# Interactions Between Specific Immune Status of Pregnant Women and SARS-CoV-2 Infection

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for the Coronavirus Disease 2019 (COVID-19) global pandemic. Because it is a new and highly contagious coronavirus, most people, especially pregnant women, lack immunity. It is therefore important to understand the interaction between why pregnant women are susceptible to SARS-CoV-2 and the specific immune systems of pregnant women. Here, we provide an overview of the changes that occur in the immune system during pregnancy, the activation and response of the immune system in pregnant women with COVID-19, adverse pregnancy outcomes in pregnant women with COVID-19, and the treatment and prevention of COVID-19 in this population.

Keywords: SARS-CoV-2, COVID-19, pregnant women, immune system, treatment

## INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has become a public health emergency of international concern in recent times. According to past epidemiological data, pregnant women are significantly more susceptible to influenza viruses and have higher morbidity from these infections than non-pregnant women (Zhao et al., 2020). With further expansion of the pandemic, pregnant women have gradually been found to be susceptible to SARS-CoV-2, which is mainly related to the special immune states of women during pregnancy (Zhu et al., 2020). Although pregnant women are at an increased risk for SARS-CoV-2 infection, the majority of pregnant women with COVID-19 have mild symptoms; about one-fifth of them develop moderate or severe disease (Andrikopoulou et al., 2020; Islam et al., 2020). The results of a meta-analysis of pregnant women and COVID-19 (n=236) showed that 51% of pregnant women infected with COVID-19 had fever (vs. 91% non-pregnant patients) and 31% had cough (vs. 67% non-pregnant patients) (Gao et al., 2020). On the other hand, studies have shown COVID-19 combined with pregnancy can lead to premature delivery, fetal distress, fetal vascular perfusion, premature rupture of membranes, and other adverse pregnancy events (Chen H. et al., 2020). Although the treatments for COVID-19 are evolving, health care providers do not have specific treatments for pregnant women. Understanding the changes that occur in the immune system during pregnancy and the interaction between the immune system and COVID-19 is extremely important, because each key

link is expected to become a potential target of COVID-19, and provides new methods and ideas for the treatment of COVID-19 in pregnant women.

## MAJOR CHANGES IN THE IMMUNE SYSTEM IN PREGNANT WOMEN

Compared to non-pregnant women, pregnant women have a unique state of immunity. This status can affect how pregnant women respond to viral infections (Silasi et al., 2015), and SARS-CoV-2 is no exception. The main changes are summarized below (**Table 1**):

The CD3+/CD4+ and CD3+/CD8+ peripheral blood T lymphocyte and specific antiviral serum antibody counts were low in the pregnant patient (Chan et al., 2010). In addition to a decrease in the number of T cells in the blood during pregnancy, these cells are significantly less active when stimulated (Vazquez et al., 2015).

Transferring CD4+ T cell populations to T helper cell 2 (Th2) phenotypes during pregnancy (a response that promotes humoral rather than cellular immune responses) (Piccinni et al., 2000), reduced T helper cell 1 (Th1) reactivity may lead to reduced clearance of infected cells, increasing susceptibility to COVID-19 (Veenstra Van Nieuwenhoven et al., 2003). B cells are also affected by pregnancy, as their production is reduced during pregnancy (Medina et al., 1993).

Circulating natural killer (NK) cells decrease during pregnancy (Veenstra Van Nieuwenhoven et al., 2003). Since NK cells make up one fifth of the lymphocytes in the lung parenchyma, their role may provide a strong and extensive innate immune response to SARS-CoV-2 infection. Therefore, the decrease of NK cells is closely related to viral infection (Bozzano et al., 2021)..

Dendritic cells (DCs) are antigen-presenting cells that play a critical role in antiviral immunity (Liu, 2005). DCs are divided into two major types known as plasmacytoid cells (pDCs) and myeloid cells (mDCs) (Merad et al., 2013). Most studies have shown that the proportion of mDC/pDC is higher in pregnant women than in non-pregnant women (Darmochwal-Kolarz et al., 2003; Shin et al., 2009). During pregnancy, the production of interferon alpha (IFN-α) increases due to stimulation by toll-like receptors (TLRs), while the occurrence frequency of pDC decreases slightly, which may reduce the initiation of adaptive antiviral immune responses (Cordeau et al., 2012).

The phagocytic function of neutrophils and monocytes was significantly reduced in pregnant compared to non-pregnant women (Lampé et al., 2015).

The levels of interferon-γ (IFN-γ), vascular endothelial growth factor (VEGF), interleukin (IL)-1α, IL-1β, IL-6, IL-12, IL-17, IL-2, TNF-α (tumor necrosis factor α), and chemokines were decreased (Elenkov et al., 2001; Dashraath et al., 2020). On the contrary, IL-4, IL-10, IL-13, and transforming growth factor-β (TGF-β) levels were increased (Elenkov et al., 2001; Dashraath et al., 2020). Their changes during pregnancy are associated with a reduction in symptoms found in patients with COVID-19 (Pazos et al., 2012; Dashraath et al., 2020).

Circulating progesterone (P4) and steroid 17β-estradiol (E2) levels are elevated during pregnancy. The anti-inflammatory effects of E2 in innate immunity include inhibition of the production of pro-inflammatory cytokines such as IL-6 and IL-1β, tumor necrosis factor-α, monocytes, and macrophages which is a major factor in the COVID-19 cytokine storm (Chen R. et al., 2021) and powerful inhibition of monocyte chemoattractant protein-1 (MCP-1), thereby preventing innate immune cells, especially neutrophils and monocytes, from migrating to inflammatory areas. E2 stimulates CD4+ T helper cells to produce anti-inflammatory cytokines such as interleukin-4 (IL-4) and IL-10. In general, high E2 concentrations favor helper T cell type 2 (Th2) anti-inflammatory responses. E2 reduces production of interleukin-17 (IL-17) by pro-inflammatory T helper cell 17 (Th17 cells). E2 enhances the expansion of regulatory T cells (Treg), thereby promoting immune tolerance. E2 also stimulates the production of antibodies by B cells (Straub, 2007). P4 facilitates the CD4+ T-helper cell response from Th1 toward Th2 and the production of anti-inflammatory IL-4 and IL-10 cytokines (Szekeres-Bartho et al., 1996; Szekeres-Bartho and Wegmann, 1996).

## ACTIVATION AND RESPONSE OF THE IMMUNE SYSTEM IN PREGNANT WOMEN WITH COVID-19

Th immune status of pregnant women with COVID-19 is unique which makes it easier for the virus to invade, and the rate of SARS-CoV-2 infection is higher in pregnant women than non-pregnant women. However, after SARS-CoV-2 invades a pregnant woman, her immune system confers a certain protective effect, and the serious consequences caused by the virus are likely reduced (Wei et al., 2020). Pregnant women hospitalized for COVID-19 are less likely to develop symptoms than non-pregnant women of similar age (Allotey et al., 2020) (**Figure 1**).

The angiotensin-converting enzyme 2 (ACE2) is a key receptor for coronavirus invasion. Similar to the way other coronaviruses invade the body, studies have shown that SARS-CoV-2 uses the spike glycoprotein (S) proteins to bind to its receptors on target cells (Wan et al., 2020; Zhou et al., 2020). ACE2 expression and activity are enhanced during pregnancy (Levy et al., 2008). Compared with non-pregnant women, pregnant women showed a two-fold increase in ACE2 receptor expression in different organs including the placenta, kidneys, and uterus (Brosnihan et al., 2004). This automatically makes pregnant women more susceptible to SARS-CoV-2 than non-pregnant women.

SARS-CoV-2 infects alveolar epithelial cells by recognizing the ACE2 receptor. Following cell invasion, the virus replicates in large quantities, which activates immune cells. Interestingly, ACE2 has a lung-protective effect (Ziegler et al., 2020), and elevated ACE2 levels in pregnant women make their lungs more protective than those of non-pregnant women, possibly reducing lung inflammation. In addition, angiopoietin 1-7 (Ang 1-7) produced by ACE2 degradation of Ang II was higher in pregnant women than in non-pregnant women, and the anti-inflammatory effect of phosphoinositide 3-kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK) signaling pathways regulated by MAS receptors specifically bound to Ang 1-7 was

**TABLE 1 |** "Physiological changes in pregnant women" and "Effects of SARS-CoV-2".

| Cell/Receptor/ Cytokine | Function | Physiological changes in pregnant women | Effects of SARS-CoV-2 |
|---|---|---|---|
| CD3+ T cell | Constructs TCR/CD3 complex and stabilizes its structure Participates T-cell activation signal transduction (Mesner et al., 2020) | Decreases in level and activity when stimulated | Weakens cellular immunity, and SARS-CoV-2 is more likely to invade |
| CD4+ T cell | Participates in the TCR antigen recognition process of TH cells (Horkova et al., 2020) | Decreases in level and activity when stimulated Differentiates to Th2 phenotype -The activity of Th 1 phenotype decreases | Weakens cellular immunity, and SARS-CoV-2 is more likely to invade Weakens humoral immunity, and the secretion of antibodies is reduced |
| CD8+ T cell | Killing effect on some antigens such as viruses and tumor cells (Horkova et al., 2020) | Decreases in level and activity when stimulated | Weakens the ability of CD8+ T cells to kill target cells, and SARS-CoV-2 is more likely to invade |
| NK cell | Identifies target cells, killing agents (Huntington et al., 2020) | Decreases | Weakens innate immune response to SARS-CoV-2 |
| DC cell | Initiates, regulates, and maintains the immune response Activates NK cell (Chen et al., 2016) | mDC/pDC↑ pDC↓ | Weakens the initiation of adaptive immune response to SARS-CoV-2 Reduced activation of NK cell weakens the innate immune response to SARS-CoV-2 |
| Neutrophil | Chemotaxis Phagocytosis -Bactericidal action (Grunwell et al., 2019; Jaillon et al., 2020) | Reduces phagocytosis | SARS-CoV-2 is more likely to invade |
| Monocytes | Phagocytosis Antigen presentation (Guilliams et al., 2018) | Reduces phagocytosis | SARS-CoV-2 is more likely to invade |
| IFN-γ | Inhibitory angiogenesis Increases cytotoxic effects Promotes the differentiation of CD4+T cells to Th1 type and maintains the stability of Th1 phenotype Chemotaxis and activation of neutrophils, monocytes, and macrophages (Haep et al., 2015; Alspach et al., 2019) | Decreases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection Delays virus clearance and increases infection rate |
| VEGF | Promotes the proliferation of vascular endothelial cells Induction of angiogenesis Increased vascular permeability (Holmes et al., 2007) | Decreases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection Delays virus clearance and increases infection rate |
| IL-1α | Activates CD4+T cells, B cells, NK cells, neutrophils, monocytes Pyrogen 1 (Mantovani et al., 2019) | Decreases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection Delays virus clearance and increases infection rate |
| IL-1β | Activates CD4+T cells, B cells, NK cells, neutrophils, monocytes Pyrogen 1 (Mantovani et al., 2019) | Decreases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection Delays virus clearance and increases infection rate |
| IL-2 | Stimulates and activates the proliferation of B and T cells (Watson et al., 1979; Wilson and Livingstone, 2008) Inhibits differentiation of the Th17 cells (Laurence et al., 2007) | Decreases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection Delays virus clearance and increases infection rate |
| IL-4 | Stimulates and activates the proliferation of B and T cells Stimulates CD4+ T cells to differentiate into the Th2 phenotype Against the action of INF-γ-activated macrophages (Junttila, 2018; Franke et al., 2020) | Increases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection |
| IL-6 | Stimulates the synthesis of APP in liver cells Stimulates the proliferation of activated B cells and secretes antibodies Stimulates T-cell proliferation and CTL activation (Hirano, 2021) | Decreases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection Delays virus clearance and increases infection rate |
| IL-10 | Inhibition of macrophage response Suppresses cellular immunity Promotes humoral immunity (Walter, 2014) | Increases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection Delays virus clearance and increases infection rate |
| IL-12 | Stimulates the proliferation of activated T cells, Promotes the differentiation of T0 cells to T1 cells Induces cytotoxic activity of CTL and NK cells 6 (Trinchieri, 2003; Furue et al., 2019) | Decreases | Delays virus clearance and increases infection rate |
| IL-13 | Inhibits the release of IL-1, IL6, and other pro-inflammatory cytokines from monocytes Promotes the immune response of TH cells (Hart et al., 1999) | Increases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection Delays virus clearance and increases infection rate |
| IL-17 | Mediates tissue inflammation (Amatya et al., 2017) | Decreases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection Delays virus clearance and increases infection rate |

*(Continued)*

**TABLE 1 |** Continued

| Cell/Receptor/ Cytokine | Function | Physiological changes in pregnant women | Effects of SARS-CoV-2 |
|---|---|---|---|
| TNF | Enhances cytotoxicity <br> Enhances phagocytosis of neutrophils <br> Damages endothelial cells (Virdis et al., 2011; Brenner et al., 2015) | Decreases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection <br> Delays virus clearance and increases infection rate |
| TGF-β | Inhibits proliferation of immunocompetent cells <br> Inhibits lymphocyte differentiation <br> Inhibits cytokine production (Travis and Sheppard, 2014) | Increases | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection <br> Delays virus clearance and increases infection rate |
| ACE2 | Promotes angiotensin conversion <br> Key receptors on cell surface that bind to SARS-CoV-2 (Levy et al., 2008; Jamilloux et al., 2020; Zhou et al., 2020) | Expression and activity are increased | Chance of SARS-CoV-2 invasion increases <br> Enhances the protective effect of ACE2 on the lung after SARS-CoV-2 infection |
| Ang 1-7) | Relaxation of blood vessels <br> -Suppresses inflammation (Patel et al., 2016) | Increases | -Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection |

*SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th cell, T helper cell; NK cell, natural killer cell; DC cell, dendritic cell; pDC, plasmacytoid cell; mDC, myeloid cell; IFN-γ, interferon gamma; VEGF, vascular endothelial growth factor; IL-1α, interleukin 1 alpha; IL-1β, interleukin 1 beta; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; IL-7, interleukin 7; IL-8,interleukin 8; IL-10, interleukin 10; IL-12, interleukin 12; IL-13, interleukin 13; IL-17, interleukin 17; TNF, tumor necrosis factor; TGF-β, transforming growth factor-beta; LT-A, lymphotoxin-A; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; M-CSF, macrophage-colony stimulating factor; ACE2, angiotensin-converting enzyme 2; Ang 1-7, angiotensin-(1-7).*

also stronger than that in non-pregnant women (Passos-Silva et al., 2013). This results in less severe COVID-19 symptoms in pregnant women than in non-pregnant women, fewer cytokine storms, and less progression towards acute respiratory distress syndrome (ARDS), multiple organ dysfunction, and death.

The pattern recognition receptors (PRRs) expressed by lung epithelial cells, macrophages, and DCs bind to damage-associated molecular patterns (DAMPs) produced by virus-infected epithelial cells and pathogen-associated molecular patterns (PAMPs) of the virus itself, which then activate nuclear factor-k-gene binding (NF-kB) and several mitogen-activated protein kinases (MAPKs), triggering a cascade of inflammatory responses and the release of chemokines. Inflammation is less severe in pregnant women and cytokine storms are less likely to occur. This is mainly caused by the following mechanisms. A physiological shift in pregnant women to a TH2 environment conducive to the expression of anti-inflammatory cytokines (IL-4 and IL-10). The levels of IFN-γ, VEGF, IL-1α, IL-1β, IL-6, IL-12, IL-17, and chemokines were decreased in pregnant woman, so the cascade of inflammatory cytokines was weaker than that of non-pregnant women. DCs activated by SARS-CoV-2 release IFN and IL-7 to promote immune inflammatory response and they trigger a direct antiviral response and manipulate the activation of NK cells and CTL (Hassanzadeh-Kiabi et al., 2017; Jamilloux et al., 2020). During pregnancy, the occurrence frequency of pDC decrease. Thus, DC-mediated inflammatory response was reduced in pregnant women. The phagocytic function of neutrophils and monocytes is significantly reduced during pregnancy and also releases fewer cytokines. NK cells help clear virus-infected cells through a variety of mechanisms including direct contact, cytokine or chemokine secretion, and indirect influence on lateral and downstream adaptive immune responses by affecting dendritic cells and T cells (Moretta, 2002; Mavilio et al., 2006; Vivier et al., 2011). The decrease of NK cells in pregnant women results in a significantly reduced inflammatory response in the body. The anti-inflammatory effects of E2 and P4 also play a role in reducing inflammatory response. As a result, the expression of

pro-inflammatory and anti-inflammatory cytokines was relatively low in pregnant women with COVID-19. In particular, macrophage chemokines, referred to as major components of the cytokine storm during COVID-19 (Jafarzadeh et al., 2020), including macrophage inflammatory protein 1-alpha (MIP1α), CTACK, RANTES, eotaxin, growth-related oncogene alpha (GRO-α), and TNF were found at significantly low levels in pregnant patients. At the same time, basic fibroblast growth factor (FGF), leukemia inhibitory factor (LIF), granulocyte colony-stimulating factor (G-CSF), platelet-derived growth factor subunit B (PDGF-BB), and other growth factors were also significantly lower in COVID-19-positive pregnant women than pregnant women without COVID-19 (Chen G. et al., 2021).

CD4+ and CD8+ T cells not only eliminate the virus, but also stimulate hypermacrophage syndrome, eventually causing a cytokine storm in SARS-CoV-2 patients (Wang et al., 2020). The CD3+/CD4+ and CD3+/CD8+ peripheral blood T lymphocytes were low, which will reduce clearance of infected cells and the appearance of cytokine storm. Patients with COVID-19 show both a B cell immune response and a follicle-assisted T cell response (Thevarajan et al., 2020). In addition to producing antibodies, activated B cells also secrete IL-1, IL-6, IL-8, TNF, lymphotoxin-α (LT-A), G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), IL-7, and other cytokines that can aggravate the cytokine storm (Vazquez et al., 2015). Production of B cell lymphocytes is reduced during pregnancy, which alleviate the occurrence of cytokine storm.

A reduced inflammatory response also leads to delayed clearance of the virus and increased infection rates. This can lead to adverse obstetric outcomes.

## ADVERSE PREGNANCY OUTCOMES DUE TO COVID-19

Adverse obstetric outcomes of COVID-19 include miscarriage, intrauterine growth restriction, premature rupture of membranes,
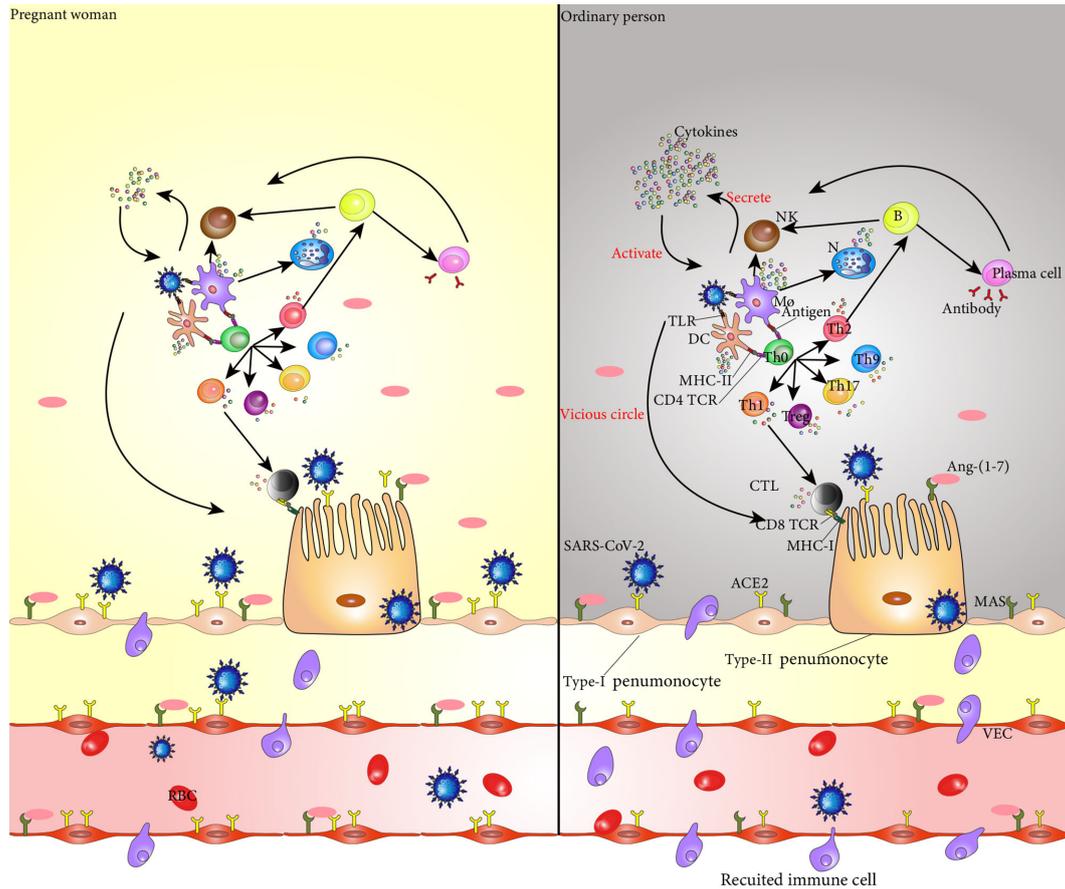
**FIGURE 1** | SARS-CoV-2 binds to ACE2 in the alveolar epithelial cells and invades these cells. Entry of SARS-CoV-2 into the body activates dendritic cells and macrophages, which secrete cytokines to activate NK cells. These NK cells kill the target cells infected by SARS-CoV-2. TLRs on dendritic cells and macrophages recognize viruses and secrete cytokines that mediate the inflammatory response. The CD4 TCR on the surface of Th0 cell membrane specifically binds to the antigen-peptide MHC II molecular complex on the surface of dendritic cells and macrophages, promoting the differentiation of Th0 cells into Th1, Th2, Treg, Th9, and Th17 cells, and the cytokines secreted by these cells promote the inflammatory response. Th1 cells secrete cytokines to activate CTL, and CD8 TCR on the surface of CTL recognizes and binds to MHC-I on the surface of cells infected with SARS-CoV-2 to kill target cells. Th2 cells secrete cytokines that assist the activation of B cells, which are activated into plasma cells that produce neutralizing antibodies to clear SARS-CoV-2. At the same time, B cells secrete cytokines to promote the killing activity of NK cells. The cytokines secreted by each immune cell in the immune response act on the immune cells themselves and promote their secretion of cytokines, forming a vicious cycle, finally resulting in a cytokine storm and aggravating the inflammatory response. In addition, Ang 1-7 produced by hydrolysis of ACE2 specifically binds to the PI3K/Akt and ERK signaling pathways regulated by MAS receptors on the cell surface, and plays an anti-inflammatory and cellular protective role. The increase of ACE2 levels in pregnant women makes invasion by SARS-CoV-2 easier; however, at the same time, the level of Ang 1-7 also increases, and the protective effect on the alveolar surface epithelial cells is stronger than that of non-pregnant women. During pregnancy, the immune system changes, and the cytokines secreted by dendritic cells and macrophages are reduced, and the activation of Th0 cells and NK cells is weakened, resulting in less cytokine. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NK cell, natural killer cell; TLR, Toll-like receptors; Th0 cell, T helper cell 0; Th1 cell, T helper cell 2; Th2 cell, T helper cell 2; Treg, regulatory cells; Th9 cell, T helper cell 9; Th17 cell, T helper cell 17; CTL, cytotoxic T lymphocyte; MHC-I, major histocompatibility complex-I; Ang-(1-7), angiotensin-(1-7); ACE2, angiotensin-converting enzyme 2; PI3K, phosphoinositide 3-kinase; ERK, extracellularsignal-regulated kinase;.

intrauterine/fetal distress, preeclampsia, vertical transmission, and preterm delivery (Dashraath et al., 2020; Schwartz, 2020) (**Table 2**).

Endothelial cell dysfunction is the core mechanism that leads to preeclampsia in pregnant women (Burton et al., 2019). Endothelial dysfunction after SARS-CoV-2 infection is the key to progression of COVID-19, so pregnant women infected with COVID-19 are at an increased risk of developing preeclampsia (Bonaventura et al., 2021).

The delicate balance between Treg and Th17 cells mediates the mother's tolerance to the fetus (Aluvihare et al., 2004; Lee J. H. et al.,

2011). In patients with COVID-19, the level of Treg cells (CD3 +CD4+CD25+ CD127low+) decreases (Wang et al., 2020; Qin et al., 2020), the level of Th17 cells (CCR6+ Th17) increases, and the ratio of Treg/Th17 cells decreases (Wu and Yang, 2020). Reduced Treg cell count and increased Th17 cell percentage are associated with pregnancy complications such as miscarriage, preeclampsia, and preterm delivery (Sasaki et al., 2007; Xiong et al., 2010; Fu et al., 2014; Koucký et al., 2014; Eghbal-Fard et al., 2019).

IFN-γ, TNF, IL-6, and IL-8 levels were significantly increased in COVID-19 patients (Huang et al., 2020), causing pregnant

**TABLE 2 |** Immune effects of COVID-19 on pregnant women and adverse pregnancy outcomes.

| Cell/Receptor/ Cytokine | Function | Effects of COVID-19 | Adverse pregnancy outcome |
|---|---|---|---|
| ECs | Release vasoactive factors to regulate vasoconstriction or relaxation<br>Promotes inflammation (Mercier et al., 2017; Lin et al., 2019) | Dysfunction | Preeclampsia |
| Treg cells | Participates in the establishment of maternal-fetal immune tolerance<br>Maintains immune homeostasis<br>Treg/Th 17 balance promotes normal pregnancy (Kimura and Kishimoto, 2010; Lee J. H. et al., 2011; Gobert and Lafaille, 2012; Zhang et al., 2018) | Decreases Treg/Th 17↓ | Abortion<br>Preeclampsia<br>Premature delivery |
| Th17 cell | Mediates tissue inflammation<br>Treg/Th 17 balance promotes normal pregnancy (Kimura and Kishimoto, 2010; Zhang et al., 2018) | Increases Treg/Th 17↓ | Abortion<br>Preeclampsia<br>Premature delivery |
| IFN-γ | Inhibition of angiogenesis<br>Increases cytotoxic effects<br>Promotes the differentiation of CD4+T cells to Th1 type and maintains the stability of Th1 phenotype<br>Chemotaxis and activation of neutrophils, monocytes, and macrophages (Haep et al., 2015; Alspach et al., 2019) | Increases | Abortion<br>Premature rupture of membranes |
| TNF | Enhances cytotoxicity<br>Enhances the phagocytosis of neutrophils<br>Damage to endothelial cells (Virdis et al., 2011; Brenner et al., 2015) | Increases | Abortion<br>Premature rupture of membranes |
| IL-6 | Stimulates the synthesis of APP in liver cells<br>Stimulates the proliferation of activated B cells and secrete antibodies<br>Stimulates T cell proliferation and CTL activation (Hirano, 2021) | Increases | Abortion<br>Premature rupture of membranes |
| IL-8 | Chemotactic neutrophils (Li Jeon et al., 2002) | Increases | Abortion<br>Premature rupture of membranes |
| ACE2 | Promotes angiotensin conversion<br>-Key cell surface receptor that binds to SARS-CoV-2 (Levy et al., 2008; Jamilloux et al., 2020; Zhou et al., 2020) | Decreases | Preeclampsia |
| Ang-(1-7) | - Relaxation of blood vessels<br>-Suppresses inflammation 10 (Patel et al., 2016) | Decreases | Preeclampsia |
| Blood coagulation factor | -Participates in blood clotting (Langarizadeh et al., 2021) | Increases | Thromboembolism |

*ECs, endothelial cells; Treg cells, regulatory cells; Th 17 cells, T helper cell 17; IFN-γ, interferon gamma; TNF, tumor necrosis factor; IL-6, interleukin 6; IL-8, interleukin 8; ACE2, angiotensin-converting enzyme 2; Ang 1-7), angiotensin-(1-7).*

women with COVID-19 to be more prone to miscarriage and premature rupture of membranes. The secretion of TNF-α, IL-8, and IL-6 by macrophages in the process of inflammation can lead to abortion, premature rupture of membranes, and preterm labor (Lee S. Y. et al., 2011; Roncari et al., 2013; Li et al., 2015; Li et al., 2020).

SARS-CoV-2 not only binds to ACE2 but also causes it to be downregulated, so Ang 1-7) also decreases (Glowacka et al., 2010). Preeclampsia is associated with reduced plasma Ang 1-7) levels in the mother (Roncari et al., 2013). COVID-19 increases the risk of preeclampsia in pregnant women.

Patients with COVID-19 have a higher incidence of thromboembolic complications (Knight et al., 2020), and healthy pregnant women have higher levels of circulating clotting and fibrinolytic factors (such as fibrinolytic enzyme) (Di Renzo and Giardina, 2020). Alterations in clotting and fibrinolysis are thought to play an important role in the pathogenesis of preeclampsia (Schjetlein et al., 1997). Pregnant women with COVID-19 may have additive or co-operative risk factors for the onset of preeclampsia.

Studies have shown that that although vertical transmission of SARS-CoV-2 *in utero* is low, it is possible and appears to occur in a minority of pregnant women with COVID-19 in the third trimester (Fenizia et al., 2020; Kotlyar et al., 2021).

# TREATMENT

There are several treatments that hold promise for preventing and treating pregnant women with COVID-19 (**Table 3**).

Bamlanivimab and etesevimab are recombinant human immunoglobulin G1 antibodies, which is a therapy that has proven to be more effective. A randomized clinical trial showed the treatment to be effective (Gottlieb et al., 2021). Phase III data on bamlanivimab plus etesevimab in COVID-19 patients showed that among non-hospitalized patients with mild-to-moderate COVID-19 disease, bamlanivimab plus etesevimab led to a lower incidence of COVID-19-related hospitalization and death than the placebo and accelerated the decline in the SARS-CoV-2 viral load (Dougan et al., 2021). The study population included high-risk groups such as immunosuppressed states, chronic diseases, immunodeficiency, and obesity. All these patients benefited from the treatment. Although there is still no data showing that it is safe for pregnant women, we believe this is a very promising treatment.

Torzumab is an IL-6 receptor antagonist and a meta-analysis of torzumab use and COVID-19 inpatient mortality showed that torzumab reduced all-cause mortality in COVID-19 inpatients within 28 days (Shankar-Hari et al., 2021). In addition, studies have shown that torzumab is effective in patients with severe

**TABLE 3 |** Treatment and prevention of COVID-19 in pregnant women. .

| Therapeutic function | Therapeutic drug | Effect |
| --- | --- | --- |
| Glucocorticoids | | |
| | Dexamethasone | IL-6↓ |
| Cytokine antagonists | Torzumab | Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection |
| | | Delays virus clearance and increases infection rate |
| Anti-virus | | |
| | Bamlanivimab | Accelerates the decline in the SARS-CoV-2 viral load (Dougan et al., 2021) |
| | Etesevimab | Accelerates the decline in the SARS-CoV-2 viral load (Dougan et al., 2021) |
| – | IFN-α | Blocks virus replication and transmission (Yang et al., 2021) |
| – | Remdesivir | Inhibits the replication of SARS coronavirus (Lamb, 2020) |
| Others | High-dose inhaled nitric oxide (160–200 ppm) | Antimicrobial effects against bacteria and viruses (including SARS-CoV) |
| – | Vit D | Regulates the imbalance of Treg/Th17 |
| – | Magnesium sulfate | Prevents and treats epilepsy in preeclampsia |
| – | Aspirin | Prevents and treats epilepsy in preeclampsia |
| – | Metformin | Inhibits cytokine storm and prevents SARS-CoV-2 infection (Burwick et al., 2020) |
| Prevent | | |
| Vaccine | | Prevention of SARS-CoV-2 infection |
| Wear mask | | Prevention of SARS-CoV-2 infection |

IL-6, interleukin 6; IFN-α, interferon alpha; vit D, vitamin D; Treg cells, regulatory cells; Th 17 cells, T helper cell 17; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

COVID-19 during pregnancy and is a treatment option for COVID-19 during pregnancy (Naqvi et al., 2020).

There is some evidence that IFN can show anti-SARS-CoV-2 effect (Busnadiego et al., 2020; Monk et al., 2021), especially as inhaled nebulized interferon beta-1a (SNG001). Studies have shown that none of the patients who received IFN during pregnancy experienced stillbirth or delivered babies with severe malformations, and IFN did not significantly increase the risk of malformation, miscarriage, stillbirth, or preterm birth. Therefore, IFN is likely effective and safe in terms of COVID-19 during pregnancy (Yazdani Brojeni et al., 2012).

Remdesivir, a novel broad-spectrum antiviral nucleotide prodrug, has been shown to inhibit the replication of SARS coronavirus *in vitro*. Published results have suggested that the use of remdesivir may reduce clinical recovery time in patients with COVID-19 (Beigel et al., 2020). The manufacturer safety data of remdesivir indicate no reproductive developmental toxicity in animals at clinically relevant doses; furthermore, embryonic toxicity was only noted when systemically toxic doses were administered to female animals before conception (Maldarelli et al., 2020). Studies of the use of remdesivir did not document specific adverse outcomes in pregnant women (Mulangu et al., 2019; Burwick et al., 2020). These data provide patients and clinicians with reliable information about the safety of remdesivir in the treatment of pregnant women with COVID-19. Remdesivir is expected to be beneficial for COVID-19 therapy.

Dexamethasone is a common anti-inflammatory drug. It is known that glucocorticoids inhibit inflammation through non-genetic mechanisms, such as binding to glucocorticoid receptors on the T-cell membrane, resulting in disorder of receptor signals and immune response, and interaction with calcium and sodium across the cell membrane, leading to rapid resolution of inflammation (Langarizadeh et al., 2021). Hence, it may play a vital role in the treatment of COVID-19. The administration of prenatal corticosteroids to women at risk of preterm birth has been shown to have significant benefits in neonatal morbidity

and mortality (Kemp et al., 2016), which make it reasonable for COVID-19 patients to use dexamethasone during pregnancy.

There is evidence for pregnant women with COVID-19 that appropriate use of magnesium sulfate, aspirin, metformin, and anticoagulants can help cure the disease and reduce adverse outcomes such as preeclampsia, premature birth, and miscarriage (Chen X. et al., 2020; D'Souza et al., 2021).

Vitamin D is an immunomodulatory hormone that has been established to be effective against a variety of upper respiratory tract infections. Vitamin D prevents excessive inflammatory response and accelerates the healing process in affected areas, primarily in lung tissue (Mohan et al., 2020). Moreover, Treg/Th17 imbalance can be corrected with vitamin D supplementation *in vivo* (Ji et al., 2019). The imbalance of Treg/Th17 in COVID-19 patients not only leads to uncontrolled cytokine release and increased inflammatory response in COVID-19 patients but also leads to adverse obstetric outcomes in pregnant patients. Vitamin D therefore holds promise as a complementary treatment.

High-dose inhaled nitric oxide (160–200 ppm) has shown antimicrobial effects against bacteria and viruses (including SARS-CoV), and is used as an adjunct treatment for ARDS and pulmonary hypertension. A case series of pregnant patients with severe COVID-19 treated with high-dose nitric oxide demonstrated improvement in hypoxemia and tachypnea with no adverse neonatal effects (Safaee Fakhr et al., 2020). Hence, it also holds promise as a complementary treatment.

We wish to highlight the need for close interdepartmental collaboration in caring for pregnant women presenting with COVID-19.

# PREVENTION

For the influenza virus, studies have shown significant reductions in low birth weight and preterm birth in vaccinated women compared to unvaccinated women (Heath et al., 2020), while other studies have not shown any association between

vaccination and spontaneous abortion, preterm birth, birth defects, or small gestational age babies. Vaccination is one of the most promising preventive measures against COVID-19. Because pregnant women are more susceptible to SARS-CoV-2, vaccination during pregnancy is the most optimal strategy for preventing maternal and neonatal disease (Andreani et al., 2020; Heath et al., 2020). A preliminary finding of mRNA safety of COVID-19 vaccine in pregnant women showed that vaccination is safe in the third trimester of pregnancy (Shimabukuro et al., 2021). In addition to vaccination protecting women against COVID-19 and its complications during pregnancy, emerging evidence has shown transplacental transfer of SARS-CoV-2 antibodies after maternal COVID-19 vaccination during the third trimester, which suggests that maternal vaccination might provide some level of protection to the neonate (Gill and Jones, 2021; Gray et al., 2021; Rottenstreich et al., 2021). To date, there is still little information on the efficacy and safety of vaccinating pregnant women. More extensive research is required regarding vaccinating pregnant women.

Studies (Cheng et al., 2021) have shown that wearing a surgical mask can be a very cost-effective method to prevent the spread of virus. Because the vaccine does not provide 100% protection against COVID-19, mask-wearing is especially important for pregnant women who are more vulnerable to infection.

## CONCLUSION

COVID-19-related immune system changes in pregnant women involve multiple cytokines, cells, and receptors. The unique immune status of pregnant women makes them more susceptible to SARS-CoV-2 invasion. However, after SARS-CoV-2 invades a pregnant woman, the immune system of the body has a certain protective effect, which reduces the serious consequences caused by the virus. However, changes in the immune system caused by the virus can also lead to poor pregnancy outcomes. Therefore, it is of great significance to accurately identify COVID-19 inflammatory pathways and therapeutic targets in pregnant women. The efficacy of the current COVID-19 treatment for pregnant women is still not satisfactory. Many clinical studies of drugs and vaccines have excluded pregnant women. The treatment of pregnant women has become a challenging problem, and more studies are needed to address these issues.

## AUTHOR CONTRIBUTIONS

HS and HY conceived and designed the study. RC, SZ, and SS performed the literature search and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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