibited high mortality rates (44, 45) and adverse pregnancy outcomes like spontaneous abortion and preterm birth (44, 46). More than 50% of influenza-infected pregnant women with pneumonia could not successfully carry the pregnancy to term (44) during the 1918 pandemic. On the other hand, the 1957 Asian flu witnessed birth defects, spontaneous abortions (47), fetal death, and preterm delivery (48). Seasonal influenza virus infections, monitored over 19 influenza seasons, exhibited a significantly higher likelihood of hospitalization of pregnant women with cardiopulmonary indications (49). Acute respiratory disease, asthma, or other underlying conditions further make pregnant women vulnerable to influenza viruses during the flu season (50, 51), and they are thus recommended for influenza vaccination.

Risk to the Developing Fetus

Although viremia is quite uncommon in influenza, it has been associated with severity of disease following infection with pH1N1/09 strain (52). Vertical transmission also seems to be a rare event (53); however, mouse model studies suggest possible adverse effects, as evident by histopathological alterations in the brain (54) or behavioral changes (55) in the progeny. Maternal influenza infection has also been linked to childhood leukemia (56), schizophrenia (57), and Parkinson disease (58). Overall, influenza viruses seem to project indirect effects on the developing fetus.

Cytomegalovirus

Cytomegalovirus is the major cause of infection during pregnancy, being responsible for infecting one in four pregnant women and 0.5–2% of all live birth infections (13). The incidence rate of CMV infection in women of a reproductive age belonging to developed and developing nations is 60 and 90%, respectively (59). The development of anti-CMV antibodies in the mother is crucial in overcoming CMV infection; however, reactivation of the virus may occur in 10% of seropositive women. The highest occurrence rate of CMV may be attributed to the multiple pathways employed by the virus to gain entry into the host (60). The various cell types prone to CMV infection include epithelial cells, endothelial cells, muscle cells, fibroblasts, trophoblasts, and monocytes/macrophages, human neuronal cells (61). Although the disease severity is unaffected during pregnancy, CMV is known to impose serious implications during such states.

Risk to the Mother

Antepartum maternal infection remains mostly undetected due to non-specific symptoms and only mild febrile illness. Once the mother is infected, CMV may be transmitted to the fetus either through the placenta or via ingestion or aspiration of cervicovaginal secretions during delivery, breastfeeding, or rarely while ascending from the genital tract of the infected mother.

Risk to the Developing Fetus

The most common adverse fetal outcomes include congenital viral infection, which occurs in about 0.5% of cases (62). The primary viral targets include the ventricle, Organ of Corti, and neurons of the eighth cranial nerve, leading to congenital hearing loss (63). The rate of vertical transmission increases with progressing gestation with 36.5% during the first trimester, 40.1% during the second trimester, and 65% during the third trimester (17, 64), while, interestingly, the disease severity decreases with the increasing gestational age (65, 66). The infected neonates remain largely asymptomatic and start exhibiting neurodevelopmental damage within the first 3 years of age (67).

Herpes Simplex Virus

HSV-1 and HSV-2 have a combined seroprevalence of 72% in pregnant women (68). The most common STD is the genital herpes simplex virus (HSV-2) infection in adult females with an estimated 16% incidence in male and female combined and detection of almost 0.8 million new cases every year (21).

Risk to the Mother

As per the National Health and Nutrition Examination Surveys (NHANES), the incidence of HSV-2 infection is greater in women (23.1%) than men (11.2%) (40). Ethnicity, financial well-being, cocaine abuse, onset of sexual activity, sexual behavior and number of partners, and the presence of bacterial vaginosis all

TABLE 1 | Various features of virus infections during pregnancy.

Virus	Year of discovery	Genome characteristics	Prevalence (year of estimation)	Signs and symptoms	Route of transmission	Risk of vertical transmission	Mortality rate and impact on infected neonate	Mortality rate and impact on maternal health	References
Influenza viruses	Influenza virus first identified in 1933 by Alphonse Raymond Dochez and co-researchers	Segmented -ve sense ssRNA genome; about 13.5 nucleotides	49.1% IAV (2020); 50.9% IBV (2020)	Signs: tachycardia, facial flushing, clear nasal discharge, and cervical adenopathy. Symptoms: Fever, cough, malaise, rhinitis, headache, sore throat, myalgia, nausea, vomiting, otitis, and conjunctiva burning	Respiratory droplets/ aerosols while coughing, sneezing, or any thrustful mouth activities; contact with nasal secretions	High	0.15 deaths per 100,000; Indirect effects to fetus include neurological disorder, leukemia	High mortality rate in pregnancy; Adverse outcomes include pre-term birth, spontaneous abortion; complications increase if co-occurrence of pneumonia: more than 50% of pregnant women with influenza and pneumonia are unable to carry the pregnancy to full term	(7–9)
Cytomegalovirus	Typical signs identified in 1881; CMV isolation and propagation from humans and mice in 1956-1957 by Weller, Smith, and Rowe	Linear dsDNA; 236 kbp	Ubiquitous prevalence- About 50% till the age of 40 years; 100% in Africa and Asia; 80% in Europe and North America	Mild illness with non-specific symptoms, such as fever, sore throat, fatigue, swollen glands; and occasionally, mononucleosis or hepatitis	Contact with infected body fluids, such as saliva, urine, blood, tears, semen, and breast milk	36–65% from 1st to last trimester	Rare; Neurodevelopmental, auditory damage, microcephaly	1 in every 4 pregnant women is infected by CMV; 0.5–2% of all live birth infections	(10–13)
HSV-1	First HSV isolation from fever blister in 1919 by Lowenstein	Linear; dsDNA; 152 kbp	12.1% (2016)	Sores around the mouth and lips	Contact with infected lesions, mucosal surface, or via genital or oral secretions	Medium during late pregnancy; Low during early pregnancy	80%; Localized skin, eye, and mouth (SEM), central nervous system (CNS) with or without SEM or disseminated disease; major impact: blindness, seizures, and learning disabilities	Spontaneous abortion, intrauterine growth restriction, preterm labor, and congenital and neonatal herpes infections	(14–18)
HSV-2		Linear; dsDNA; linear; 154.7 kbp	48.1% (2016)	Sores around genitals or rectum					
Varicella zoster virus	First isolated in 1954 by Thomas Huckle Weller	Linear dsDNA; 125 kb	97% decline in VSV infections since pre-vaccine era from 1993–1995 to 2013–2014 in the U.S.	In children, rash on scalp, face, and trunk are the first signs, followed by rash on extremities, fever, malaise, headache. In adults, fever and malaise for initial 2 days of infection followed by appearance of rash	Contact with infected lesion fluid; person-to-person	High in 8–20 weeks of gestation	30%; congenital varicella syndrome	10–20% VSV infections during pregnancy are accompanied by pneumonia, which may cause up to 40% mortality	(19–21)

(Continued)

TABLE 1 | Continued

Virus	Year of discovery	Genome characteristics	Prevalence (year of estimation)	Signs and symptoms	Route of transmission	Risk of vertical transmission	Mortality rate and impact on infected neonate	Mortality rate and impact on maternal health	References
Hepatitis C virus	1987 by Michael Houghton, Qui-Lim Choo, George Kuo, and Daniel W. Bradley; 1988 by Harvey J. Alter and his team	ssRNA; positive-sense; 9600 nucleotides long	1% viraemic prevalence accounting for 71.1 million cases (2015) with genotypes 1 and 3 being the most common; 2.8% (sero-prevalence as per systematic review, 2013)	Acute hepatitis C usually shows no signs/symptoms, but may exhibit: jaundice, along with fatigue, nausea, fever, and muscle ache; Chronic hepatitis C is generally a silent infection not causing any disease until the liver gets substantially damaged and leads to easy bleeding and bruising, fatigue, poor appetite, jaundice, dark-color urine, itchy skin, ascites, swelling in legs, weight loss, confusion, drowsiness and slurred speech (hepatic encephalopathy), spider-like appearance of blood vessels on skin (spider angiomas)	Infected blood	5.8%; With higher risk in case of co-infection with HIV (10.8%)	Preterm birth, late neonatal death	Intrahepatic cholestasis pregnancy	[(22, 23), https://www.mayoclinic.org/diseases-conditions/hepatitis-c/symptoms-causes/syc-20354278]
Hepatitis E virus	1978	ssRNA, positive-sense; 7.2 kb	About 20 million cases including 3.3 million symptomatic infections per year; 3.3% mortality estimate (2015)	Acute hepatitis E shows no signs/symptoms; Chronic disease exhibits: fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, jaundice, dark color urine, clay-color stool, pain in the joints	Fecal-oral route	High during the second and third trimester	High perinatal morbidity and mortality	20–25% mortality in pregnancy during the third trimester; Fulminant hepatitis, acute liver failure, death	[(24), https://www.cdc.gov/hepatitis/hev/hevfaq.htm; https://www.who.int/news-room/fact-sheets/detail/hepatitis-e#:\sim:text=Hepatitis%20E%20is%20a%20liver,of%20hepatitis%20E%20(1)]

(Continued)

TABLE 1 | Continued

Virus	Year of discovery	Genome characteristics	Prevalence (year of estimation)	Signs and symptoms	Route of transmission	Risk of vertical transmission	Mortality rate and impact on infected neonate	Mortality rate and impact on maternal health	References
HIV	First isolated and identified by Luc Montagnier's team (Luc Montagnier and Françoise Barré-Sinoussi received the Nobel Prize in 2008)	two copies of +ve sense ssRNA; 9,200–9,800 nucleotides	0.8% in adults (2018); 75.7 million diagnosed HIV+ since 1981; 21% unaware of their HIV status	Non-specific symptoms, such as fever, lymph node enlargement, fatigue, malaise, rash with small, only slightly raised lesions, and/or gastrointestinal symptoms	Blood or transplanted organs, including bone, vertical transmission, breast milk	>90% in late pregnancy	0.04–0.094%; If left untreated- Repeated fungal mouth infections (thrush); Poor weight gain; Enlarged lymph nodes; Neurological problems; Multiple bacterial infections (i.e., pneumonia)		(25–29)
Lassa virus	1969	Two ssRNA segments; 10.4 kb combined length (short strand: 3.4 kb; long strand 7 kb)	0.1 million- 0.3 million cases per year including about 5,000 deaths per year in the west of Africa	Mild in 80% cases: fever, malaise, weakness, and headache; Serious in rest of the 20% cases: hemorrhage in gums, eyes, or nose, etc., respiratory distress, frequent vomiting, facial swelling, chest- back- and abdomen- pain, shock, neurological symptoms, like, loss of hearing, tremors, and encephalitis. Multi-organ failure in more severe cases leading to death	Zoonotic transmission: via excretions of infected rodent multi-mammate rat, *Mastomys natalensis*; Human-human transmission via contact with body fluids of the infected person	High risk due to high viral load in the placenta and maternal blood	Premature birth Note:-More evidence with well-planned studies is required, although the risk is high due to serious outcomes of infection and high viral load in infected maternal and fetal tissues	high viral load in the placenta, fetal tissue, and maternal blood impose adverse outcomes	https://www.cdc.gov/vhf/lassa/pdf/factsheet.pdf
Zika virus	1947	Positive sense; ssRNA; about 11 kb	27% confirmed cases out of 0.7 million suspected cases in America (2015–2017)	Mostly asymptomatic; otherwise mild clinical features that are typical of maculopapular rash, like, fever, arthralgia, non-purulent conjunctivitis	Through infected *Ae. aegypti* and *Ae. Albopictus* vectors	47, 28, and 25% in first, second, and third trimesters, respectively	Congenital microcephaly, serious brain anomalies, Guillain-Barré syndrome, rare cases of encephalopathy, meningoencephalitis, myelitis, uveitis, paresthesia, and severe thrombocytopenia	Fetal loss, IUGR pregnancies	(30–32)

(Continued)

TABLE 1 | Continued

Virus	Year of discovery	Genome characteristics	Prevalence (year of estimation)	Signs and symptoms	Route of transmission	Risk of vertical transmission	Mortality rate and impact on infected neonate	Mortality rate and impact on maternal health	References
Ebola virus	1976	Non-segmented; negative sense RNA; 18–19 kb	28,000 confirmed cases and 11,000 deaths (2013–2016); case fatality rate 25–90% (average nearly 50%) as per previous outbreaks	Sudden symptoms: include fever, fatigue, muscle pain, headache, and sore throat; Other symptoms: vomiting, diarrhea, rash, impaired kidney and liver function, internal and external bleeding, like, gum-bleeding or blood excretion in stool	Zoonotic transmission: via contact of blood, body fluids/secretions, tissues, etc. of infected fruit bats, chimpanzees, gorillas, monkeys, forest antelope, or porcupines; Human-human transmission: direct contact via broken skin tissue or mucous membranes	Pregnant women recovered from acute Ebola may express virus in breastmilk, or in pregnancy-related body-fluids and tissues, which exhibits a high risk of transmission to baby and to others.	Preterm labor and spontaneous abortion	Vaginal and uterine bleeding causing maternal death	[(33), https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease]
SARS-CoV-2	Identified in 2020 by the China Novel Coronavirus Investigating and Research Team and named by the Coronaviridae Study Group of the International Committee on Taxonomy of Viruses in the same year	+ve sense ssRNA; 29,811 nucleotides	79.2 million cases and over 1.7 million deaths since onset of the pandemic in 2019	Major: fever, dry cough, tiredness; Minor: aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on the skin, or discoloration of fingers or toes Occasional serious symptoms: difficulty breathing or shortness of breath, chest pain or pressure, loss of speech or movement	Respiratory droplets/aerosols; fomites	2–3.9%; however true estimate yet known	True estimate not known yet; preterm labor and delivery, premature rupture of membranes, low birth weight, intrauterine fetal distress and growth restraint, feeding intolerance, asphyxia, pneumonia, and respiratory distress	Preterm labor and delivery, premature rupture of membranes	(1, 34, 35)

seem to affect women's vulnerability to HSV before pregnancy (69). HSV infection during pregnancy causes spontaneous abortion, intrauterine growth restriction, preterm labor, and congenital and neonatal herpes infections (70).

Risk to the Developing Fetus

The development of anti-HSV antibodies seems to have no effect on neonates. However, the risk of neonatal herpes infection increases with the gestational period from <1% during early pregnancy to up to 50% during late pregnancy (21, 71). The reason for this may be the inability of antibody development before labor to enable inhibition of HSV replication and shedding. Transplacental vertical transmission is rare, and 80–90% of perinatal transmission happens during delivery (17). HSV infection in neonates may affect localized skin, eye, and mouth (SEM) and the central nervous system (CNS) with or without SEM or disseminated disease. The untreated latter cases exhibit high (80%) mortality (14–17). The major neurological defects in infected neonates include blindness, seizures, and learning disabilities.

Varicella Zoster Virus

VSV infection causes chickenpox, which is a common but highly contagious illness primarily experienced during childhood. The major delinquent manifestation is the development of maculopapular to vesicular rashes all over the body. The virus gets transmitted through aerosols and close contact (72). An initial varicella zoster infection following chickenpox may lead to the latent stay of the virus in dorsal root ganglia for years and may reactivate as herpes zoster during adulthood. Although VSV infection occurs during childhood and most women of reproductive age have developed considerable immunity against it, it may still occur in 0.7/1,000 pregnancies.

Risk to the Mother and the Developing Fetus

Primary VSV infection in pregnant women causes considerable maternal and fetal morbidity and mortality. Although the pediatric infection is self-limiting, 10–20% of VSV infections in pregnancy are accompanied by pneumonia, a condition that may lead to up to 40% fatality (21). Fetal morbidity and mortality are linked to the development of congenital varicella syndrome, which may occur in 0.4–2% VSV-confirmed pregnancies within the initial 20 weeks of gestation (73). The syndrome is characterized by limb hypoplasia, microcephaly, hydrocephaly, cataracts, intrauterine growth restriction, and mental retardation (74) and is believed to be caused due to *in utero* VSV reactivation instead of primary fetal infection (75).

Hepatitis C Virus

Risk to the Mother

HCV poses a severe threat to pregnant women with adverse fetal outcomes, such as preterm birth (76), late neonatal death (77), and intrahepatic cholestasis of pregnancy (the risk of which increases if the mother has been HCV positive before pregnancy) (78). Much of the disease burden data come from the United States, where the elevated incidence of HCV aligned with the opioid epidemic. The HCV burden increased in IDU-associated HCV cases in the younger population, consisting of women who were pregnant and of reproductive age (79). There are geographical inequities in HCV healthcare management, and the prevalence thus varies across the globe. The incidence of HCV cases elevated from 1.8 to 4.7 per 1,000 live births according to a recent analysis of the National Center for Health Statistics data (80). As per the CDC, the rate of HCV infection increased by over 400% (0.8 to 4.1 per 1,000) in cases of women where live births were recorded. In pregnant women belonging to the European Union/European Economic Area, the HCV incidence is 0.1–0.9% (81) while that of Africa is 3.4% (82).

Risk to the Developing Fetus

Vertical transmission of HCV is estimated at 5.8% with a significantly higher rate among HIV-co-infected (10.8%) pregnancies (83). In the US, the incidence is 3.6% (84), whereas in Spain it is 7% (85) in HCV/HIV co-infected pregnant women. In spite of these statistics, the true estimate is still a challenge owing to the availability of scarce information on the subject and also the substantial time gap between childbirth and testing for HCV antibodies (currently recommended at ≥18 months of age), which may lead to loss of contact with the cases to be examined (79). The mode of delivery or breastfeeding does not appear to impact the risk of HCV transmission, while the prolonged duration of ruptured membranes may be a risk factor for the same (86). The association between the viral load and vertical transmission of HCV is under speculation, but conclusive recommendations cannot be made due to insufficient data (79).

Hepatitis E Virus

Hepatitis E Virus is the major cause of self-limiting acute viral hepatitis in healthy adults and chronic viral hepatitis in immunocompromised individuals.

Risk to the Mother

There have been several investigations to understand the effects of HEV infection on maternal and fetal health; however, definitive conclusions cannot be made due to contradictory observations among the different studies (87–90). In a recent 5-years single-center study in India, 1,088 patients (550 pregnant and 538 non-pregnant controls) were evaluated to understand the course and severity of HEV infection during pregnancy (91). All the patients were confirmed for either acute viral hepatitis (AVH) or acute liver failure (ALF) through clinical examination and biochemical investigations. The HEV infection was observed in 80.36% of pregnant women, with 73.38% prevalence in ALF cases alone. Also, the mortality rate was recorded at almost 76% due to HEV-infection in the studied subjects (91). Other studies suggest fulminant hepatitis failure with a mortality rate of up to 30% in pregnant women due to HEV infection (88, 90, 92).

Risk to the Developing Fetus

Vertical transmission of HEV with significant perinatal morbidity and mortality has been reported (90, 93, 94), and ribavirin and IFN-α administration is thus not carried out during pregnancy due to the risk of birth defects (42, 95, 96).

The adverse fetal outcomes include preterm labor (97, 98) and disseminated intravascular coagulation (DIC) (93).

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

HIV/AIDS continues to be the worst pandemic ever with 75.7 million individuals diagnosed with HIV infection and about 32.7 million deaths between 1981 and up until the end of 2019 (99). Globally, in 2019, women represented almost 48% of the total new HIV cases, and, likewise, in 2018, the incidence of new HIV cases in women aged 15–24 years was 55% higher as compared to men of the same age range. While the majority of adult women contract HIV infection via heterosexual contact, most childhood infections are caused due to vertical transmission (100). Almost 90% of untreated HIV cases proceed to develop AIDS and subsequent death with opportunistic infections due to the significant reduction in CD4 T cells. However, with significant improvements in medical care management of HIV cases, the life expectancy can be increased by as long as 15 years through the administration of anti-retroviral therapy.

Risk to the Mother and the Developing Fetus

Vertical transmission accounted for about 180,000 global new HIV infections in 2017 (100). Fortunately, with advanced healthcare systems and the use of cART, rates of perinatal transmission have reduced, leading to a smaller number of childhood exposures progressing into full-blown AIDS. Although the development of illness following HIV infection is not affected by the pregnant state, the risk of mother-to-child transmission forms a major concern. Vertical transmission of HIV can occur during intrauterine life, delivery, or breastfeeding. The adverse fetal outcomes include preterm birth, low birth weight, small size for gestational age, and stillbirth (101).

Lassa Virus

The Lassa virus causes Lassa fever, or Lassa hemorrhagic fever (LHF), an acute viral hemorrhagic fever that was first identified in 1969 in Lassa, Nigeria (96) and is transmitted through "multimammate rat" (*Mastomys natalensis*).

Risk to the Mother

The illness is endemic and a major cause of mortality for pregnant women in the West African regions, viz., Sierra Leone, Liberia, Guinea, and Nigeria (102). Fascinatingly, in cases of Lassa virus infection, maternal health rapidly improves as soon as the fetus is removed from the uterus either by spontaneous abortion or delivery (38). Also, the mortality is higher in cases of non-evacuated uterus (10/26 fatal outcomes) as compared to the cases where delivery was ensured (4/39 fatalities) (38). This may be due to placenta-mediated regulation of the maternal immune system. Even if the placenta is not directly infected, it is capable of responding to invading pathogens and hence seems to be a crucial regulator of a pregnant woman's response to virus infection (103). High viral load in maternal blood, placenta, and fetal tissue accounts for higher mortality rates of pregnant women than the non-pregnant counterparts (104). Maternal mortality risk increases with the progressing gestational period: from 7% during the first two trimesters to as high as 30% in the last trimester. Almost 50% mortality has been recorded within a month post-partum in contrast to 13% in non-pregnant females (104).

Risk to the Developing Fetus

Lassa virus infection is speculated to impose adverse outcomes to the developing fetus, given the high viral load in placenta, fetal tissue, and maternal blood. However, due to extremely limited evidence on clinical characteristics and course of Lassa fever in pregnancy and variability in study design and methodologies employed, the exact maternal and perinatal outcomes cannot be convincingly described (105). The vertical transmission and premature birth have been reported, though.

RE-EMERGING AND LESS UNDERSTOOD VIRAL THREATS

Zika Virus

The unexpected re-emergence of the Zika virus in 2015 and the subsequent outbreak in Brazil reinforced that the management of viral infections is of utmost significance during pregnancy.

Risk to the Mother and the Developing Fetus

Zika virus is transmitted by mosquitoes and potentially via a sexual route (106).

What was previously known to progress from fever and rash to Guillain-Barre syndrome is now reported to cause fetal brain and CNS anomalies in neonates born to Zika-virus-infected women (95, 107), as confirmed by the presence of viral nucleic acid in amniotic fluid (108). The adverse fetal outcomes include microcephaly, abortions and IUGR pregnancies, and other complications. Viral load in amniotic epithelia during mid-gestation is reported to be higher than in the late-gestation period (109). Cytotrophoblasts were also observed as viral targets, and, during early gestation, they were linked to loss of proliferation. Such a condition may explain the miscarriage and growth restriction outcomes.

Ebola Virus

Ebola virus, the cause of Ebola Hemorrhagic fever (EHF), primarily causes human infections in Africa (110). However, with extensive global travel, infectious nature of the pathogen, and potential effects on maternal and fetal health the virus has become a global threat. Although quite uncommon, the Ebola virus has imposed severe illness and considerable EHF outbreaks in Africa. The causative species, *Zaire ebolavirus,* was identified in 1976 in Kikwit and, during the then epidemic incidence of Ebola virus infection, saw a higher incidence among women than men (111, 112). Also, mortality was higher in pregnant than non-pregnant women. The 1976 Ebola epidemic witnessed 46% infections and 89% mortality among pregnant women.

Risk to the Mother

One of the main manifestations during the 1976 epidemic was vaginal and uterine bleeding leading to the death of infected pregnant females (93% mortality rate) within 10 days of onset of symptoms (113, 114).

Risk to the Developing Fetus

The adverse fetal outcomes of EHF during pregnancy include preterm birth and abortion. The 1976 epidemic led to a 23% incidence of spontaneous abortions of pregnancies, while the same was considerably higher (67%) in the 1995 epidemic (113, 114).

SARS-CoV-2

Adverse outcomes of pregnancy have been reported following infection with the previous SARS- and MERS- coronaviruses (15, 51, 86); hence the current pandemic SARS-CoV-2 aggravates the apprehension related to maternal and fetal well-being. Initially, there have been fears associated with SARS-CoV-2 led pregnancy complications and adverse fetal outcomes (26, 28, 115, 116). Further studies with large sample sizes (116 in China and 427 in the UK) ruled out such apprehensions, however, and demonstrated a higher rate of cesarian section deliveries (4, 104, 117, 118).

Risk to the Mother

Few studies suggest mild illness in COVID-19 confirmed pregnant females with lower mortality than the non-pregnant COVID-19 patients (119) and premature delivery as a major adverse fetal outcome (119). As per a month's rigorous surveillance in Sweden, a requirement of intensive care for COVID-19 confirmed pregnant and early postpartum women has been reported (120) at a relative risk of 5.4 (95% CI, 2.89–10.08). The patients also required invasive mechanical ventilation with a relative risk of 4.0 (95% CI 1.75–9.14) in contrast to the non-pregnant women of similar age. An expansion of the denominator to include 50% more pregnancies (possible miscarriages and early intrauterine fatalities), still exhibited a high RR 3.5 (95% CI, 1.86–6.52). These findings, although are from only 53 patients aged between 20 and 45 years without any information on co-morbidities, reflect the need to focus and further study the possible risks associated with SARS-CoV-2 infection in pregnant women (120). Another recent study aimed at investigating the outcomes of pregnancy and analysis of the clinical features in COVID-19 confirmed pregnancies vs. non-pregnant cases highlighted the worsening of morbidity with the progression of pregnancy due to SARS-CoV-2 infection. The mortality rate seemed to be unaffected in this retrospective analysis. The study analyzed the record of 188 pregnant cases and 799 age-matched non-pregnant counterparts from four tertiary care hospitals in Turkey. The severity of SARS-CoV-2 infection was significantly high in pregnant women especially at >20 weeks of gestation ($p < 0.001$). In comparison to non-pregnant cases, pregnant cases displayed significantly high frequency of oxygen support (10.1 vs. 4.8%; $p \leq 0.001$), intensive care unit admission (3.2 vs. 0.6%; $p = 0.009$), presence of fever (12.8 vs. 4.4%; $p < 0.001$), tachypnea (7.0 vs. 2.4%; $p = 0.003$), and tachycardia (16.0 vs. 1.9%; $p < 0.001$). Co-morbidities were present in 14.4% of pregnant women. Of the 188 pregnant cases, about 32% delivered (18.3% vaginal and 81.7% cesarean) during the SARS-CoV-2 infected state, with 66.7% at <37 weeks of the gestation period (121). Similar to Turkey, maternal mortalities have not been associated with SARS-CoV-2 infection in China (117, 122, 123). However, deaths have been reported from developing as well as developed nations (124, 125).

Although, under-reporting of maternal deaths due to COVID-19-related complications is highly likely, another issue while elucidating SARS-CoV-2 infected pregnancies is the lack of true denominator value. A possible solution may be to include the entire pregnancies in investigations, but the use of sophisticated and expensive techniques, like real-time RT-PCR for confirmatory diagnosis of SARS-CoV-2 infection, poses limitations. Reliable serological assays become when available may aid in resolving this constraint. Assessment of seroconversion rates in stratified unselected samples can be another approach (given the fact that blood specimens are commonly collected from pregnant women for routine antenatal investigations). Nevertheless, at present, robust estimates of COVID-19 severity and risk of morbidity and mortality in pregnant women are needed. For this, large-scale analysis from different geographical regions is required. Converging data from different countries would be necessary to neutralize the effects of confounding factors and outcome modifiers. Simulation/prediction models are only assumptions and hence, accurate clinical data with rigorous collection protocols, although more nuanced, would enable the generation of real scenarios. Although analysis and conclusions made out of small-scale uncontrolled studies need to be done cautiously, the risk of COVID-19 in pregnancy cannot be avoided.

Risk to the Developing Fetus

One of the major concerns of the medical fraternity during COVID-19 has been the vertical transmission of the SARS-CoV-2 infection and the adverse fetal outcomes. Although, there have been no reported cases of vertical transmission from SARS-/MERS-CoV infections, the fear existed in the case of SARS-CoV-2. The SARS-CoV-2 gains entry into the host cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is present in the placenta (126) and also expressed in syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle cells from both primary and secondary villi (127). Furthermore, there have been reports suggesting the presence of ACE2 in female reproductive organs, viz., ovary, uterus, and vagina (128). In a nutshell, the ACE2 receptor is expressed in a variety of tissues involved throughout a pregnancy period. A recent single-cell RNA sequencing investigation demonstrated ACE2 expression in the cells (stromal, perivascular, placental, and decidual) at the maternal-fetal interface (129). Another similar investigation by single-cell RNA sequencing highlighted the limited co-expression of ACE2 with the TMPRSS2 in placental cells throughout the pregnancy period, however, suggested viral entry into placenta cells via ACE2 and a non-canonical cell-entry mediator (130).

The adverse fetal outcomes include preterm labor and delivery, premature rupture of membranes, low birth weight, intrauterine fetal distress and growth restraint, feeding intolerance, asphyxia, pneumonia, and respiratory distress.

Such observations require further confirmatory studies, though. In one such case, a COVID-19 confirmed mother with severe complications, i.e., pneumonia with mechanical ventilation support, ECMO (extracorporeal membrane oxygenation), and MODS delivered a stillborne infant who was negative for SARS-CoV-2 infection (37).

With regard to vertical transmission, different studies involving patients in China, indicated an overall 2% (8/397) incidence of mother to fetus transmission of the virus (1). Yan and colleagues investigated 116 SARS-CoV-2 infected pregnant women (forming one of the largest cohorts) in China. Of the 100 neonates, 86 were sampled for nasopharyngeal swab (NPS) testing, and none of them were positive for the SARS-CoV-2 virus (117). Another large cohort study conducted in the United Kingdom investigated 427 pregnant COVID-19 patients. Of the 244 neonates sampled for NPS, 12 were positive for the SARS-CoV-2, indicating a 4.9% rate of vertical transmission (118). In another analysis done in a hospital located in New York, it was found that none of the 48 newborns, who were tested on the same day of birth, were positive for SARS-CoV-2 (131). In Italy, 3 out of 42 newborns, within 48 h of birth, exhibited positive SARS-CoV-2 NPS tests (132). As per the current data, a 3.5% (19/539) incidence of SARS-CoV-2 vertical transmission can be recorded (1) for the neonates tested outside China. As per a meta-analysis, of 38 cohort/case studies, performed by Kotlyar and the research group, an overall 3.2% pooled proportion tested positive for viral RNA in NPS of newborns sampled right after or within 48 h of birth (1). In another analysis, a rate of 3.91% was indicated for vertical transmission of the SARS-CoV-2 based on viral RNA positivity (119). In an interesting study on a neonate born to a COVID-19 confirmed mother, anti-SARS-CoV-2 IgG and IgM antibodies were detected 2 h after delivery. Also, the infant showed elevated levels of cytokines, however, the viral RNA could not be detected in NPS, placenta, umbilical cord blood, amniotic fluid, maternal blood, vaginal secretions, or even breastmilk (133). Few initial investigations done in China demonstrated the presence of anti-SARS-CoV-2 IgM antibodies in neonates born to COVID-19 confirmed mothers (134, 135), suggesting *in utero* viral transfer of IgM cannot pass through the placenta.

CHANGES IN MATERNAL IMMUNE SYSTEM DURING PREGNANCY

The onset of pregnancy imposes considerable challenges to maternal health. Right from the beginning, the pregnant female encounters risk from as close as the paternal alloantigens (expressed by both fetus and placenta). Fortunately, mother nature has taken care of the mothers-to-be, and, thus, a classic response to the paternal alloantigens is not observed in general (136); the alloantigens may retain maternal blood and tissue for a prolonged duration even after childbirth (137).

During pregnancy, circulation of monocytes, granulocytes, pDCs, and mDCs increases in blood with peaks occurring in two trimesters, with a parallel decrease in CD3, CD4, and CD8 T cells, as compared to the post-partum period. While the number of B cells declines in the third trimester, NK cells CD56 decline in the last two trimesters of pregnancy. The latter is also the time when levels of IFN-γ, TNF, and IL-6 decline in contrast to the post-partum period (138); however, these observations are contradictory (139). The number of maternal monocytes remains unaffected; instead, phenotypic alterations have been noted, such as elevated expression of CD11a, CD11b, CD54, and CD64 (139). By the 13th week of gestation, the maternal PBMCs begin to harbor phenotypic and functional modifications. Elevated secretion of IL-1β and IL-12 with a simultaneous decline in TNF-α is observed (140).

Maternal-Fetal Interface

The maternal-fetal interface is essentially formed by the placenta, which develops from the uterine wall and is capable to express various receptors and micro-vesicles (141). The placenta connects and provides hormonal, nutritional, and oxygen supply to the developing fetus while also moderating the mother's immune responses (142). Decidual cells, uterine NK cells, DCs, and Tregs form at the maternal side of the placenta, while the placental villus (fetal blood vessels along with fibroblasts) and placental villous macrophages are of fetal origin, and Hofbauer cells constitute the fetal side of the placenta (61, 143). The number of regulatory T cells (Tregs) increases in pregnancy, specifically in peripheral, deciduous, and umbilical cord blood (144). Such elevated numbers are important as the Tregs stimulate expression of IL-10 and TGF-β, which, in turn, modulates CD4+ T and CD8+ T lymphocyte levels during pregnancy (145).

Furthermore, in the early pregnancy period, NK cells (contributing to about 70% of decicuous leukocytes) are accumulated at the maternal-fetal interface in early pregnancy (146). Such an interesting feature is important since the NK cells modulate the release of cytokines and chemokines, control the invasion of trophoblasts, and warrant a sufficient supply of maternal blood (143, 146, 147). Also, changes in the hormone levels regulate maternal immune responses during pregnancy, for instance, the number of DCs and monocytes reduces, activation of macrophages, T, and B cells also declines (148). Estrogen reportedly stimulates Foxp3 Tregs in order to efficiently establish a tolerogenic milieu (149).

IMMUNOLOGICAL ACCOUNT OF SARS-COV-2 INFECTION DURING PREGNANCY

Serological investigations have indicated incidence of lymphopenia, neutrophilia, elevated CRP (C-reactive protein) (133, 150), ALT, AST, and D-dimer upon SARS-CoV-2 infection during pregnancy (133, 135, 151). In a study, few COVID-19 positive cases developed anemia and dyspnea (152). Another report highlighted the potential effects of altered calcium and albumin levels in the severity of SARS-CoV-2 infection during pregnancy (153, 154). Low platelet count has been linked to COVID-19 related deaths in pregnancy (155, 156). In spite of the indications from few cases, conclusive statements cannot be made on the effects exerted by SARS-CoV-2 on maternal and fetal health due to limited evidence. Long-term effects of stress and physiological temperature control in COVID-19 confirmed pregnancies are speculated. Elevated IL-10 levels in COVID-19 confirmed mothers may modulate inflammation and sustain pregnancy (64, 157).

A noteworthy observation following the 2009 influenza pandemic was a decline in cytokine response to bacterial infections. This is finding is crucial as it indicates that SARS-CoV-2 infection may also cause impaired immune responses to any other future infections or even insufficient immunological responses to vaccines.

CONCLUSION

Although, the role of virus infections in increasing morbidity and mortality during pregnancy is well-perceived, yet limited information is available on the mechanism of pregnancy-led maternal responses to viral invasion. The emergence of the current pandemic virus strain, i.e., SARS-CoV-2, has spanned a year; little is known about its pathogenesis, clinical signs, and symptoms, disease course, and the adverse outcomes it may have on maternal/fetal health. Furthermore, harboring of different mutations as per the geographical regions (158) suggests the adaptation of the SARS-CoV-2 and its continued circulation among humans. Dedicated studies involving appropriate methodology, controls, effective sample size, and assessment of various parameters need to be performed to ascertain the exact effects of the SARS-CoV-2 infection during different trimesters of pregnancy, effects of cytokine storm to neonatal well-being, and other potential implications. This would be essential in defining guidelines for mandatory testing and post-diagnosis perinatal care.

AUTHOR CONTRIBUTIONS

RR conceived, conceptualized, searched, analyzed the information/data, drafted the initial manuscript, and reviewed the final version. JS provided considerable intellectual input, analyzed the data, and reviewed the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Perinatal Mental Health Care for Women With Severe Mental Illness During the COVID-19 Pandemic in India—Challenges and Potential Solutions Based on Two Case Reports

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The ongoing COVID-19 pandemic in India has created several challenges in the care of women with perinatal mental illness. Access to healthcare has been disrupted by lockdowns, travel restrictions, and the unavailability of outpatient services. This report aims to discuss the challenges faced by women with severe mental illnesses during the perinatal period with the help of two case reports. Accordingly, we have highlighted the role of COVID-19 infection as a traumatic event during childbirth and its role in triggering a psychotic episode in women with vulnerabilities; difficulties faced by women with postpartum psychosis in accessing perinatal psychiatry services; and the challenges of admission into an inpatient Mother-Baby Unit (MBU). Further, we have discussed potential solutions from the perspectives of Lower and Middle-income (LAMI) countries that need to be extended beyond the pandemic. They include offering video consultations, reviewing hospital policies, and evolving strategies to mitigate traumatic experiences for pregnant and postpartum women with severe mental illnesses in both obstetric and psychiatric care.

Keywords: severe mental illness, COVID-19, challenges, virtual care, perinatal mental health

INTRODUCTION

Pregnancy and postpartum in women are vulnerable periods for developing severe mental illness (SMI) or exacerbating pre-existing psychiatric illnesses (1, 2). Globally, the COVID-19 pandemic has significantly affected the clinical care of patients with mental illnesses particularly those with severe mental illness. High-income countries have made necessary modifications which include reorganization of services for persons with SMI, early discharges, reduced ratio of the number of mental health care staff per inpatient in psychiatric hospitals, and the use of telepsychiatry services to cater to the population's mental health needs (3–5).

In India, the first case of COVID-19 was detected on 3rd February 2020. By mid-September 2020, India reached the peak of the first wave with 93,198 cases. At the height of the 1st wave, India had 0.85 deaths per million people. After that, there was a declining trend noted until 17th February 2021. The second wave hit the country in March 2021. At the time of this report, May 2021, India has the 2nd most active COVID-19 cases globally, with 2.31 deaths per million people due to COVID-19. During the last weeks of April 2021, India reported more than 3.5 Lakh cases in a single day. As of now, there is no official data on pregnant and postpartum women contracting COVID-19. As per the latest data on 3rd May 2021, India has 2,02,92,331 confirmed cases, among which 34,51,826 were active cases and 2,22,478 deceased due to COVID-19 (6, 7).

Like many other countries, India faced challenges in caring for people with mental illnesses due to specific changes imperative to the COVID-19 pandemic. These included the nationwide lockdown, which was imposed from 25th March 2020 to 30th May 2020. The lockdown necessitated travel restrictions and the closure of psychiatric outpatient services. In addition, several general hospitals were converted to COVID-19 designated hospitals to meet the increasing demand. As published reports indicate, psychiatric services were reorganized, whereby patients were primarily seen in emergency settings rather than in outpatient settings while being highly selective with inpatient admissions (8–10). However, there is no data on how perinatal psychiatric services were affected during the COVID-19 in LAMI countries.

The psychological impact of the COVID-19 pandemic on women during pregnancy and the postpartum period has been relatively high. Globally, evidence shows an increase in anxiety and depression and thoughts of self-harm among women in the perinatal period (11, 12). Fears due to pandemic-related measures like quarantine and isolation; and risk of exposure to infection and fetal transmission are a few factors related to the high psychological morbidity (11, 13, 14). Changes in the schedule of appointments, restrictions related to birth companions and a decrease in the number of postnatal visits have been other contributing factors (12). However, most of the data on COVID-19 related perinatal mental health problems focuses on common mental disorders such as anxiety and depression. There is limited literature on the challenges faced by women with severe mental illness in pregnancy or postpartum during the pandemic. Additionally, studies have shown a rise in intimate partner violence during the lockdown emphasizing the need for adequate and appropriate services (15–17).

Disruptions in healthcare due to disasters are common and the immense psychological distress caused in such circumstances is often overlooked. For example, a longitudinal study (18) from Japan highlights how the emotional upheaval caused by the Tsunami affected mothers' mental health and the struggle they went through to get appropriate help. Psychological distress continued to be prevalent up to 4 years after the disaster and common issues related to distress were economic problems, dissatisfaction in the marital relationship, and no support with childcare. A study from Nepal (19) indicates that there was an increased risk of common mental disorders among pregnant and postpartum women during the aftermath of an earthquake. The study also noted an increase in adverse birth outcomes. The study further suggests prioritizing the mental health of pregnant women in post-disaster management because of the burden experienced by the women and the associated risk to the growth and development of their babies. However, there is no data to draw parallels on the implications of COVID-19 for women with postpartum severe mental illness. The current report discusses through case examples, the challenges that women faced and how the perinatal psychiatric services in a LAMIC setting changed to accommodate the emerging needs of women with SMI during postpartum.

Case Study: Setting

The two women being described sought help from the Perinatal Psychiatric Services at the National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, India. The Perinatal Psychiatric Services include an exclusive weekly outpatient clinic for women with perinatal mental health problems and an inpatient Mother-Baby Unit (MBU). The clinic receives an average of 35–40 women every week, and the MBU has an average of 60–70 admissions a year (20).

The perinatal outpatient clinic and the MBU had to be closed as soon as the pandemic started. The MBU unit remained closed for 2 months, following which it was opened with restricted number of admissions. Outpatient services remained shut throughout. In the perinatal period, most women with SMI were attended to by emergency psychiatric services and a brief admission of 48 hours in a short stay ward. Women could reach the perinatal psychiatry services using a pre-existing perinatal helpline as well. Depending on the clinical severity, they were either admitted to the MBU or treated in the community setting, a preferred option. However, every attempt was made to liaise with the obstetric care services throughout pregnancy and postpartum. The two case reports described in the next section were chosen to describe challenges at two different points of care, i.e., the emergency psychiatry service and in the MBU. They represent similar experiences faced by other pregnant and postpartum women during this period.

Case 1

A woman in her thirties who tested positive for COVID-19 infection in July 2020, 4 days before her due date for delivery was referred for psychiatry care. She had no physical symptoms of COVID-19, such as fever, breathlessness, cough, or sore throat. She was admitted to a COVID-19 designated hospital for delivery instead of the hospital where she had earlier registered for delivery and received antenatal care. The baby was delivered in the COVID-19 designated hospital through an elective Cesarean section because of cephalo-pelvic disproportion (CPD) diagnosed earlier. Following the delivery, the infant was kept away from the mother for 5 days in the hospital nursery, and she was not allowed to breastfeed as per the hospital's policy at that time.

The infant was shown to her over video calls by a relative and the nursing staff. While speaking over the phone to her family, she described feeling isolated in the hospital, worried about not being able to breastfeed the baby, and feeling neglected by the hospital staff. She was discharged from the hospital on the 5th day postpartum and was advised home quarantine for the next 2 weeks as per government guidelines. All clinical decisions (i.e., the infant being kept away from the mother for 5 days, not being permitted to breastfeed or give expressed milk) were in line only with the hospital's protocol where she delivered. Available guidelines by WHO and others during that time however, did not restrict breastfeeding among mothers with COVID-19 infection or rooming-in (21–24).

On the tenth day postpartum, she started expressing guilt for having contracted COVID-19 and inconveniencing family members. She was afraid and anxious that she would transmit the COVID-19 infection to the infant and family members and had left home on one occasion saying that the infant was better off without her. However, the family grew concerned when they observed that she poured water over herself for no reason, started neglecting the infant, stopped caring for herself, and expressed ideas of self-harm. The family knew about the perinatal psychiatry helpline as she had been treated for a previous episode of postpartum psychosis and contacted the service.

During the previous postpartum period, she was diagnosed to have Psychosis NOS when she reported suspiciousness, hearing voices, and irritability. As a result, she was on Risperidone 4 mg for 3 years, after which she stopped medication on her own. However, she was well during her pregnancy.

Through video calls, patient was assessed by our team, and an ICD-10 diagnosis of Acute Polymorphic Psychotic disorder-without symptoms of schizophrenia (ICD Code-F23.0) with postpartum onset was made. In addition, a differential diagnosis of Organic Psychotic Disorder was considered keeping in mind possible neuropsychiatric manifestation of COVID-19. However, there was no history of delirium or symptoms and signs of an organic disorder.

It appeared that the combination of a COVID-19 diagnosis, the subsequent isolation, and separation from the infant was a traumatic experience and a possible triggering factor for postpartum psychiatric illness. She was advised inpatient admission. However, the family requested home-based care.

Challenges in the Inpatient Care and Mother-Infant Care

Mental status examinations had to be done via video calls. It was a challenge to rule out organicity through video calls, and a physical examination was not possible. Her progress was reviewed daily over video consultation by the senior resident in the team for a week and weekly once thereafter. The assessments focused on symptoms of psychosis, anxiety, and PTSD as well as any risk of harm to self or infant. Given the good initial response to Tab. Risperidone, she was prescribed the same up to 6 mg. She showed gradual improvement over 2 weeks and was encouraged to breastfeed her infant using all precautions. However, she continued to be anxious about spreading COVID-19 infection to her infant.

Maternal-infant bonding assessment and infant's developmental assessment were also done over video calls. Overall, based on observation, informal review, and parental reports, the infant had age-appropriate development, and mother-infant bonding gradually improved.

While all attempts were made to use telepsychiatry for infant assessment and mother-infant bonding which are essential components of care when the mother has postpartum psychosis, these were difficult to conduct. Postpartum psychiatric illnesses affect mother-infant bonding and warrant early interventions to prevent long-term effects (20, 25, 26). Assessment of infants for attention, object tracking, play, and other parameters of cognitive development is challenging to conduct virtually, and clinicians need to rely on the information given by the family. Also, one cannot expect the infant always to face the phone screen during a virtual assessment. In our dyadic assessment, appointments were canceled twice due to the infant's immunization schedule, and the infant was asleep. Technical difficulties in the evaluation included not getting the mother and the baby in one frame and frequent interruptions due to poor internet connectivity.

Overcoming the Barriers

Many of the challenges were handled by teleconsultations (video calls over the phone). Prescriptions were sent online, and when in doubt, the family contacted us through the perinatal phone helpline. A virtual physical examination using questions to rule out organicity was performed. Infant's development and mother infant bonding were assessed over video calls, and weekly follow-ups ensured contact with the dyad and the family.

Case 2

Our second case is a 25 year old woman who sought help for relapse of her mental illness in the postpartum following an unplanned pregnancy. She had been receiving treatment for bipolar affective disorder, and the current episode, which started in the second trimester, worsened on the 20th day of the postpartum. This episode was precipitated by treatment non-adherence for 2 weeks as the patient was unable to follow up in the outpatient due to travel restrictions and had stopped medications as they were not available during the lockdown. In addition to Bipolar Disorder, she also had several personality traits such as impulsivity and sensitivity to criticism which added to the clinical problems. She had been prescribed Tab. Lithium 900 mg and Tab Risperidone 2 mg, but she was irregular with her medications after fights with family members. Two weeks after stopping the medication during the lockdown, she started showing several symptoms such as irritability, increased energy levels, overfamiliarity, disinhibition, overspending, overgrooming, elevated self-esteem, decreased need for sleep, and multiple delusions of infidelity, reference, and persecution. She had also made suicidal attempts of high intentionality and lethality.

She delivered a male baby in a charitable health care center, where no psychiatrist was available. Her manic symptoms were not identified or treated, and gradually she became unmanageable at home. In the emergency psychiatry service, the initial assessment revealed a high risk of harm to self and others. Patient and her caregiver were required to take the COVID-19 test in the emergency ward before inpatient care as per hospital protocol. The infant had to be under the supervision of his grandmother because she was unable to care for him and the family was concerned about COVID 19 infection. She was admitted to the MBU (which had reopened in July 2020) but left against medical advice as she found it difficult to follow COVID 19 appropriate behavior. She was brought back by family members on the second day as she remained challenging to manage at home. The treating team decided on providing electroconvulsive therapy (ECT) because of high suicidal risk. She was given six bifrontal ECTs on alternate days, with threshold ECT charge being 120 mC, Pulse amplitude 800 mA, pulse width 1.5 ms, pulse pair frequency 62.5 Hz, average motor seizure duration 30 s. She showed improvement following the ECTs. The hospital had developed a specific protocol for ECTs for the COVID 19 pandemic which included organization and training of ECT services team such as mandatory COVID-19 testing before initiating ECTs, use of personal protective equipments, modifications in ECT administration and recovery areas, use of heat and moisture exchanger (HME) filters, appropriate cleaning and disinfection (27).

In the MBU, where she was admitted with her mother in law as a caregiver (who also had to be tested for COVID 19 before admission), she was disinterested in infant care and had poor mother-infant bonding. The team planned mother-infant bonding interventions, but within a few days, she had to be categorized at high risk of exposure to COVID-19 after another patient in the adjacent ward tested positive for the virus. Due to her symptoms, she would insist on interacting with other patients without a mask and without keeping social distance. The family was worried about the possibility of COVID-19 exposure due to her behavior and requested early discharge despite only partial clinical improvement and poor bonding with the infant.

Challenges in Inpatient Care and Mother-Infant Care

The woman had to undergo repeated testing for COVID-19 infection, which caused a lot of stress and inconvenience for both the patient and the family. Her admission was delayed due to the protocol of mandatory testing for COVID-19 for inpatients as well as any caregivers who stayed with them. After being discharged from the hospital, she found it difficult to come for follow-ups due to travel restrictions.

Overcoming the Barriers

Despite the interruption in her routine inpatient care, the family continued to stay in touch with the service over the perinatal psychiatry helpline. However, mother-infant bonding and infant care continued to be poor, and the infant had to be under the supervision of his grandmother. The family was advised to bring the patient and infant for mother-infant bonding and developmental assessment on an outpatient basis in the perinatal clinic. However, she did not adhere to the advice due to fear of COVID-19. Telephonic follows up were done with the grandmother, who reported that the infant was doing well and was on formula feeds as the mother did not want to breastfeed.

DISCUSSION

Any natural disaster can have cross-sectional and longitudinal implications for the mental health of pregnant and postpartum women. However, research focusing on perinatal women with severe mental illness is scarce. The two cases described above exemplify the challenges faced by women who need perinatal mental health services during the pandemic and how the system may adapt itself to suit these needs. With the COVID-19 pandemic, numerous unforeseen barriers have emerged which have negatively impacted the mental health of pregnant and postpartum women. Having a severe mental illness itself causes many challenges, and when a crisis like COVID-19 happens, the challenges become more complex. A survey conducted in the UK to understand the perception of mental health staff who closely worked with women with mental health problems in the perinatal period has highlighted some critical concerns (28). The survey revealed that lack of access to usual support networks, feeling lonely, lack of work and activities, worries about contracting COVID-19 infection, poor access to mental health services, increased risk from abusive domestic relationships, and the risks of relapse were significant concerns. We have observed and faced similar circumstances in our MBU in India, as highlighted by the two case reports.

Perinatal psychiatric services include outpatient services and MBU, which are dedicated to women with severe mental illnesses. Studies have shown that mother-infant dyads admitted to MBUs have good clinical outcomes and low readmission rates (20). MBUs provide holistic services ranging from pre-conception counseling to handling mental health problems during pregnancy and postpartum and providing dyadic interventions. While most high-income countries have these facilities, such specialized services are scarce in most LAMI countries, where the mental healthcare systems are often fragmented. The current pandemic has worsened the situation, and it has been reported that many women have had no access to medical termination of pregnancy or contraceptive services during lockdowns (29) which might have led to unplanned pregnancies in women with severe mental illness. Besides, there has been an inadequate supply of medications for those with pre-existing psychiatric problems and ineffective communication between mental health providers and women with mental illnesses of the child-bearing age. Existing literature also suggests a rise in intimate partner violence in women during the COVID-19 pandemic, which adds to the challenges of providing optimum mental health care and increases the risk of postpartum mental health problems (30).

The COVID-19 task force of the Research Innovation and Sustainable Pan-European Network in Peripartum Depression Disorder (RISEUP-PPD) report discusses good practices in perinatal mental health care during the COVID-19 pandemic (12). The report includes providing information about psychological issues and ensuring adequate social support involving partners and immediate caregivers in the care of mothers during pregnancy and childbirth. The report also emphasizes the need for identifying and facilitating sources for help, case detection, and emotional support for women facing intimate partner violence in the postpartum period. While the International Marcé Society for perinatal psychiatry has developed a series of COVID-19 related resources, most of these are about women with anxiety, depression, or trauma-related symptoms (31). Not much has been written about pregnant or postpartum women with severe mental illnesses and their care during the COVD-19 pandemic, especially in LAMI countries.

POTENTIAL SOLUTIONS WHICH HELP DURING THE PANDEMIC MUST CONTINUE BEYOND THE PANDEMIC

There is a need for "women friendly" hospital policies focusing on COVID-19 and for the post-pandemic period to identify, screen and treat common and severe mental illness during pregnancy and postpartum. Appropriate changes are needed at the policy level for women at risk of mental health problems, which include maternity hospitals ensuring the presence of caregivers during delivery and postpartum; adequate counseling to the mothers if they have COVID-19 infection; and sensitive guidance regarding rooming-in and breastfeeding keeping the interest of the mother-infant dyad. There is also a great need to integrate mental health services in existing COVID-19 related obstetric health care services (32, 33). Guidelines and policies in obstetric units should emphasize liaison with mental health professionals to address women's mental health concerns in the perinatal period, especially for those women who have pre existing mental health problems and are more vulnerable. Priority should be given to provide prompt COVID-19 test results for postpartum mothers in psychiatric services so that they can be provided inpatient care early. All the above measures may help prevent excessive trauma and stress, especially in vulnerable women. Obstetricians, midwives and pediatricians need to be trained in early identification and there is a need to strengthen referral services.

Trauma-Informed Care

In addition to the usual perinatal mental health problems that one sees, there has been an increase in trauma-related symptoms during the pandemic. Hence, there is a need to evolve trauma-informed services in MBUs (34, 35). The goal is to address fear, anxiety, stress, grief, and other signs of psychological distress and provide psychological support in COVID-19 care maternity wards.

Virtual Interventions and Perinatal Phone Helplines

In LAMI countries like India, there is a significant treatment gap for persons with mental illness, which has worsened during the pandemic. The COVID-19 pandemic has taught us that this gap could be bridged to some extent by using technology (36). However, technology comes with its own set of unique challenges such as internet connectivity issues, privacy problems when women live in joint families and crowded housing, and problems related to virtual assessment of mother-infant dyadic relationships. There is a need to evolve telepsychiatry protocols for helping women with infants living in remote locations, in low-income settings, and those facing IPV (37). Virtual interventions have shown promise in delivering care adequately to perinatal women with depression and anxiety. However, their role in women with postpartum psychosis is still not very clear (38, 39).

Telephonic helpline services provide a more accessible alternative for women to access health care even in LAMI countries. Through helplines, women can access information, identify and manage symptoms, and seek help when necessary, including post-discharge care (40). For example, a study from our MBU in India prior to the pandemic found that a Perinatal Mental Health helpline is useful in addressing a wide range of concerns including medication schedules and side effects, symptom exacerbation, suicide risk, pre conception planning, breastfeeding problems, and seeking appointments (41). Started much before the COVID-19 pandemic, in 2016, the already existing perinatal phone helpline was an extremely useful resource for women with SMI during the pandemic, as exemplified in the cases discussed above.

CONCLUSIONS AND FUTURE DIRECTIONS

Mental health implications of the COVID-19 pandemic for pregnant and postpartum women are comparable to other disasters. However, the COVID-19 pandemic created a different set of challenges because of the risk of infection, the prolonged nature of the pandemic and inability to access resources due to lockdowns and travel restrictions. It led to a decline in women accessing care for perinatal mental health problems and this had a negative impact especially among those with SMI. The pandemic has also exposed the inadequacies of liaison between obstetric and mental health care systems in LAMI countries and revealed pre-existing deficiencies in the care of pregnant and postpartum women with mental illness. Immediate attention is needed to support postnatal mothers and provisions made for continued mother-infant interactions. There is also a need for revisiting hospital policies that restrict the physical presence of caregivers during childbirth in obstetric units. Attempts must be made to enhance care, security, and safety which may alleviate traumatic experiences and psychological distress during and following childbirth. In psychiatric settings, special consideration must be given to mothers with infants for rapid testing and reporting for COVID infection to prevent delays in admission and intervention. There is also a need for further research in the most appropriate methods for virtual assessments of mental status of women with postpartum psychosis, mother-infant interaction and infant development and addressing the needs of perinatal women facing domestic violence.

ETHICS STATEMENT

Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Health and Gender Inequalities of the COVID-19 Pandemic: Adverse Impacts on Women's Health, Wealth and Social Welfare

Roberta Guerrina[1†], Bettina Borisch[2†], Leigh F. Callahan[3,4,5†], Jeremy Howick[6†], Jean-Yves Reginster[7†] and Ali Mobasheri[7,8,9,10,11*†]

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In this paper we discuss the nexus of health and gender inequalities associated with the COVID-19 pandemic and highlight its adverse impacts on women's health, welfare and social standing. The COVID-19 pandemic has exposed the link between socio-economic inequalities and health outcomes, especially in the area of rheumatic and musculoskeletal (RMDs) diseases. Women are more adversely affected by RMDs diseases compared to men. Epidemiological research carried out over several decades has demonstrated the presence of clear gender patterns in the manifestation of musculoskeletal diseases, including osteoarthritis (OA), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SS) and osteoporosis (OP). The public health measures that have been adopted to curb the spread of Sars-COV-2 are expected to have a particularly detrimental impact on women in the long term precisely because of the nexus between health outcomes and socio-economic structures. Moreover, the prioritization of urgent care will further compound this effect. COVID-19 has created a condition of ontological insecurity that is becoming increasingly manifested through various chronic diseases and associated comorbidities. RMDs and their impact on mobility and the ability of individuals to be independent, happy and mobile is a key public health challenge in the post-COVID-19 reality and a key part of the ongoing pandemic. There is an urgent need to engage with policymakers to publicize and prioritize this problem and develop viable solutions to address it.

Keywords: COVID-19, pandemic, gender, global health, women's health

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus (1). Most people infected with the COVID-19 virus experience mild to moderate respiratory illness and recover without requiring special treatment (2). However, older individuals, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness and die from COVID-19 (3). At the time of writing (20 February 2021) this pandemic has resulted in more than 2,467,342 deaths according to the World Health Organization[1] and the European Center for Disease Prevention and Control[2].

The COVID-19 pandemic has had unprecedented and potentially irreversible impacts on health and healthcare globally with ongoing and adverse impacts on the economy (4). There are significant health, race and gender inequalities associated with the COVID-19 pandemic (5). There are therefore many complex issues and factors that need to be accounted for as we look at the long-term impact of COVID-19 on the very fabric of humanity and society and how this ongoing crisis continues to affect health and social care outcomes for different groups. This paper aims to summarize our key concerns in relation to the social determinants of health (SDH).

A very brief analysis of both gender and race in the context of the global pandemic highlight a number of issues that warrant further consideration:

- Frontline workers are overwhelmingly women (**Figure 1**) and employed women are much more likely than employed men to have care responsibilities (**Figure 2**). The high proportion of women deployed as "frontline" service workers across a range of professions (6). This arises from both the vertical and the horizontal segregation of the labor market. In other words, women tend to occupy lower paid positions and are often associated with social function of "care." These same positions have historically been classed as "low skilled" to justify lower pay in care services and delivery. Women thus play a disproportionate role in frontline health and social care roles and perform the majority of caregiving responsibilities.
- Growing awareness of the role of key workers during this latest crisis could provide a moment of reflection and recognition about the centrality of these roles to society and the economy. It *should* thus open a space to revalue "care" as a function that is central to the human condition; such reckoning or recognition, however, will require the political ambition to imagine a post-COVID-19 recovery in which care is an integral part of the economic infrastructure.
- Gender disparities are also emerging in terms of health outcomes. As a result gendered work and division of the healthcare labor market, women are more exposed to COVID-19, and at a much higher viral load than men (6). We do not yet know the long term health consequences of this level of exposure. Whereas, women make up a smaller percentage of the severe COVID-19 cases presenting in hospitals (7), they seem to be more likely to suffer from long-COVID-19 (8).
- There are also serious issues regarding the impact of COVID-19 on Black, Asian and Minority Ethnic (BAME) communities. A systematic review of the published literature on COVID-19 articles in some of the most prestigious medical journals including New England Journal of Medicine, Lancet, British Medical Journal and the Journal of the American Medical Association plus EMBASE, MEDLINE, Cochrane Library, PROSPERO, clinical trial protocols, gray literature, surveillance data and preprint articles in MedRxiv has revealed that BAME individuals had an increased risk of infection with SARS-CoV-2 compared to white individuals and, 12 studies eported worse clinical outcomes, including intensive care unit admission and mortality (9). It is interesting to note that traditionally, very few analyses have drawn the link between co-morbidities associated with pandemics and socio-economic structures e.g., gender, class and race. The wealth of data collected during this pandemic is forcing us to re-evaluate the way we think about the serious shortcoming of any socio-political, economic and medical analysis of the pandemic that does not centers the link between these "social issues" and health outcomes.
- COVID-19 is bringing to light a number of "blind-spots" in public and health policy (10). It is thus an opportunity to draw attention to the importance of impact assessments, not just in policy making but also research in order to avoid "unintended" consequences that have an asymmetrical impact on different demographic groups.

This paper is the result of a series of e-mail exchanges, Zoom meetings, telephone conversations and videoconferences between a group of scientists working in different disciplines including medicine, political sciences, global health and philosophy. Three of the authors have interest and expertise in the field of musculoskeletal diseases. Therefore, an inevitable consequence of this collaboration is the framing of some of the adverse impacts of the COVID-19 pandemic in the context of mobility, or rather reduced physical activity during the lockdown phases of the pandemic and musculoskeletal health and disease in women. However, before focusing on musculoskeletal health in women we explore the concept of gender imbalance in the aftermath of the COVID-19 pandemic.

GENDERING COVID-19

Mapping the multiple and intersecting ways that governments respond to COVID-19 affects different demographic groups in the short, medium and long term is crucial for understanding the immediate and long-term socio-economic impacts of the 2020 pandemic (11–15). There is a wealth of evidence that directly links health outcomes to socio-economic factors. Poverty, poor education, tobacco use, unhealthy diets, physical inactivity and excessive consumption of alcohol are factors that determine poor health outcomes (16). Often cited predictors of positive health outcomes are a nutritional balanced diet and free access

[1] https://www.who.int
[2] https://www.ecdc.europa.eu/en/covid-19-pandemic

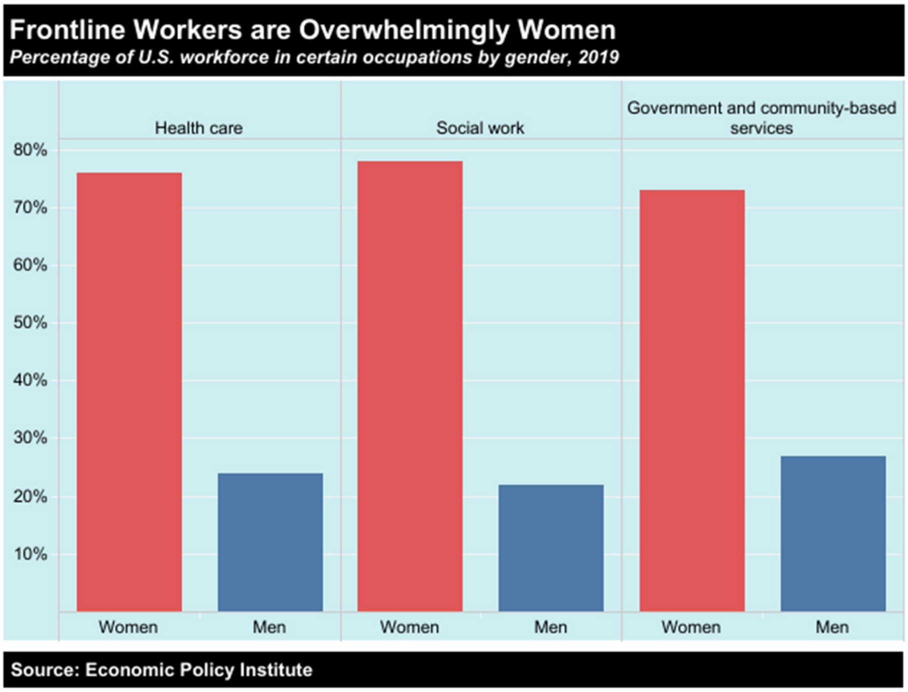

FIGURE 1 | Frontline jobs, which are deemed "essential" and require people to work in-person, are heavily staffed by women. The healthcare, social work, and government and community-based services sectors are overwhelmingly made up of female employees, according to research from the Economic Policy Institute (https://www.epi.org/).

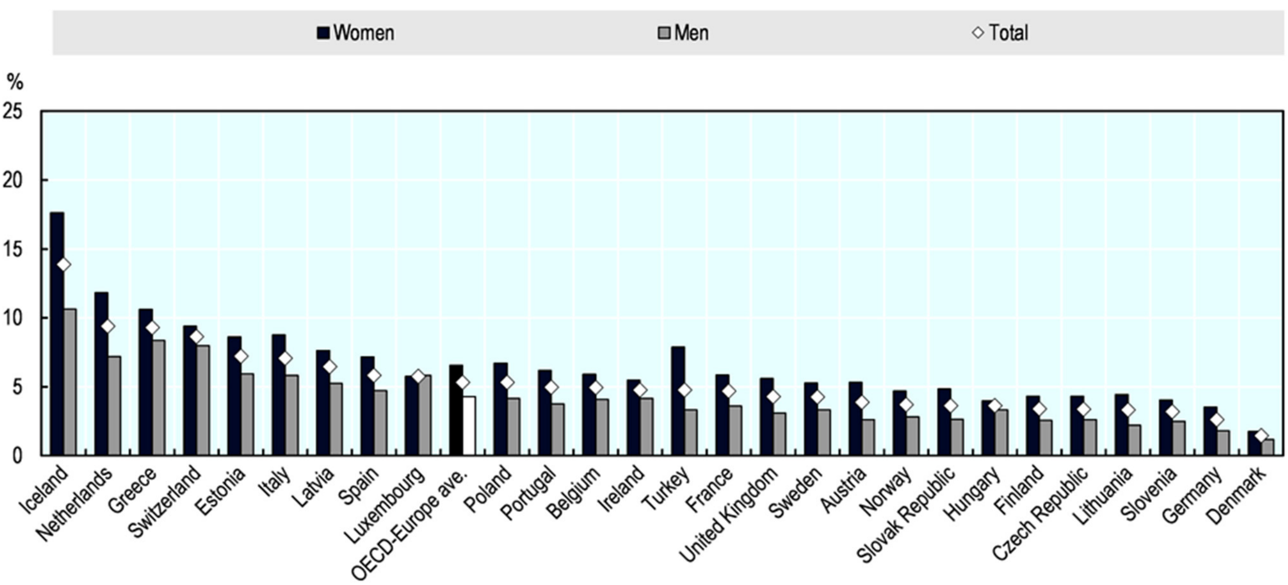

FIGURE 2 | Employed women are much more likely than employed men to have care responsibilities. Share of employed persons reporting that they regularly take care of ill or disabled or elderly adult relatives, by sex, European OECD countries, 2018. The data represents share of the employed population who report taking care of ill or disabled or elderly adult relatives (15-year-olds and older), regularly. The relative may live in- or outside the household. Source: Eurostat Database, based on the European Union Labor Force Survey *ad-hoc* module 2018, https://ec.europa.eu/eurostat/data/database.

to safe places for engaging in physical activity (17–20). Perhaps focusing on diet and exercise is not surprising as they can be easily quantified and correlated to the onset of disease, as well as its course of progression. However, there are also a number of "soft" factors that intervene and exacerbate the impact of economic and environmental factors on health outcomes. These soft factors, e.g., gender divisions of labor in the domestic sphere or cultural factors/norms determine opportunities and constraints for different groups of the population to adhere to health advice. When trying to understand the equality and diversity impact of government responses to COVID-19 it is essential that population groups are not treated as homogenous. Populations are extremely heterogeneous at all levels of society and it is crucial for the society to be viewed as multi-layered and diverse. For instance the experience of women during the various COVID-19 "lockdowns" and quarantines will be determined by their socio-economic status, their religious and cultural affiliations, education, ethnic background, employment and parental status, specifically the age of their children.

The focus of our analysis revolves around the "unintended consequences" of policy decisions that fail to carry out adequate equality and diversity impact assessment at the point in which policies are being designed and decided. There is a note of caution here: the nature of the current crisis created an inevitable urgency to act or be seen to act. It also required policy makers to identify priorities, including health priorities. This is not in itself a problem, however lack of representation of diverse sets of interests at the conceptualization stages of any policy are likely to entrench implicit bias by overlooking the concerns of minoritized and marginalized groups.

In terms of gendered dynamics a few initial observations can give us pause for thought. First and foremost, quarantine is predicated on the assumption that the "threat" to an individual's health and safety occurs in the public sphere. Hence the slogan: "stay home, save lives…" Another important aspect is the "individualization of experience," primarily lived inside one's home, is a building block of civic responsibility … "we are in it together." This discursive framing, however, disregards the fact that the domestic sphere is not a place of safety for survivors of domestic abuse. Hence the increase in calls to helplines which speaks to current work on (gendered) regimes of violence (21).

It is in this context that important dynamics can be observed that highlight the continued impact of gender regimes in women's experience of work-life balance. Aside from gender differences in patients with COVID-19 (22), recent surveys are pointing to the reassertion of private gender regime as a result of the pandemic. Social reproduction increases women's responsibilities to provide care, in many cases in addition to paid work. Quarantine decisions have had a direct impact on women's freedom and their ability to exercise and adhere to medical advice. For instance, school closures and requirements for home schooling, particularly of primary age children is having an impact on women's earnings and their financial independence. As a result of the struggle to balance paid work and social reproduction many women are likely to be affected in the short, medium and long term by the decisions taken in the first half of 2020 and, in the UK and many other countries in lockdowns introduced as the second wave was starting. These patterns have, in turn, had a detrimental impact on women's access to "leisure" including exercise required for managing musculoskeletal conditions, which we will focus on.

Women make up the majority of the health and social care workforce on the "front line" of the COVID-19 pandemic, e.g., as nurses and carers (23–25). It is interesting to note that the feminisation of the labor force and economic activity in the public sphere during the pandemic also reflects women's nurturing role in social reproduction. Quarantine requires individuals to take responsibility for their health by decreasing movement and adhering to strict confinement guidelines. In this context, "failure" to continue with exercise regimes and physical activity to manage health conditions is the responsibility of an individual and in some countries and territories it is a shared decision-making process with a healthcare practitioner.

This has allowed policy-makers to overlook the impact of women's role in social reproduction and the increasing weight of the double burden in the domestic sphere. Quarantine is also prioritizing COVID-19 as a health "threat." This approach reinforces the health pyramid, which positions musculoskeletal health much lower on list of priorities for healthcare providers. It is well-established that a range of chronic conditions that affect minoritized and marginal groups are often overlooked. The question to address here is whether COVID-19 will compound existing problems of unconscious bias in medicine, and how these interact with wider gender norms and hierarchies during times of crisis.

Here are some key questions from an Equality, Diversity and Inclusion (EDI) perspective:

- What are the pathways for incorporating concerns around equality and inclusion into the story of COVID-19? There is substantial discussion at the moment about highly visible issues, e.g., higher death rates amongst black and minority communities, domestic abuse, but will this be included in the official record of the 2020 pandemic?
- What are the "blind spots" of policy? For example the impact of gender divisions of labor and the double burden on women's experience of public health measures during the Covid-19 crisis. What is the short, medium and long term impact of such omissions?
- How will the policy decisions of the first 6 months of 2020 affect men and women's experiences and health outcomes in the next 5 or 10 years?
- What are the costs of failing to carry out equality and diversity impact assessments in the context of this crisis?

These questions need to be examined within a broad context that positions the equalities agenda at the heart of the national and transnational policy agenda. The Sustainable Development Goals specifically include obligations to advance gender equality (SDG5) and reducing inequalities (SDG10).

THE INTERNATIONAL CONTEXT: THE SUSTAINABLE DEVELOPMENT GOALS 5 AND 10

A total of 17 Sustainable Development Goals (SDG) were established by the United Nations in 2015[3]. Sustainable

[3]https://www.un.org/sustainabledevelopment/blog/2015/12/sustainable-development-goals-kick-off-with-start-of-new-year/

Development Goals 5 and 10 focusing, respectively, on gender equality and reduced inequalities are particularly relevant to this paper. The official wording of SDG 5 is "Achieve gender equality and empower all women and girls." The official wording of SDG 10 is "Reduce inequality within and among countries" (26).

With regard to SDG 10 and COVID-19, there are two area to focus on, especially in relation to health outcomes:

- It is important not to assume that women's experience of COVID is homogeneous. Although a lot of the focus of the media coverage is on reconciliation between work and family life experienced by mostly white professional women, who became responsible for home schooling etc., the challenges faced by many BAME or minoritised women, often employed as frontline workers, is significantly different.
- The international picture is becoming increasingly complex, though there are some trends that can be identified. Intersectionality it's becoming more important and in relation to SDGs and the international trajectory of the COVID-19 pandemic, what is not yet clear is what role are women playing in the global south in managing community based responses to the pandemic.

The SDG implicitly and explicitly recognize that development, cohesion, and social justice go hand in hand. COVID-19, however, expose the varied ways in which socio-economic inequalities shape public health approaches and thus defined health outcomes. In the next two sections we will explore the interaction between the social and the physical generates a deep sense of ontological insecurity (27, 28).

EXACERBATION OF MUSCULOSKELETAL HEALTH INEQUALITIES

Women have a higher prevalence of RMDs including osteoarthritis (OA), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SS) and osteoporosis (OP) and probably sarcopenia as well. Therefore, as a consequence women have a much higher risk of developing cardiovascular comorbidities (29–34). Subsequently, any external threats, such as the restrictions and lockdowns experienced during the COVID-19 pandemic, are clearly going to have adverse effects on musculoskeletal disease diagnosis and management and this will affect females more significantly than males (35).

Osteoporosis, Fractures and Bone Health

The endogenous production of vitamin D is dependent on sunshine exposure (36). However, because of lockdowns and containment, particularly at the end of the Winter and during the Spring, many elderly subjects, especially those in care homes will remain with circulating levels of vitamin D which are insufficient for bone, joint and muscle health, hence increasing their risk for falls and fractures (37).

In many low income countries musculoskeletal diseases are not considered to be health priorities and when epidemics and pandemics occur low income countries take the brunt and bear the harshest consequences (38–40). Even in the global North musculoskeletal disease has had to take second place to the health emergency associated with the pandemic. The pandemic has crystallized a heath hierarchy that prioritizes life threatening conditions over chronic disease. Visits to general practitioners have been significantly hampered during the COVID-19 lockdown (41, 42). Routine and planned diagnostic procedures such as radiography, ultrasound, and magnetic resonance imaging (MRI) have been delayed and postponed. Subsequently, the initiation of treatment for many musculoskeletal diseases has been delayed for many weeks and months with adverse effects on patients who desperately needed it; many of these patients are women. There is evidence from the most advanced economies that orthopedic surgery is now several months behind schedule. It will be extremely difficult, if not almost impossible to catch up. As a result many patients will not receive the surgical care that had been planned for them before the outbreak.

There is now an acute and almost frightening problem in OP management where patients with an incident fracture (spinal, forearm) which does not require hospitalization have had their post-fracture visit postponed until the re-opening of non-urgent consultations/technical examinations (e.g., DXA, X-Rays). Knowing that a recent fracture is one of the major risk factors to present with a new subsequent fracture, this may generate a major risk for these patients.

Monitoring Treatment

One of the major issues in the management of chronic silent disorders is the lack of adherence to treatment goals. The lockdown has prevented patients from getting their prescriptions renewed on time. Also, many patients have gone without consultations with their general practitioner, which means that they have not received the positive feedback that is normally provided by consultation with their regular physician, hence increasing the risk of premature treatment discontinuation. Some of the drugs (IV formulations) are given under the responsibility of a registered nurse or of a physician. All these treatments were delayed during the lockdown with long-term adverse impacts on women's health.

Mental Health and Anxiety

Depression and anxiety and physical violence will occur, particularly in people who are contained in small apartments, with children and/or pets. In this case, most of the house work will frequently be the responsibility of the homemaker, frequently women. This additional burden, leading to some kind of domestic burn-out will impact also on the motivation to either take the needed medications, to take physical exercise or to comply with the principles of bone/joint/muscle-health and nutrition. Compliance and adherence often requires input from healthcare practitioners. The lockdown has meant reduced opportunities for interactions between patients and their healthcare practitioners, exacerbating the anxiety associated with disease and the burden of the disease itself.

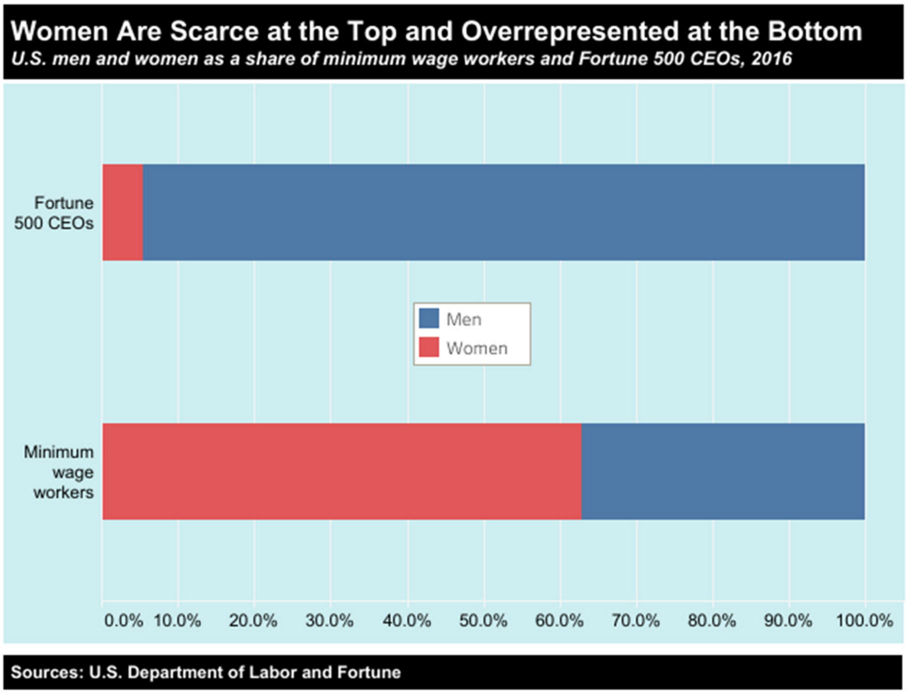

FIGURE 3 | Women are under represented at the top of the wealth pyramid and over represented at the bottom, occupying the lowest paid jobs in society, according to the United States Department of Labor (https://www.dol.gov).

COVID-19 AS A JUNCTURE FOR SOCIO-ECONOMIC INEQUALITIES IN MUSCULOSKELETAL HEALTH OUTCOMES

As outlined previously COVID-19 has laid bare long standing socio-economic inequalities (5, 43) and wealth inequalities. Beyond the increase in women's double burdened due to remote learning and childcare closures, there are important links to be made between these broader trends and long-term health outcomes for women. Rising levels of gender based violence and abuse have received significant attention, however there are also needs to be research on the impact of public health measures on women's long-term musculoskeletal health, especially relating to OP and OA.

There are important parallels between economic and medical hierarchies. Female-dominated occupations—such as childcare and hospitality—continue to occupy the lower rungs of the wage ladder. In the United States women make up 63 percent of workers earning the federal minimum wage, a wage rate that has been stuck at $7.25 since 2009. In contrast, women represent only 5 percent of CEOs at Fortune 500 firms (**Figure 3**). The loss of income resulting from public health measures associated with COVID-19 will exacerbate social inequalities in access to healthcare. Musculoskeletal diseases are also located lower in the hierarchy of needs and individuals relying on national health provisions to access treatment for musculoskeletal diseases are likely to be one of the worst affected. Delay in treatment however will not only have an impact on their health outcomes, but it will also curtail their ability to participate fully in the employment market. This will in turn increase the medium and long terms social and economic costs to the individual and society.

Throughout the pandemic political leaders have claimed to "follow the science" (44). The explicit implication of this statement is that science determines a particular policy approach has damaged the relationship between science, society and the development of and implementation of policy (45). Decision making processes, however, are much more complex as scientific evidence is balanced against, or perhaps alongside, wider political priorities. What COVID-19 has highlighted is that it is politics, rather than science, that determines policy. The inference from science to policy is not straightforward and is often highly problematic. If it were, there would not be the wide range of policies being implemented within and across countries. While it is disputed, the Scottish philosopher David Hume warned us against inferring an *ought* from an *is*. Leaving aside the question of whether the science tells us what is (the facts about COVID-19, at least initially, were murky at best), it does not imply any particular course of action. For example, we have known for several months now that COVID-19 is virulent and dangerous, but it does not represent the existential risk that some feared initially. Determining the right policy based on those facts depends on what the harms of the policy are, and what the individual and societal values are. Here are just a few of the considerations that need to be taken into account when "following the science":

- The economic cost of losing one's job are greater in countries without strong social networks.
- Severe lockdowns cause harm to those without strong social networks, especially individuals who lived alone, and those in isolated communities.
- As mentioned previously, women and BAME people are disproportionately affected.
- The long-term economic damage caused by COVID-19 induced lockdowns will cause more indirect deaths by starvation than deaths caused by the virus according to the United Nations.

Taking these considerations into account doesn't make choosing the right policy any easier. But if we willfully ignore them by continuing to hold on to the mistaken belief that science determines policy, we have no chance of addressing the important issues, which are clearly beyond the scope of this paper.

CONCLUSIONS

In April 2020 the United Nations (UN) published a policy brief on the impact of COVID-19 on girls and women[4]. Although the policy brief was published fairly a few weeks into the start of the pandemic, it did highlight three important priority areas:

1. Ensuring women's equal representation in all COVID-19 response planning and decision-making.
2. Driving transformative change for equality by addressing the care economy, both paid and unpaid.
3. Targeting women and girls in all efforts to address the socio-economic impact of COVID-19.

Almost a year later, it is clear that we have a lot of work left to do. As EU countries re-enter lockdowns during the second wave of COVID-19, governments must learn important lessons from the positive actions taken during the first wave of the pandemic and reflect on the shortcomings of their inevitably reactive approaches during the first wave. In the majority of EU countries, the pandemic has exposed overall shaky support systems for the most vulnerable in society. The crisis continues and despite emerging vaccines and implementation of mass vaccination programmes in 2021, COVID-19 has transformed the way we live and work and made us question our relationships with each other and with our governments. The pandemic has shone a harsh light on how unprepared we have been and highlights the anxieties and uncertainties that will follow us into 2021 and beyond. There is emerging consensus that a better understanding of public perceptions of government responses to COVID-19 may foster improved public cooperation (46). We must work hard to ensure that future efforts emphasize the gender dimension in all possible ways. We must also engage with policymakers to publicize and prioritize this problem and develop viable solutions to address it.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AM conceived the paper, produced the first draft, and edited the manuscript. All authors contributed to the article and approved the submitted version.

[4]https://www.un.org/sexualviolenceinconflict/wp-content/uploads/2020/06/report/policy-brief-the-impact-of-covid-19-on-women/policy-brief-the-impact-of-covid-19-on-women-en-1.pd

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BRIEF RESEARCH REPORT
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The Global Impact of COVID-19 on the Care of People With Endometriosis

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Endometriosis is a chronic condition affecting ∼10% of women globally. Little is known about the impact of the coronavirus disease 2019 (COVID-19) pandemic on their care. This brief report is aimed to explore the impact of COVID-19 on the care of people with endometriosis around the world, their priorities in relation to their clinical care during and coming out of the pandemic, and whether they believed that endometriosis makes them more vulnerable to COVID-19. An internet-based survey collected data in five languages between May 11, 2020, and June 8, 2020. Only participants with a surgical or radiological diagnosis of endometriosis aged 18 years or over were included. A total of 6,729 eligible respondents completed the survey with 80.7% [95% CI (79.7, 81.6)] reporting a negative impact on their care. This included difficulties obtaining medication (20.3%), cancelled/postponed gynaecology appointments (50.0%), and cancelled/postponed procedures (37.2%). More than half worried that their endometrioses make them more vulnerable to COVID-19 [54.2%; 95% CI (53.0, 55.4)]. The top three priorities were remarkably consistent around the world: contact with gynaecologists, knowing when procedures would be performed, and support with mental health (20.3% prioritising this aspect during the pandemic and 13.0% as restrictions begin to ease). This study shows the substantial impact the COVID-19 pandemic has had on people with endometriosis and describes how they would like care prioritised moving forwards. The findings regarding significant support needs for mental health add further weight to the growing recognition of attending to such issues as part of good patient-centred care.

Keywords: endometriosis, COVID-19, mental health support, survey, prioritisation

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic meant an abrupt change in healthcare provision around the world. Whilst the primary focus was (rightly) on the care of those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and public health measures to prevent transmission or identify those most at risk, individuals with chronic conditions saw their treatments halted, cancelled, or changed, with little information available and extremely limited access to clinicians (1–3). Endometriosis is a chronic disease associated with pelvic pain and infertility, affecting ∼10% of women and known to have high personal, societal, and financial costs (4). Due to its chronic nature, many of those affected rely on long-term medication, whilst others require one or more procedures (surgery or fertility treatment) (5, 6).

During the challenging times of the COVID-19 pandemic, the lives of people across the world have been majorly impacted. The lockdown restrictions have affected all domains of life: work routine, healthcare, education and leisure time, and for some employment or personal relationships status. Recent studies on the psychological impacts of the pandemic on the general population have shown increased psychological distress, higher than the already expected upwards trend even before the pandemic (7), and specifically a rise in depressive and anxiety symptoms (8). A recent study on the COVID-19 pandemic and endometriosis in Turkey has provided some evidence that people with endometriosis worry about the management of their condition during the pandemic (3). Additionally, several reports have been published that highlight the expected worsening of chronic pain conditions during the pandemic (9–11). Therefore, endometriosis with a chronic pain component and increased prevalence of psychological disorders could be perceived as a condition at high risk for worsening of both endometriosis-associated pain symptoms and mental health. We, therefore, considered it important to understand both how COVID-19 had affected access to care relating to endometriosis and what people with the condition would prioritise whilst the pandemic continued and as health services begin to return to a "new normal." This study aimed to determine this on a global level.

METHODS

An online survey (JISC: https://www.jisc.ac.uk/online-surveys) was undertaken between May 11, 2020, and June 8, 2020 [Ethics Approval: The Central University Research Ethics Committee, University of Oxford (reference number R69636/RE001)]. The survey was prepared in English and translated by native speakers into French, German, Spanish, and Portuguese. The study was advertised widely on social media by researchers and clinicians in endometriosis, women and reproductive health, and relevant support groups around the world (see Acknowledgements section below). The survey (available as **Supplementary Materials**) assessed a variety of areas relevant to endometriosis, the COVID-19 pandemic, and the impact of the pandemic on endometriosis-associated care and symptoms. These included endometriosis symptomatology and any change after the onset of the COVID-19 pandemic, mental health, social support, access to care, and personal experience of COVID-19.

TABLE 1 | Alterations to current and planned treatments.

Alterations to treatments	Global (*N* = 6,603)		Europe (*N* = 4,433)		Oceania (*N* = 374)		North America (*N* = 961)		Latin America and Caribbean (*N* = 649)	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
No impact	4,267	64.62	2,898	65.37	231	61.76	597	62.12	419	64.56
Difficulty with repeat prescriptions	1,337	20.25	853	19.24	105	28.07	205	21.33	127	19.57
Change hormone treatments	295	4.47	207	4.67	9	2.41	42	4.37	25	3.85
Change painkillers	459	6.95	331	7.47	29	7.75	50	5.20	34	5.24
Stop hormone treatments	222	3.36	150	3.38	7	1.87	24	2.50	32	4.93
Stop painkillers	434	6.57	295	6.65	26	6.95	55	5.72	44	6.78
Alterations to planned treatments	**Global (*N* = 4,943)**		**Europe (*N* = 3,266)**		**Oceania (*N* = 264)**		**North America (*N* = 676)**		**Latin America and Caribbean (*N* = 587)**	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Gynaecologist appointments cancelled/postponed	2,473	50.03	1,696	51.93	88	33.33	294	43.49	321	54.68
GP appointments cancelled/postponed	726	14.69	455	13.93	27	10.23	121	17.90	96	16.35
Surgeries cancelled/postponed	1,333	26.97	840	25.72	112	42.42	222	32.84	128	21.81
Fertility treatments cancelled/postponed	591	11.96	400	12.25	25	9.47	75	11.09	76	12.95

Global and regional results for Europe, Oceania, North America, Latin America, and Caribbean to the questions "Has the pandemic altered the availability of your treatments for endometriosis?" and "Has the pandemic altered your planned treatments relating to endometriosis?" For clarity, the table includes answers that had more than 5% frequency. Regions are defined as per the WHO recommendations (https://www.ghsindex.org/). Data presented as frequencies (No.) and percentages (%). Percentages are calculated using the number of responders in each region for each question as the denominator.

Additionally, we asked what aspects of healthcare would be a priority to the participants during the COVID-19 pandemic and with the ease of lockdown restrictions.

Data were extracted and analysed in SPSS (Version 26). Responses from participants not meeting inclusion criteria ($\geq$18 years old; self-reported diagnosis of endometriosis by surgery or imaging) were excluded, and free-text responses were translated into English by native speakers of the relevant languages and categorised by two researchers (LD and KV). The data were analysed as a single dataset (across 84 countries) and then at a continental level (Europe, North America, Latin America and Caribbean, and Oceania). Chi-squared tests were conducted to explore how the priorities of people with endometriosis might differ between the continents. Finally, the results are also presented per country for countries that each comprised more than 5% of the sample (United Kingdom, France, the USA, Brazil, Germany, and Australia). The data comprised of categorical variables thus results are presented as frequencies and percentages.

RESULTS

A total of 7,246 respondents completed the survey with 6,729 meeting inclusion criteria. The mean age of eligible responder was 32.5 years (range: 18–73 years). Respondents were from around the world, with the greatest proportion in Europe (Europe: $n = 4{,}517$; North America: $n = 963$;

TABLE 2 | Alterations to current and planned treatments and priorities during and as restrictions ease.

	United Kingdom	France	USA	Brazil	Germany	Australia
Date of 1st lockdown announcement	**23rd March, 2020**	**17th March, 2020**	**19th March, 2020**	**21st March, 2020**	**23rd March, 2020**	**21st March, 2020**
Date of 1st confirmed COVID-19 case	**31st January, 2020**	**24th January, 2020**	**21st January, 2020**	**25th February, 2020**	**27th January, 2020**	**25th January, 2020**
	(%)	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
Alterations to treatments						
No impact	42.69	34.33	35.55	42.83	24.95	39.82
Difficulty with repeat prescriptions	25.36	12.35	18.98	22.87	16.42	28.02
Change hormone treatments	5.71	4.63	3.68	4.44	2.99	2.36
Change painkillers	7.79	9.63	4.53	5.46	5.12	8.26
Stop hormone treatments	4.60	2.00	2.12	2.56	1.49	1.77
Stop painkillers	5.76	12.72	6.09	7.34	2.35	7.67
Other	15.44	0.36	19.83	21.16	10.87	16.52
Alterations to planned treatments						
Gynaecologist appointments cancelled/postponed	52.56	55.79	43.85	56.31	53.31	37.24
GP appointments cancelled/postponed	16.36	8.76	19.47	16.38	12.45	10.46
Surgeries cancelled/postponed	36.20	12.29	32.38	22.98	19.46	42.26
Fertility treatments cancelled/postponed	9.84	16.53	11.07	14.12	13.23	10.88
Other	19.09	10.03	25.00	15.63	27.63	27.62
Priorities during the pandemic						
Mental health support	17.56	23.24	23.72	29.02	12.50	21.64
Primary care appointments	10.67	8.33	7.39	5.01	5.39	8.19
Arrange procedures	24.75	11.99	24.72	18.83	9.05	50.88
Medicine availability	8.83	11.62	9.80	4.66	39.66	20.18
Gynaecologist appointments	32.85	36.87	28.27	35.92	15.95	58.19
Priorities as restrictions ease						
Mental health support	8.60	12.65	14.62	18.74	19.15	14.33
Primary care appointments	4.21	3.07	3.03	3.41	2.90	5.56
Arrange procedures	49.95	37.31	51.17	26.24	26.95	52.05
Medicine availability	3.15	7.77	8.55	2.90	5.57	8.77
Gynaecologist appointments	31.69	34.69	19.45	46.34	38.53	15.79

Results presented by country to the questions "Has the pandemic altered the availability of your treatments for endometriosis?" and "Has the pandemic altered your planned treatments relating to endometriosis?," "During the pandemic, what one thing would be most helpful to you, relating to endometriosis?," and "As restrictions begin to ease and healthcare starts to go back to normal, what one thing do you think should be prioritised with regards to endometriosis?" For clarity, the table includes answers that had more than 5% frequency. Data presented as percentages (%) calculated using the number of responders in each country for each question as the denominator.

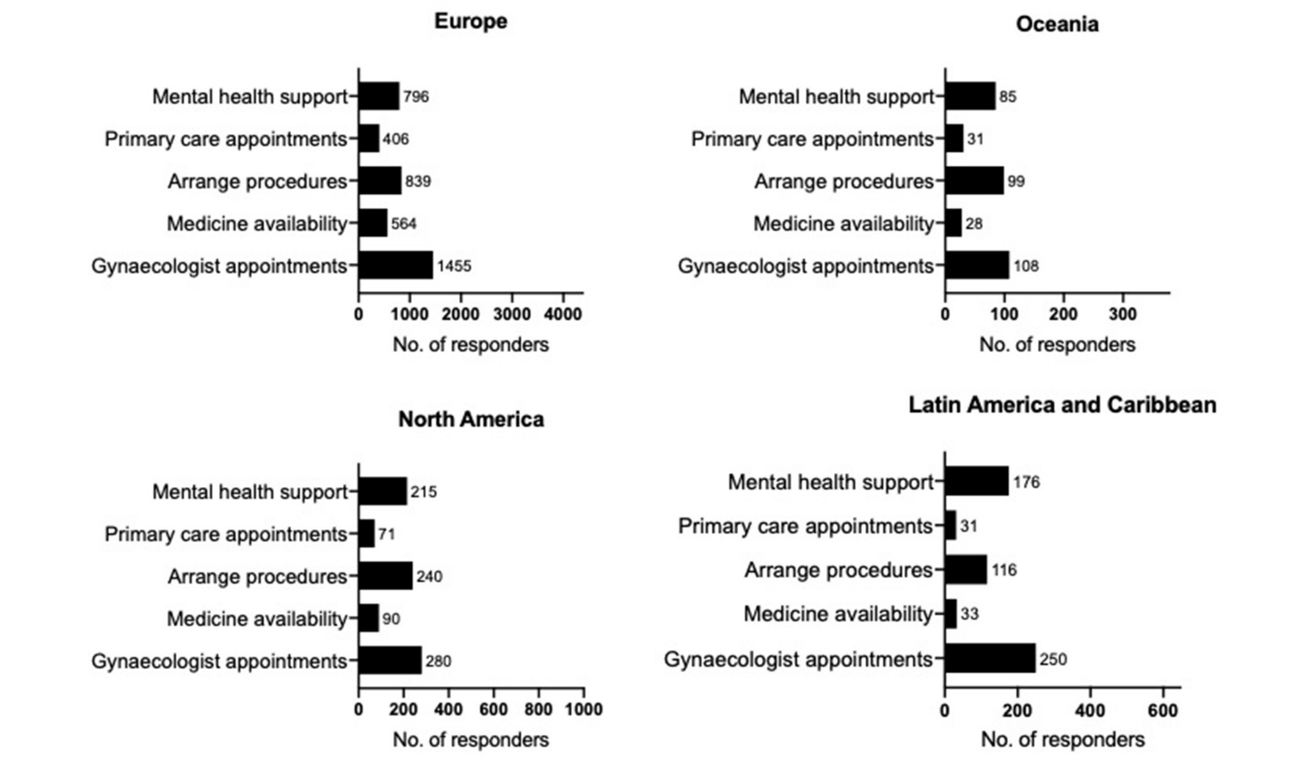

FIGURE 1 | Priorities during the pandemic. Regional results for Europe (N = 4,398), Oceania (N = 370), North America (N = 939), Latin America, and Caribbean (N = 642) to the question "During the pandemic, what one thing would be most helpful to you, relating to endometriosis?**"** For clarity, the graphs include answers that had more than 2% frequency. Regions are defined as per WHO recommendations. Data presented as frequencies (No.).

Latin America and Caribbean: n = 656; Oceania: n = 378; Asia: n = 36; Africa: n = 27; and unknown location: n = 152).

Overall, 64.6% reported no impact of the pandemic on the availability of their usual treatments for endometriosis (n = 4,267). However, 20.3% (n = 1,337) reported difficulty obtaining repeat prescriptions, 10.5% having to change their hormone and/or painkiller (4.5 and 7.0%, respectively), whilst 9.5% had to stop a medication altogether (hormones: 3.4%; painkillers: 6.6%). The impact on planned care was much greater: 50.0% of responders reported cancelled/postponed appointments with gynaecologists, and 14.7% described cancelled/postponed primary care appointments; 37.2% had procedures cancelled/postponed (surgery: 27.0% and fertility: 12.0%). Overall, 80.7% [95% CI (79.7, 81.6)] reported an impact on their current or planned treatments. These proportions were similar around the world (**Tables 1**, **2**).

Respondents considered that during the pandemic, the most helpful things would be the following: contact with their gynaecologist (32.6%), dates booked for future surgery/fertility treatments (20.5%), and mental health support (20.3%). Improving the availability of medication and contact with primary care was less popular (11.1 and 8.6%, respectively). As restrictions ease, priorities are arranging cancelled/postponed procedures (42.7%) or appointments with their gynaecologists (32.1%) and mental health support (13.0%). Considerably less chose medication availability (5.3%) or primary care appointments (3.8%). Whilst trends appear similar across regions statistical comparisons of the proportions showed significant regional variations for what the participants would find most helpful during the pandemic [$\chi^2_{(12)} = 115.0$, $p = 0.000$] and once restrictions ease [$\chi^2_{(12)} = 127.8$, $p = 0.000$]. Nonetheless, contact with gynaecologist, arranging procedures, and mental health support were the top three priorities across regions for both priorities during the pandemic and as restrictions ease even though the order of these three varied between regions (**Figures 1**, **2**).

More than half of respondents worried that their endometrioses make them more vulnerable to COVID-19 [n = 3,635, 54.2% 95% CI (53.0, 55.4); only n = 22 did not answer this question].

DISCUSSION

Our data demonstrate the considerable impact the COVID-19 pandemic has had on the care of people around the world with endometriosis. In fact, of 6,729 eligible respondents, 5,428 (80.7%) indicated they had been affected in at least one way. It was essential that clinical practise in obstetrics and gynaecology changed during the pandemic to protect both patients and healthcare staff (12–14). However, understanding

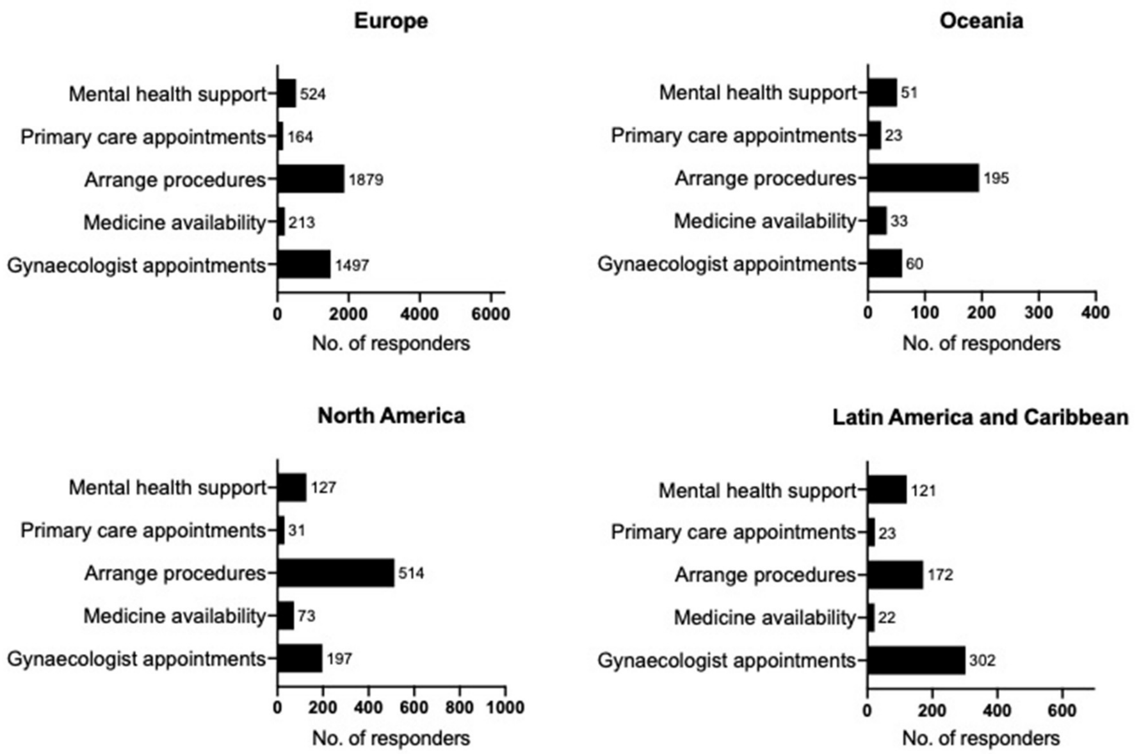

FIGURE 2 | Priorities as restrictions ease. Regional results for Europe ($N = 6,334$), Oceania ($N = 370$), North America ($N = 951$), Latin America, and Caribbean ($N = 649$) to the question *"As restrictions begin to ease and healthcare starts to go back to normal, what one thing do you think should be prioritised with regards to endometriosis?"* For clarity, the graphs include answers that had more than 2% frequency. Regions are defined as per the WHO recommendations. Data presented as frequencies (No.).

what is important to people with endometriosis will be essential as we redesign/reprioritise services.

This is the largest study of the experiences and wishes of those with endometriosis during COVID-19. A small Turkish study ($n = 261$) described 53.6% believing management of their endometriosis was affected by the pandemic with 83.9% being scared of having endometriosis-related problems during this period (3). Our findings agree with Urology and Dermatology studies, suggesting a significant impact on benign services (1, 2). Concerns have also been expressed about the impact on those with chronic pain, both in terms of difficulties accessing treatments, such as physiotherapy and psychology and the possibility of medication issues due to telephone prescribing (9).

Worldwide, respondents to our survey were remarkably consistent about the top three priorities during and immediately after the pandemic. Interestingly, the announcement of the first lockdown in the countries that we have received the most responses from happened within 7 days between March 11, 2020, and March 23, 2020. Even though the restrictions themselves differed between countries, with some going into national lockdowns whilst others introduced regional lockdowns or other less strict measures, they all saw an immediate change in healthcare services that had to adapt to deal with the new pandemic. Therefore, it is not surprising that, across countries, we see similar impacts on treatments and priorities of people with endometriosis. Whilst it was perhaps not surprising that contact with gynaecologists and knowing when procedures would be performed was important, we did not expect to see such a high proportion prioritising mental health. There has been an increasing focus on comorbid mental health conditions in people with endometriosis over recent years (15, 16); however, guidance on the management of the condition has not been updated to reflect this (5, 6). Our data have important implications on how we design services during the current infection wave and beyond. There has been a large shift toward telemedicine in all specialties (17) and ensuring the availability of gynaecologists to provide this service will be important, arguing against them being redeployed to cover emergency services as commonly occurred during the height of the first wave. It appears that talking to a primary care physician is not the priority. Given the considerable pressures placed on primary care services during the pandemic (18), this should not be recommended as a substitute for gynaecology appointments. Mental health support, on the other hand, can be delivered virtually, both standalone and in the context of pain management (11). Given the increasing prevalence of psychological distress since the onset of the COVID-19 pandemic (7, 19), it would seem prudent for healthcare providers to invest in this area for all affected not just those with endometriosis and/or chronic pain. This will be of even greater importance if concerns about increasing numbers of chronic pain patients as a consequence of this pandemic are borne out (10).

Additionally, we were concerned to see that more than 50% of those with endometriosis worried that this disease might make them more vulnerable to COVID-19. This may be because the known link to altered immunological responses has been misinterpreted as endometriosis being an autoimmune condition (4), plus additional concerns for those with thoracic endometriosis. Given that so far there is no evidence to support this belief, we consider it essential that clinicians address this issue with their patients, and education campaigns should be considered.

The size of the response over a 4-week period demonstrates the importance of this topic to those with endometriosis, and our global coverage, captured in five languages, is a strength of the study. Nonetheless, as with any survey study, there are limitations to these data. We could not access medical records to confirm the diagnosis. However, respondents who did not describe a surgical or imaging diagnosis were excluded and at the time of data collection, a face-to-face study or contact through designated hospital clinics was not a possibility. Whilst we did assess for comorbid long-term medical conditions, we did not explore how these or other aspects of the health of the participants, such as postpartum or mental health conditions, may have influenced their healthcare priorities. Additionally, it is likely that the participants may not be representative of the background population of those with endometriosis. Instead, they may represent those who interact regularly with endometriosis support groups or whose particular worries relating to their endometriosis during the pandemic had led them to visit support group sites for advice during the time our study was advertised. Nonetheless, the study was advertised globally, and we received respondents from across the globe, such as areas of the world that are usually overlooked in endometriosis studies. Given the inherent differences in healthcare systems around the world, it is perhaps surprising that we did not find more variation in the priorities of the participants or the impact of the pandemic on them. However, slight variations in the order of the top priorities between regions could be explained by differences in the healthcare systems; for example, in Latin America and the Caribbean the second highest priority is mental health support, this may reflect the large treatment gap in mental health in many of the countries in the region (20).

CONCLUSIONS

The COVID-19 pandemic has affected the care of the majority of people with endometriosis. Moving forwards, it will be important to prioritise the components most valued by those suffering from the condition. Whilst surgery or fertility-related procedures may be challenging at times of high infection/transmission rates, contact with gynaecologists via telemedicine and the provision of remote mental health support need to be prioritised.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Central University Research Ethics Committee, University of Oxford. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KV conceived the study and drafted the manuscript. EC, CL, CB, AI, BM-B, MK, KG, EE, EF, KZ, and KV designed the study including translations. LD, CB, AI, BM-B, and MK analysed the data. All authors contributed to reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2021.662732/full#supplementary-material

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REVIEW
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Focusing Treatment on Pregnant Women With COVID Disease

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Since the emergence of a novel coronavirus in China at the end of December 2019, its infection - COVID-19 - has been associated with high morbidity and mortality and has left healthcare systems wrestling with the optimal management strategy, especially for vulnerable populations, such as pregnant women. At this moment, few resources exist to guide the multi-disciplinary team through decisions regarding optimal maternal-fetal treatment and delivery timing. In this article, we present the drugs and vaccines under investigation as potential treatments and prevention for COVID-19 infection. Based on a comprehensive evaluation, we prioritized these possible treatments, and provide dose-response and dose-toxicity information on each drug. Currently, there is limited but very increasing reassuring information concerning vaccines to prevent SARS-CoV-2 during pregnancy, and in this review, we also emphasize the results (mostly positive) provided by the few small trials evaluating COVID-19 vaccines in pregnant patients.

Keywords: COVID-19, SARS-CoV-2, pregnancy, coronavirus, treatment, COVID-19 vaccine

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INTRODUCTION

Coronavirus 2019 disease (COVID-19) is a recently emerged infection caused by a ribonucleic acid virus that leads to mild to severe respiratory tract infections (1). This virus emerged in December 2019 in China and was named severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) (2, 3). The main source of infection is people already infected with SARS-CoV-2. Asymptomatic carriers can also be a source of infection. The transmission routes are via airborne exposure, via droplets and close contact (4). According to the World Health Organization (WHO), international statistics have demonstrated the severity of this public health crisis and that COVID-19 infected pregnant women are a potentially vulnerable population (5–8).

In this review, we assessed the potential strategies for optimal maternal treatment, fetal surveillance and delivery timing, taking into account that pregnant women have a modified immune and respiratory system, especially at the end of the gestation period, making them more susceptible to severe symptoms such as pneumonia and marked hypoxia (9, 10). At the same time, we reviewed the subject of SARS-CoV-2 vaccines safety and efficacy for pregnant and lactating women. The latest publications on this subject recommend to consider COVID-19 vaccination during pregnancy, especially for the pregnant women who present a higher risk of exposure or severe disease if infected. For this vulnerable population, it would be better to inject the COVID-19 vaccine during pregnancy than to postpone vaccination until the postpartum period. Also, it is important to acknowledge the timing of SARS-CoV-2 vaccination in pregnant women. They should not receive this type of vaccine within 14 days of the administration of a routine vaccine (e.g., influenza). As an exception, this interval may be shortened in the case of important vaccines in a life-threatening situation (e.g., tetanus vaccination following wound treatment) (11–21).

The WHO has identified four clinical stages of COVID-19 infection: *a mild form* in patients with no specific symptoms (fatigue, cough, muscle pain, nasal congestion, headache, fever, sore throat, sometimes nausea, diarrhea, vomiting and anosmia); a *moderate form* with pneumonia but no need for supplemental oxygen; a *severe form* of pneumonia with the need for oxygen and a *very severe form* requiring mechanical ventilation, sometimes accompanied by shock and organ failure (4). Comorbidities that usually appear in the second trimester of pregnancy (hypertension, cholestasis, diabetes), as well as obesity and increased maternal age, often make pregnant women more susceptible to severe COVID-19 symptoms, which will put them at a higher risk of being admitted to the intensive care unit with mechanical ventilation compared to the general population (22).

There is no clear evidence that the coronavirus has an impact of the fetus, either in the first or second trimester as miscarriage or late pregnancy loss, nor as preterm birth, whether this is iatrogenic (maternal viral infection) or spontaneous (prelabour premature rupture of the membranes) (7, 23–26). Many studies are in progress, and there is already a meta-analysis published suggesting that patients with severe COVID-19 symptoms during pregnancy may experience spontaneous premature birth and, as a consequence, their newborns require the neonatal department for vital support (27). On the other hand, vertical transmission is not excluded, even though there have been no studies showing the presence of SARS-CoV-2 in the placenta, amniotic fluid, cord blood, neonatal throat or breast milk (24–26, 28, 29). Mazur-Bialy et al. indicated a very slight possibility (about 3–8%) of vertical transmission from women infected with coronavirus to their newborns (22).

Due to the absence of clear guidelines based on conclusive studies, at this moment, there is an urgent need for effective treatment strategies for COVID-19, especially for pregnant women (30). With this purpose, a very good critical review by Favilli et al. was published on the effectiveness and safety of available treatments for COVID-19 during pregnancy, drawing attention to the potential adverse fetal and neonatal effects of drugs, as this is an important problem for medical practitioners (31). At the same time, more data concerning the safety and efficacy of SARS-CoV-2 vaccines during pregnancy and postpartum is essential for both obstetricians and patients (11). In this article we performed a literature review for relevant publications appearing in the scientific database up to 7 May, 2021.

PREVENTION

There are currently no data suggesting clear management strategies for treating COVID-19 infection in pregnant woman, so prevention remains the principal strategy. There is evidence of two routes for human transmission: direct (contact with an infected person within 2 m) and indirect (by touching an object already touched by an infected person) (30). For these reasons, pregnant women should be advised to avoid close contact by maintaining the proper distance, wash their hands often with soap and water, disinfect touched surfaces daily, use a face mask in the community, avoid contact with vulnerable groups (people with cancer, people with known immunosuppression or organ transplant recipients), stay at home if sick and cove the mouth and nose when coughing or sneezing (32).

In the postpartum period, women with COVID-19 infection and willing to breastfeed should take precautions in order to protect the newborn: correct hand hygiene before and after contact, cleaning the breast skin and use of a face mask. According to the current evidence, international scientific organizations allow breastfeeding if both maternal and neonatal conditions are favorable (33, 34).

All around the world, when evaluating COVID-19 vaccines, trials have excluded pregnant women and those breastfeeding because of the limited data about safety and efficacy in this vulnerable population (11). So, considering that there is still no specific treatment for COVID infection and no specific COVID-19 vaccine for pregnant and lactating women, it should be well-acknowledged that prevention is the best option.

VACCINES

There are numerous vaccines to prevent infection to SARS-CoV-2 available worldwide, the two basic principles being the mRNA vaccine and the replication-incompetent adenovirus recombinant vector vaccine. They do not contain virus that replicates and they do not cause disease, but there may be some non-specific side effects due to activation of the immune system (11).

The COVID-19 vaccines have been granted emergency use of authorization in specific doses and series for individuals older than 18 years of age. Usually, they are administered intramuscularly (into the deltoid) in a two-dose series or only one dose, depending on the type of vaccine (12, 20). The interval of time between the two doses is 21–28 days, specifically for each type of vaccine. If impossible to respect this timing, it is suggested to administer the second dose as soon as possible, but no longer than 42 days after the first dose (12, 19). Ideally, the type of vaccine initially used as first dose should be the same for the second dose (19) as there is no data to confirm the efficacy and safety if using two different vaccines for each dose (12).

Even though experts believe that these vaccines (both mRNA and viral vector) do not present a risk either for pregnant women or for their fetus or breastfeeding newborn (21), trials that have evaluated COVID-19 vaccines until now have excluded pregnant and lactating women. Therefore, current date is from animal studies and small prospective cohort studies on vaccinated pregnant women (11, 13). Researchers have demonstrated that antibody titres after maternal vaccination were higher than those induced by COVID-19 infection during pregnancy. Most importantly, they were able to identify vaccine-generated antibodies in umbilical cord blood and breastmilk samples (13).

Some reports on vaccination among pregnant women (mainly vaccinated in the third trimester) show no evidence of harmful effects such as neonatal death, stillbirth, congenital anomalies, fetal growth, preterm birth or miscarriage (11, 17). These are the arguments why experts strongly advise that pregnant patients have the COVID-19 vaccine, especially those who present an important risk of exposure to SARS-CoV-2 (e.g., health care workers) or with comorbidities (e.g., obesity, diabetes, heart disease) that will increase their risk of developing a severe disease if infected with coronavirus (11, 20)[1].

It is well-known that pregnancy itself represents a high risk of severe infection, but due to the limited current data about the safety and efficacy of vaccines to prevent SARS-CoV-2 during the gestational period, some pregnant women may choose to defer COVID-19 vaccination, for the moment (11, 12). When women opt for COVID-19 vaccine during pregnancy the timing with non-COVID-19 vaccines should not be neglected. As there is no information about the safety and efficacy of SARS-CoV-2 vaccines being co-administered with other vaccines, an interval of 14 days has been suggested between COVID-19 vaccine and others. There may be some exceptions, such as the tetanus vaccination in case of injury and wound treatment (12).

One of the major side effects after undergoing COVID-19 vaccine is thrombosis. There are few cases mentioned in the literature at this moment (thrombosis associated with thrombocytopenia) and they are reported especially after viral vector vaccines (35). Taking into consideration this data, experts on the subject suggest that women during gestational or postpartum period should opt for mRNA vaccines if accessible. If not, they believe that any viral vector vaccine would be better than no vaccine at all (11). Another relevant aspect on this topic is that RhD alloimmunisation seems to have no interference with the immune response when pregnant patients choose to get vaccinated against SARS-CoV-2. So, the Anti-D immunoglobulin should be administered as standard clinical protocols recommend (11, 36). Concerning the timing of a pregnancy after undergoing the first or both COVID-19 vaccine series, experts believe that there is no impact on pregnancy and that vaccination against SARS-CoV-2 infection should take place or continue based on standard protocols (11). Another key matter related to the COVID-19 vaccines is the breastfeeding. As we specified in the beginning of this topic, lactating patients were excluded from vaccine trials. Officially, breastfeeding is not an exclusion criteria as specialists have demonstrated that patient COVID-19 antibodies after vaccination may have a potential protective effects on the newborn, by crossing into the breastmilk (11, 16, 37).

Nowadays, the published vaccine registries report no significant risk to either the pregnant woman or her fetus (11).

TREATMENTS

In the current literature, there is limited information on the effects of drugs in pregnant women affected by coronavirus. Clinical findings are similar in the case of non-pregnant adults, but knowing that the immune system changes during gestation, pregnant women might be at a greater risk for morbidity and mortality related to COVID-19 compared to the general population. Clearly, pregnant woman should receive the same care as other people regarding screening, radiology and laboratory evaluations as well as treatment and critic care (38).

As very clearly stated by Favilli et al. (31), COVID-19 treatment and especially antiviral drugs during pregnancy may be difficult to manage considering that it is part of their life cycle for the viruses to mutate constantly and so it is a challenge to develop curative drugs. Moreover, clinical trials do not include pregnant and lactating women and therefore, antiviral drugs that are safe and effective in general population cannot be used during pregnancy and breastfeeding (39).

The management of COVID-19 in pregnant women in terms of prescribing pharmacological treatment must take into consideration the gestational age in order to minimize fetal risks. In the severe forms of the disease, it is suggested to end the pregnancy by cesarean section before starting treatment, but always with the consent of the patient (4). The standard treatment for patients who need only home isolation includes bed rest, hydration, adequate calorie intake, paracetamol up to 4 g/day and antiviral drugs, but with continuous evaluation of the effectiveness of the drugs in use by routine visits (medical staff), at home preferably, at least four times per week (40).

There are still several drugs being used off-label, and it is important to note that there may be serious adverse effects. Below we will list the drugs that are available for the management of COVID in pregnant women and in the immediate postpartum period. We focused on the safety and effectiveness of currently known treatments for COVID-19 infection during pregnancy after analyzing clinical studies and literature reviews.

ANTIMALARIALS

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine (HCQ) are oral drugs are used for the treatment of malaria and some autoimmune conditions. Both drugs have *in vitro* activity against SARS-CoV-2, with HCQ having relatively higher potency. HCQ can be used during breastfeeding and pregnancy even though it crosses the placenta. Because there does not appear to be fetal toxicity and breastfed infants are exposed to only 2% of the maternal dose, it is considered to be safe (41). It is well-known that chloroquine has been used for more than 20 years in regions with malaria, with no side effects either on pregnancy or the fetus (31, 42).

The drug dose necessary to treat a viral infection is lower than in malaria (31), and the majority of authors agree with the following protocol: if the patient's weight is $\geq$ 50 kg, 500 mg x 2/day for 7 days; if the weight is $<$ 50 kg, 500 mg x 2/day in the first 2 days, 500 mg x 1/day from the third to the 7th day (4). The contraindications and cautions for HCQ are: QT prolongation, G6PD deficiency, epilepsy, porphyria, myasthenia gravis and retinal pathology. Serious adverse events generally result from prolonged use. Complications may include cardiomyopathy, torsade des pointes, bone marrow suppression (thrombocytopaenia, agranulocytosis, and leukopaenia), hypoglycaemia. These drugs should be used with caution in diabetic patients (43).

There are insufficient data to show the benefits of HCQ or chloroquine in the treatment of COVID-19 in pregnant

[1] www.ACOG.org (accessed September 16, 2020).

women, mostly given the lack of clear benefit; according to the literature, these drugs are no longer recommended for COVID-19 treatment (22). Studies around the world have highlighted the potential for the toxicity of these drugs and, in some institutions, studies were stopped because of a higher mortality rate. Therefore, the US FDA revoked authorization for these agents in patients with severe COVID-19, noting that the known and potential benefits no longer outweighed the known and potential risks (44).

ANTIVIRALS

Lopinavir/Ritonavir (LPV/r)

Lopinavir and ritonavir are anti-retroviral protease inhibitors that are currently approved for the treatment of HIV infection (32). LPV/r has been chosen in the treatment of coronavirus infection due to its attachment *in vitro* to SARS-CoV-1 and to the sequence similarity between SARS-CoV-1 and SARS-CoV-2 (31). This drug has been widely used during pregnancy, based on data concerning the safety and efficacy of its use in pregnant women known to be HIV-positive. No teratogenic effects or preterm labor have been observed (31, 45). After several clinical trials for the treatment of COVID-19, lopinavir 400 mg/ritonavir 100 mg for COVID-19 patients diminished the risk of adverse clinical outcomes (acute respiratory distress syndrome [ARDS] or death) (46). For adults, LPV/r are used at 200 mg/50 mg 2cp x 2/day, not exceeding 10 days of treatment and ideally in the first 7–10 days, when the peak phase of virus replication occurs (4, 31, 47).

The most common side effects are nausea, vomiting, diarrhea, abdominal pain, anorexia, gastritis, cutaneous manifestations, insomnia and anxiety. More serious adverse effects may include QT prolongation, AV block, anemia, leukopaenia, neutropaenia, hyperglycaemia, renal failure, pancreatitis and hepatotoxicity. Lopinavir/ritonavir is contraindicated in cardiac disease and liver disease (43). Moreover, it is important not to forget that 20–30% of patients with COVID infection have transaminase elevation (31).

Taking into account all the information above, LPV/r remains a choice of treatment for pregnant patients infected with coronavirus. However, lopinavir/ritonavir appear to have minimal role in the treatment of COVID-19 infection. Trials on this matter are ongoing, but it should not be neglected the fact that there are some studies that mention the possible crossing of the placenta by this drug (44, 48).

Remdesivir

Remdesivir is a novel, investigational, intravenous drug with broad antiviral activity against SARS-CoV-2 and seems to be effective in mild to severe forms of COVID-19 infection to reduce pulmonary pathology due to its characteristic of reducing viral replication by inhibiting RNA dependent RNA polymerase (31). The recommended dose is 200 mg IV on day 1 (loading dose), followed by 100 mg IV daily, up to 10 days. The possible side effects are gastrointestinal intolerance and hepato- and renal toxicity. Several authors suggest that remdesivir should not be used in combination with other experimental antiviral agents (49). This drug has been used without fetal toxicity in pregnant women receiving supplemental oxygen, intubated or not, and in non-severe disease (45).

Several studies revealed its safety during pregnancy (31), but we find it important to mention that the literature around the efficacy of remdesivir is continually changing. If in the beginning of the COVID-19 pandemic, authors reported that this drug improved the time to recovery in patients with severe coronavirus symptoms (31), more recent trials have demonstrated that remdesivir not only does not lead to a shorter hospital stay, but also it does not minimize the risk of death (22, 50).

Antibiotics

COVID-19 itself is not an indication for antibiotics, but regarding the possibility of a superimposed bacterial pneumonia, some protocols recommend it. The decision regarding the choice of antibiotic and initiation of antibiotic therapy should depend on the culture results of blood, urine and other fluids and on COVID-19 symptom severity. In mild COVID-19 patients, it is recommended to choose based on the patient's condition and wait for the culture results if possible, in order to administer a specific antibiotic. In severe COVID-19 patients, it is suggested to cover all possible organisms until culture results are available (31).

Azithromycin is a macrolide antibiotic which is known not only for its antimicrobial properties, but also for its immunomodulatory activity. As a consequence, macrolides are commonly used in infectious pneumonia and in inflammatory lung disease. Of all the macrolides, azithromycin is considered to have the strongest immunomodulatory effects (51). Azithromycin 500 mg (first day), followed by 250 mg every 24 h for up to 5 days, orally or intravenously, seems to be adequate for a pregnant woman (40). The most common side effects are abdominal pain, diarrhea, nausea and vomiting (31). Some of its contraindications are myasthenia gravis, torsade des pointes, prolongation of QT interval and liver failure. It is appropriate to avoid the indiscriminate use of antibiotics, especially those with a broad spectrum of action (4). Azithromycin was used in combination with HCQ for treating COVID-19 at the beginning of the pandemic, but recent studies have shown that there is no clinical benefit. Crucially, the rate of cardiac arrest is higher because of the potential adverse effects of both of these drugs (QTc prolongation) (44).

Amoxicillin is a beta lactam antibiotic and is used for most of bacterial infections as it has activity against both Gram-positive and Gram-negative bacteria. It is well-tolerated, and side effects are rare: nausea, vomiting and diarrhea. It is important to mention that as amoxicillin is a semi-synthetic penicillin, so a skin rash, erythema and anaphylaxis may appear if hypersensitivity is present (31).

It has to be taken into consideration the possibility of starting ceftriaxone 1–2 g every 24 h intravenously and teicoplanin 400 mg every 12 h for 3 doses followed by 400 mg every 24 h if the patient has alveolar infiltration and/or elevated procalcitonin (suspected bacterial superinfection) (40) until the culture results (blood, urine and/or other fluids) arrive, and after that to continue with a specific antibiotic as soon as possible (31).

All the Antibiotic Drugs Mentioned Above are Safely Used During Pregnancy and Breastfeeding (31, 52–54).

Corticosteroids

For pregnant patients at high risk of preterm delivery within 7 days, between 24+0 and 33+6 weeks of gestation, there are clear benefits of antenatal corticosteroid administration. However, at 34+0 to 36+6 weeks of gestation, the neonatal benefits are less clear, so it is suggested to not administer corticosteroids to such patients. It is recommended to initiate therapy with the usual doses of dexamethasone (4 doses of 6 mg given intramuscularly 12 h apart) or betamethasone (2 doses of 12 mg given intramuscularly 24 h apart) in order to induce fetal pulmonary maturation. In addition, this therapy should be followed by prednisolone (40 mg orally daily) or hydrocortisone (80 mg intravenously twice daily) to complete the maternal steroid course. The objective is to avoid fetal exposure to a prolonged course of dexamethasone or betamethasone, which may have some adverse effects by crossing the placenta (long-term neurodevelopmental impairment, increased risk of preterm birth) (48).

Corticosteroids are recommended specifically for severe illness and should not be routinely used in the prevention or treatment of mild to moderate COVID-19 (44). The main adverse effects of these drugs are hyperglycaemia and hypernatraemia, but low-to-moderate doses are harmless. This is another reason why dexamethasone should be followed by prednisolone (orally) or hydrocortisone (intravenously) (55–57). It is also important to pay attention to pregnant women with gestational diabetes, pre-existing diabetes and mostly if the patient is on insulin treatment. Some studies show that betamethasone may worsen the situation, so authors suggest the administration of only one dose of betamethasone (12 mg) to keep the patient's blood sugar as normal as possible (31). Recent publications mention that methylprednisolone (1–2 mg/kg per day) should replace dexamethasone, as there is little actual data regarding the consequences on breastfeeding when dexamethasone is administered (22, 31).

Low Molecular Weight Heparin

Direct data on thromboembolic risk with COVID-19 are limited but suggest an increased risk (58). All pregnant women admitted with COVID-19 infection or suspected COVID-19 infection should receive prophylactic low molecular weight heparin (LMWH) in a dose of 4000 IU per day unless birth is expected within 12 h (23, 31). If the pregnant woman is close to delivery, it is generally preferred to use unfractionated heparin rather than LMWH due to its readily reversible properties (58).

All pregnant women with confirmed COVID-19 infection should be prescribed at least 10 days of prophylactic LMWH (e.g., enoxaparin 40 mg daily subcutaneously) after hospital discharge. At the same time, postnatal care for women immediately following hospitalization for confirmed COVID-19 illness, which includes the birth of the baby, should undergo at least 10 days of prophylactic LMWH, regardless of the mode of birth (23).

Postpartum venous thromboembolism (VTE) prophylaxis in women with COVID-19 should be considered based on an individual risk assessment. We have noted a considerable variation in practice. For patients who did not receive antepartum prophylaxis because of COVID-19, it is not necessary to administer postpartum prophylaxis in non-severe illness and with no standard indication for postpartum VTE prophylaxis. On the other hand, for patients who received antepartum prophylaxis because of COVID-19, some studies suggest stopping treatment upon hospital discharge if there are no risk factors for VTE (e.g., recent surgery, immobilization). Nonetheless, other authors recommend continuing prophylaxis for 7 to 14 days (and up to 6 weeks) in pregnant women who had moderate/severe disease or mild disease with VTE risk factors (59–61).

There are four important concepts that will lead the medical practitioners in deciding when, how and for how long a pregnant patient with coronavirus infection will receive anticoagulation prophylaxis and/or treatment: the severity of the illness; if the woman is in hospital care or at home, in isolation; if the delivery is approaching or not; and if the patient presents any comorbidities or complications which may put her at a high risk of thrombosis (22).

Other Therapies

It is true that, in the absence of other options, some institutions may choose to use certain agents like interleukin [IL]-6 pathway inhibitors and interferon beta. It is obvious that we need more research and clear data on the treatment of SARS-CoV-2.

Tocilizumab is an anti-inflammatory monoclonal antibody with IL-6-inhibitory effects, usually used for cytokine release syndrome and rheumatic disease. Currently, it is recommended for the treatment of critical and severe COVID-19 infection exactly due to its properties of decreasing elevated pro-inflammatory cytokine levels (e.g., IL-6) and marked elevated inflammatory markers (e.g., C-reactive protein, ferritin, D-dimer) associated with severe COVID-19 disease (22, 44). The suggested doses are 4–8 mg/kg, usually 400 mg diluted in 0.9% NaCl solution, with an infusion time of 1 h. The same dose can be re-administered after 12 h if little benefit is seen after the first administration. The maximum dose for each administration is 800 mg. Attention should be paid to allergic reactions and to contraindications, especially tuberculosis (4).

The results of the few trials on pregnant women using tocilizumab are not so reassuring. Cases of miscarriage, preterm birth and even stillbirth are mentioned. Furthermore, congenital malformations were also detected, so if the pregnancy is advancing an extra ultrasound at around 20 weeks of gestation is suggested. Currently, more studies are needed about the use of tocilizumab for COVID-19 treatment in pregnant and lactating women (31).

Interferon beta B1 is a cytokine in the interferon family with an immunomodulatory role, capable of enhancing innate and adaptive viral immunity (62). According to clinical trials, these drugs are safe during pregnancy. The risk of miscarriage, premature birth, stillbirth and fetal malformation is reported to be low. In the current literature, there are reviews that describe the interest of this treatment for COVID-19 infection, alone or in combination with other antiviral drugs, especially after finding that SARS-CoV-2 is sensitive to both interferon alpha and interferon beta (31). The interest in interferon beta is mostly in non-severe COVID-19 patients, but only in combination with ribavirin and/or lopinavir/ritonavir. Randomized trials have shown that the three drugs together are more efficient than interferon beta with lopinavir/ritonavir alone in terms of clinical improvement and hospital discharge. Also, there less time to a negative SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test on a nasopharyngeal swab after triple therapy (44). Nonetheless, the WHO has recently established that treatment with interferon for COVID-19 infection does not lead to any significant improvement in the patient (22). More studies are needed to clarify the role of interferon beta in COVID-19 treatment for pregnant women (44).

Convalescent Plasma

Convalescent plasma from patients who have recovered from COVID-19 infection has been used as a treatment for patients with severe or life-threatening COVID-19 (44), but trial data on its use are still emerging (31). Some authors have concluded that convalescent plasma is efficient in COVID-19 patients who are not severe or critically ill but in a state of immunosuppression (63). Current evidence shows that, on one hand, convalescent plasma improves the rate of nasopharyngeal viral RNA clearance (compared with standard treatment alone), but on the other hand, there is no significant difference in clinical improvement or mortality rate (44).

The donors have to be between 18 and 55 years old, with a weight > 50 kg (for men) or > 45 kg (for women), more than 2 weeks since last blood donation, and at least 2 weeks after recovery. Plasmapheresis is the collection method, with 200–400 mL collected each time. The blood samples must be tested for SARS-CoV-2 by nucleic acid testing and for SARS-CoV-2 specific IgG and IgM antibodies, in addition to general quality tests. It is generally well-tolerated at a dosage of 400 mL for one infusion or 200 mL per infusion for multiple infusions. Patients with a history of allergy to plasma, methylene blue or sodium citrate present contraindications for convalescent plasma (63).

There are a few studies in the literature with a small number of patients, but with results that should not pass unobserved. They showed good results in oxygen saturation after 3 days of plasma infusion, improvement in lung lesions after 7 days of convalescent plasma treatment and a better clinical condition of the patient (31).

For the general population, there seems to be no important side effects after receiving convalescent plasma for COVID-19 treatment (31), but currently there are data neither supporting nor refuting its use in pregnant women after a close look at recent publications. The authors consider that there is a need for more data, especially concerning the efficacy and safety of this therapy for COVID-19 pregnant or lactating patients (31).

DISCUSSION

In this brief review of the literature concerning the prevention and the treatment for COVID-19 infection during pregnancy and in the immediate postpartum, we intended to highlight and summarize the main drugs that provided the best results until the present moment. Pregnant patients have a higher risk of developing sever symptoms if infected with coronavirus, especially if they are more than 35 years old and and/or with a high BMI and if they present comorbidities such as diabetes, hypertension and/or cholestasis, which often occur in the second trimester of gestation (22).

The maternal adaptations to pregnancy place women in a more difficult management state if cardiopulmonary decompensation occurs. The pregnant woman brings together two patients while knowing that the priorities will be defined according to the gestational age. The pandemic emergency has led to the administration of numerous treatments without proof of effectiveness and without guarantees of no fetal effect in the long term. The fetal-maternal transmission of COVID-19 is probably low and has been demonstrated in very few clinical trials. Placental inflammation by COVID-19 followed by infection of the fetus is a possibility that we must take into account in the management of these patients (64).

In this article, we presented the drugs for potential treatment for COVID-19. Based on a comprehensive evaluation, we prioritized these possible treatments, and presented the dose-response and dose-toxicity effects for each drug. In pregnant women, it is important to adjust the treatment and to choose the timing of delivery. Above all, prevention is essential; pregnant women should follow the same recommendations as non-pregnant persons to avoid exposure to the virus (social distancing, wearing a mask in public, disinfecting surfaces, hand hygiene) (48). Regarding the newborn, there is no contraindication to breastfeeding in the case of a postpartum woman with COVID-19 infection, but precautions are recommended (surgical mask, hand, and breast hygiene) (40, 65).

Even if up to the present moment pregnant and lactating women have not been included in COVID-19 vaccination trials, experts highly recommend vaccination to avoid SARS-CoV-2 infection in patients during pregnancy and breastfeeding. The COVID-19 vaccines (either mRNA or viral vector) do not contain virus that replicates, so it is strongly suggested that pregnant and lactating women with a high risk of exposure to coronavirus or developing a severe disease if infected should undergo COVID-19 vaccination despite the non-specific side effects that may occur (11, 20). It is also important to pay attention to the type of vaccine administered, since some in a single dose while others require a two dose-series, to respect the timing between the two doses and to acknowledge that the second dose should be with the same type of vaccine as the first one (12, 19). Clear guidance is needed on the subject of COVID-19 vaccines administered during pregnancy and postpartum as, until now, this vulnerable population has been excluded from trials. Pregnant women with their obstetricians must decide to accept COVID-19 vaccination or not based on the limited data available at the moment (11, 12, 20).

Of the antiviral agents that have been evaluated, lopinavir/ritonavir appear to have minimal to little role in the treatment of SARS-CoV-2 infection, but remdesivir remains promising for the treatment of COVID-19, especially in severely ill pregnant women, as it has no reported fetal toxicity (48). It is appropriate to avoid the indiscriminate use of antibiotics, especially those with a broad spectrum of action (4). Bacterial pneumonia is seldom found during the hospital course, especially in patients who are intubated, but antibiotics may be stopped in <48 h if there is no evidence of bacterial infection (bacterial cultures and procalcitonin results) (43). At the beginning of the pandemic, azithromycin was highly used because of its antimicrobial properties and immunomodulatory activity (51), but recent studies have shown no clinical benefit (44).

The administration of antenatal corticosteroids prior to anticipated preterm birth is controversial in COVID-19 infection, but still important for patients at a high risk of preterm delivery between 24+0 and 33+6 weeks of gestation (58). Considering the studies and reviews that we analyzed on the subject of corticosteroids as a treatment for COVID-19 infection during pregnancy, we may conclude that experts confirm that the decision of corticosteroid therapy should be evaluated individually for each case.

Several studies suggest a high rate of thromboembolic complications among hospitalized patients with COVID-19, particularly those who are critically ill. Additionally, pregnant women admitted with COVID-19 infection, both suspected and confirmed, should benefit from prophylactic low molecular weight heparin (LMWH) (44, 65).

Other therapies are being used as treatment in critically patients, such as tocilizumab and interferon, but there are safety concerns regarding their use in pregnant women (40). To establish the safety of these drugs during pregnancy and postpartum for patients with COVID-19 infection, further studies are needed (31).

It is possible that convalescent plasma provides a clinical benefit in severe COVID-19 infection and also in patients who do not require mechanical intubation, but this remains uncertain for the moment, especially for pregnant women.

None of these treatments are contraindicated during pregnancy or breast-feeding, but require informed consent for use (40).

When choosing a certain drug for a patient infected with coronavirus during pregnancy or breastfeeding, physicians should take into consideration all the risks and benefits specific for each patient, knowing the lack of clear information on the safety and effectiveness of available treatment for this population (31). Taking into consideration that, at the present time, there are no clear management strategies for treating COVID-19 infection in pregnant women, it is obvious that prevention remains the principal strategy, even though we need more information about the safety and efficacy of SARS-CoV-2 vaccines. It is a certain fact that the literature about the coronavirus disease and COVID-19 vaccine for pregnant and lactating patients is evolving rapidly and that the guidelines around the world are constantly being updated and expended (11, 20). In the absence of sufficient data regarding COVID-19 in pregnant women, it is suggested to follow the same recommendations as non-pregnant persons for avoiding exposure to SARS-CoV-2, the virus that causes COVID-19, and in terms of treatment, regardless of disease severity (46).

It is important to acknowledge the speed and the rapidity of clinical trials and development of management, treatment and prevention related to COVID-19 disease during pregnancy since December 2019 until now. At the same time, the fact that study results concerning COVID-19 infection in pregnant and lactating women are coming out so fast may be a limitation of any review of the literature.

CONCLUSIONS

The different types of treatment presented are safe during pregnancy and lactating period, with no teratogenic effects and minimal exposure to breastfed infants, but their effectiveness remains limited or even absent against the COVID-19 infection. It is important to stay alert that the pregnancy constitutes a state predisposing to thromboembolic complications exacerbated by the COVID-19 infection. For this reason, the preventive administration of a low molecular weight heparin is recommended as long as the mobility of the patient is reduced by the infection. The corticosteroids are to be taken into account for their role for the fetal pulmonary maturation between 24+0 and 33+6 weeks of gestation but also for their benefice in the management of pregnant patients with pulmonary COVID-19 involvement. Antibiotics (amoxicillin, ceftriaxone) are useful only in case of a co-bacterial infection. Therapies like tocilizumab, interferon beta B1 and convalescent plasma are used in critical and life-threatening COVID-19 infection but the data are too limited in pregnant women.

Concerning the vaccination, we strongly advise all pregnant women in the second and third trimester to receive the COVID-19 vaccine using a shared decision-making model with healthcare providers. These patients must be recorded in a comprehensive vaccine registry because additional studies are needed to examine rare adverse outcomes following vaccination during pregnancy. The COVID-19 vaccination does not represent an absolute protection again a re-infection and those cases of re-infection need to be treated with the same protocols as the no vaccinated population.

AUTHOR CONTRIBUTIONS

A-RE and ES conceived and drafted the original version of the article. NB developed the idea. NB and AF verified and supervised the manuscript. All authors contributed to the article and approved the submitted version.

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