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Gestational diabetes mellitus and long-term maternal outcomes

Edited by
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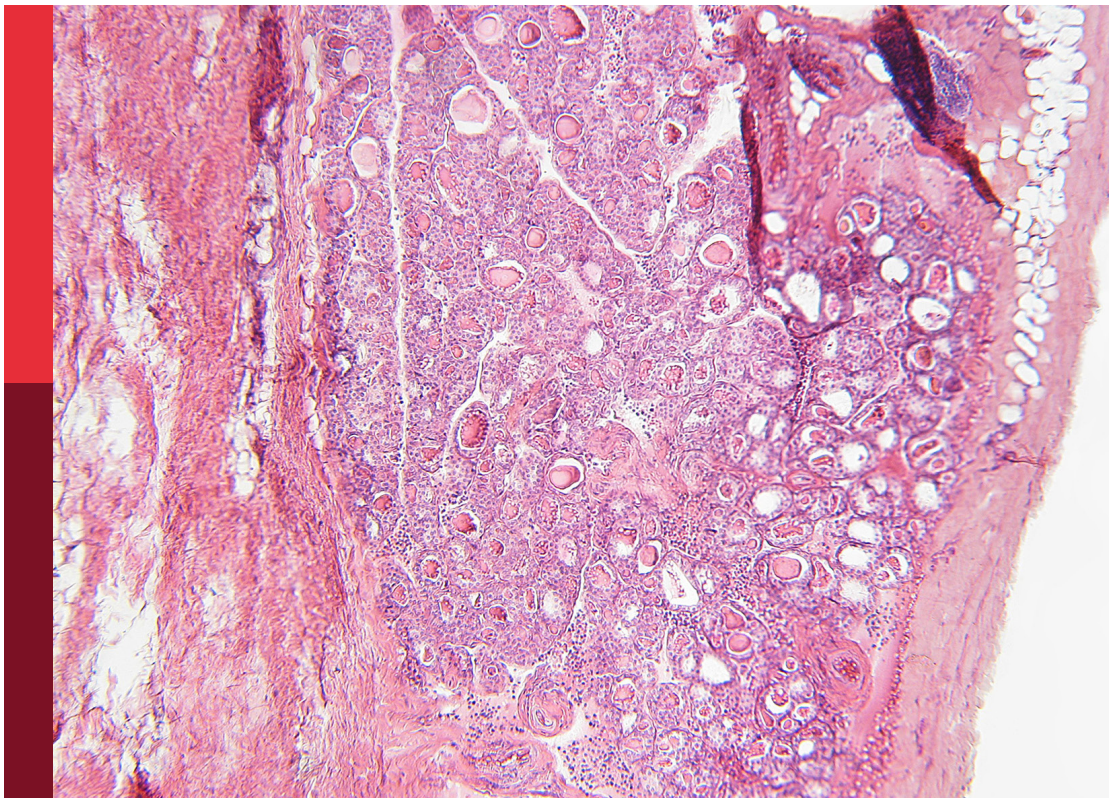

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Gestational diabetes mellitus and long-term maternal outcomes

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ORIGINAL RESEARCH
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Blood Glucose Level, Gestational Diabetes Mellitus and Maternal Birth Season: A Retrospective Cohort Study

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Background: Previous evidence indicates that birth season is associated with type 2 diabetes in adults. However, information on the association of birth with gestational diabetes mellitus (GDM) is lacking. The present study explores the association between birth seasonality and GDM in East China.

Methods: This retrospective cohort study was conducted at the International Peace Maternal and child health hospital between 2014 and 2019. A total of 79, 292 pregnant women were included in the study after excluding participants with previous GDM, stillbirth, polycystic ovary syndrome, and lack of GDM laboratory records. The multivariate logistic regression model was employed to estimate the odds ratio and 95% confidence interval. After log transformation of blood glucose level, the percentage change and 95% confidence interval were estimated by a multivariate linear model.

Results: The risk of GDM among pregnant women born in spring, autumn, and winter was not significantly different compared to that among participants born in summer. Pregnant women born in autumn had significantly higher 1-hour postprandial blood glucose (PBG-1h) and 2-hour postprandial blood glucose (PBG-2h) levels than pregnant women born in summer. Compared to pregnant women born in August, the PBG-1h level of pregnant women born in October, November, and December increased significantly, whereas the PBG-2h levels of pregnant women born in November and December increased significantly.

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Conclusion: Pregnant women born in autumn exhibit higher postprandial blood glucose levels during pregnancy than in those born in summer. The findings provide evidence that exposure to seasonal changes in early life may influence blood glucose metabolism during pregnancy.

Keywords: GDM, birth, blood glucose, EPI - epidemiology, pregnant woman

INTRODUCTION

Gestational diabetes mellitus (GDM) is a common pregnancy complication. Emerging evidence shows that nearly 1% to 30% of pregnant women experience GDM worldwide (1). The adverse effects of GDM birth outcomes, the health of offspring and mother are documented (2–4). Reducing the incidence of GDM and its impact on health warrants in-depth investigation of underlying mechanisms and associated risk factors.

The impact of prenatal environmental exposure on the risk of type 2 diabetes in adulthood is of increasing concern. Studies have demonstrated that an unfavorable prenatal environment may increase the risk of future health conditions whose outcomes are related to diabetes or GDM (5). Evidence shows that environmental impact during the critical period of prenatal may program the structure and function of organs and tissues critical to glucose homeostasis later in life (6). However, the underlying mechanism of GDM prenatal programming is elusive.

The season or month of birth is a surrogate factor for potential environmental exposure during the perinatal period. Factors associated with seasonal changes include but are not limited to temperature, sunshine, food supply, eating habits, outdoor sports activities, vitamin D synthesis, breastfeeding, infection status, etc (7–13). Although a few studies have investigated the association of birth season or month with adult type 2 diabetes, the results are inconsistent (14–16). Researchers have demonstrated that maternal blood glucose is more sensitive to environmental changes (17). However, data on the relationship between GDM and birth season or month is missing. Here, we retrospectively explored the association of birth season or month of pregnant women with the risk of GDM in Eastern China.

METHODS

Study Population

The study investigated a retrospective cohort from International Peace Maternity and Child Health Hospital, affiliated with Shanghai Jiaotong University School, from January 2014 to December 2019. Information of 94, 942 medical records from the electronic medical record system, including blood glucose levels, demographic data (date of birth, medical insurance, ethnicity, ward types), disease history, pre-pregnancy BMI, smoking, drinking, birth history (parity, gravidity), etc. were retrieved. The exclusion criteria included pregnant women with no available date of birth, no GDM diagnosis record, previous GDM, multiple births, stillbirths, and abortions. Eventually, 79, 292 pregnant women were investigated (**Figure S1**). Ethical approval was issued by the ethics committee of International Peace Maternity and Child Health Hospital. Written informed consent requirement from patients was waived due to the retrospective design of this study.

Outcomes

The Oral Glucose Tolerance Test (OGTT) was used to diagnosis GDM at 24-28 weeks of gestation according to the recommendations of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (18). Pregnant women took 75 grams of glucose after fasting the night before, and then measured their blood glucose levels at 1 and 2 hours. GDM was defined as fasting blood glucose (FBG) ≥5.1 mmol/L, or/and 1-hour postprandial blood glucose (PBG-1h) ≥10 mmol/L, or/and 2-hour postprandial blood glucose (PBG-2h) ≥8.5 mmol/L.

Statistical Analysis

The birth season was classified based on astronomical seasons (winter, winter solstice-vernal equinox; spring, spring breeze-summer solstice; summer, summer solstice-autumnal equinox; autumn, autumnal equinox-winter solstice). To assess the effect of seasonal variation in birth on GDM, logistic regression analysis was performed with month and season of birth as the predictor. The reference group was set as the category with the lowest risk of GDM to birth month (FBG: May; PBG-1h and PBG-2h: August) and birth season (Summer). The multivariate logistic regression model of the association between GDM risk and birth season or birth month was adjusted for pregnancy age (years), fetal sex (male or female), the education level (below university, university, or above), drinking (yes, no), smoking (yes, no), family history of diabetes (No, Yes), pre-pregnancy BMI (<18.5, 18.5-23.9, ≥24), parity (1 and ≥2), and gravidity (1, 2, and ≥3), conception method (natural conception, assisted reproduction technology [ART]), medical insurance type (urban or employee, others), ward type (general ward, senior ward), etc.

Logistic regression analysis was conducted after stratification for birth cohort (year of birth ≤ 1985, year of birth>1985), parity (1, ≥2), type of registration (locals, outsiders), and pre-pregnancy BMI (<24, ≥24). Log-transformed blood glucose levels (including PBG-1h, PBG-2h, and FBG) at 24-8 weeks served as the outcome for linear regression analysis in exploring the influence of birth month and birth season on blood glucose. The blood glucose level was closer to a normal distribution after log-transformation (**Figure S2**). Percentage change (PC) and 95% confidence interval (95%CI) represented association.

For sensitivity analysis, the effect of different season classifications (the birth season), including Spring (March, April, May), Summer (June, July, August), and Autumn (September, October, November), Winter (December, January, February), was investigated. To exclude the effect of birth season of offspring on the association between maternal birth season and GDM, we took the pregnancy season as the covariate in the above analyses. The pregnancy season was classified based on astronomical seasons

R software (Version: 3.6.3) was employed for data analysis. Statistical significance was set at two-tailed $P<0.05$.

RESULTS

Participant Characteristics

Of the 79,296 pregnant women were included in this study, the average age of pregnancy was 30.54 ± 3.88 years, the average pre-pregnancy BMI was 20.97 ± 2.75. As shown in **Table 1**, the number of births in the four seasons in descending order is Autumn (29.45%), Summer (25.04%), Winter (24.80%) and Spring (20.72%); the prevalence of GDM in pregnant women born in all seasons is descending from high to low in Spring (14.42%), Autumn (14.36%), Winter (14.34%) and Summer (13.87%); Among all participants, the proportion of primipara was 51.21%, the proportion of drinking during pregnancy was 0.86%, and the proportion of smoking during pregnancy was 0.35%. **Table S1** shows the baseline characteristics of participants by birth season. Pregnant women born in summer exhibited higher pre-pregnancy BMI levels before pregnancy, and higher levels of PBG-1h and PBG-2h in autumn.

Association of GDM With Birth Months or Seasons

According to the multivariate-adjusted model, the birth season and month were not significantly associated with the risk factors of GDM (**Figures 1**, **2**). No substantial change in the correlation was reported even after adjusting for pre-pregnancy BMI, family history (hypertension and diabetes), birth history, smoking, and drinking. After further adjusting for pregnancy season, there was no significant correlation between birth season and GDM risk (**Figure S3**). Similarly, when we changed the criteria for the classification of the birth season and conducted another correlation test, results showed no significant association between birth season and GDM risk (**Figure S4**).

Association of Blood Glucose With Birth Months or Seasons

Compared to pregnant women born in summer, those born in spring, autumn and winter exhibited no significant difference in fasting blood glucose between 24-28 weeks of gestation (**Figure 3A**). However, the PBG-1h level of pregnant women born in the autumn increased significantly by 0.50% (0.17%, 0.84%) and the PBG-2h level increased significantly by 0.78% (0.38%, 1.19%); the PBG-1h and PBG-2h levels of pregnant women born in winter increased significantly; however, the significance disappeared after an adjustment by other factors (**Figures 3B, C**). In addition, the results of the above analysis by seasonal grouping using months show that the results of birth season and blood glucose level are similar to those described above (**Figure S5**). Compared to pregnant women born in August, the PBG-1h levels of pregnant women born in October, November, and December increased significantly by 0.65%, 0.98%, and 0.87%, respectively (**Figure 4B**); the PBG-2h levels of pregnant women born in November, and December increased significantly by 1.05%, and 1.23%, respectively and the correlation existed after multi-factor adjustment (**Figure 4C**); but the FBG level of pregnant women had no significant difference in different birth months (**Figure 4A**).

Association of GDM With Birth Seasons, Stratified by Birth Cohort

The consistency of the association of birth season with the risk of GDM between different subgroups defined by multiple characteristics of the participants was explored through subgroup analysis. Participants were grouped based on whether they were born locally, parity, age of birth, and pre-pregnancy BMI (**Figures 5A–E**). **Figure 5B** showed that compared to pregnant women born in summer, those born after 1985 exhibited a higher risk of GDM (OR: 1.13, 95% CI: 1.03-1.24). Further analysis of the relationship between birth season and blood sugar level was performed after grouping according to birth year (**Figure S6**). **Figure S6C** demonstrated that for pregnant women born after 1985, those born in autumn and winter have higher PBG-2h levels (PC:1.00%, 95% CI: 0.40%-1.50%).

DISCUSSION

The relationship between different birth seasons with the risk of GDM during pregnancy has been explored in a large cohort of pregnant women. The hypothesis was that pregnancy at different times of the year and the subsequent changes in the seasonality of various environmental exposure could influence the risk of GDM in the future. The present findings revealed no significant association of the incidence of GDM with the season and month of birth. However, compared with pregnant women born in summer, childbirth in autumn and winter was associated with increased blood glucose in the second trimester. Of note, defined by BMI before pregnancy residence, and parity, this association was consistent across subgroups. Among pregnant women born after 1985, those born in spring showed a higher risk of GDM compared to those born in summer.

To the best of our knowledge, this is the first study to explore the association of birth seasonality with GDM risk during pregnancy. Four studies had previously investigated the association of birth seasonality with the risk of type 2 diabetes in adulthood but the results were inconsistent. A study examining the association of Chinese birth seasonality with the risk of adult type 2 diabetes demonstrated that subjects born in spring, autumn, and winter exhibited a higher risk of diabetes than those born in summer (16). Elsewhere, a study conducted in three regions of Ukraine reported changes in the birth season in 52,214 patients with type 2 diabetes born before 1960, with the

TABLE 1 | Maternal characteristics of study participants according GDM[a].

Characteristics	Pregnancy women			P-value
	All	GDM	No-GDM	
Pre-pregnancy BMI, mean (SD)	20.97 (2.75)	22.17 (2.64)	21.14 (3.14)	<0.001[b]
Pregnant age, mean (SD)	30.32 (3.88)	31.86 (3.79)	30.54 (4.09)	<0.001[b]
Ethnicity, n (%)				
han	77994 (98.36)	66901 (85.78)	11093 (14.22)	0.2604
others	1302 (1.64)	1102 (84.64)	200 (15.36)	
Fetal sex, n (%)				
Female	38346 (48.36)	32951 (85.93)	5395 (14.07)	0.1824
Male	40950 (51.64)	35052 (85.60)	5898 (14.40)	
Gravidity, n (%)				
0	40602 (51.21)	35557 (87.57)	5045 (12.43)	<0.001
1	22418 (28.27)	19007 (84.78)	3411 (15.22)	
>1	16266 (20.52)	13431 (82.57)	2835 (17.43)	
Parity, n (%)				
1	56806 (71.64)	49244 (86.69)	7562 (13.31)	<0.001
>1	22490 (28.36)	18759 (83.41)	3731 (16.59)	
Birth Season				
Spring	16427 (20.72)	14059 (85.58)	2368 (14.42)	0.3793
Summer	19852 (25.04)	17099 (86.13)	2753 (13.87)	
Autumn	23352 (29.45)	19999 (85.64)	3353 (14.36)	
Winter	19665 (24.80)	16846 (85.66)	2819 (14.34)	
Ward type, n (%)				
General ward	72398 (91.30)	62111 (85.79)	10287 (14.21)	0.4046
Senior ward	6898 (8.70)	5892 (85.42)	1006 (14.58)	
Conception mode, n (%)				
Nature conceived	55462 (69.94)	47947 (86.45)	7515 (13.55)	<0.001
ART	23834 (30.06)	20056 (84.15)	3778 (15.85)	
Insurance type, n (%)				
No	62992 (79.46)	54144 (85.95)	8848 (14.05)	0.0021
Yes	16284 (20.54)	13842 (85.00)	2442 (15.00)	
Drinking, n (%)				
No	78611 (99.14)	67417 (85.76)	11194 (14.24)	0.9173
Yes	685 (0.86)	586 (85.55)	99 (14.45)	
Smoking, n (%)				
No	79016 (99.65)	67771 (85.77)	11245 (14.23)	0.1916
Yes	280 (0.35)	232 (82.86)	48 (17.14)	
Family history of diabetes, n (%)				
No	73447 (92.62)	63570 (86.55)	9877 (13.45)	<0.001
Yes	5849 (7.38)	4433 (75.79)	1416 (24.21)	
Family history of hypertension, n (%)				
No	64599 (81.47)	55632 (86.12)	8967 (13.88)	<0.001
Yes	14697 (18.53)	12371 (84.17)	2326 (15.83)	
Blood glucose at 24-28 weeks of gestation				
FBG, mean (SD)	4.14 (0.41)	4.53 (0.35)	4.2 (0.57)	<0.001
PBG-1h, mean (SD)	7.57 (1.42)	10.12 (1.06)	7.93 (1.39)	<0.001
PBG-1h, mean (SD)	6.2 (1.42)	8.72 (1.06)	6.56 (1.42)	<0.001

[a]*two independent samples t-test.*
[b]*Chi-square test.*

peak in April and the lowest in November and December (19). Moreover, in a series of studies conducted by Dutch hospitals on 282 patients with type 2 diabetes aged 30-90 years, when the month of birth was compared to the standard, there were several individuals born with diabetes in the first quarter of this year, and the number of births in the last quarter fell under the birth curve (14). Additional evidence from a prospective study conducted in a cohort of 223,099 adults born in Denmark between 1930 and 1989 demonstrated no association between birth seasonality and the risk of type 2 diabetes (15). The present findings are inconsistent with previous results, which may be ascribed to population specificity of pregnant and lying-in women, GDM diagnosis methods, and differences in regions. In addition, the participants in our study were younger, most of whom had not experienced periods of food scarcity, and younger age is a protective factor for diabetes, which also may account for the inconsistent results.

The above-mentioned studies are aimed at the association between birth season and diabetes in adult. Compelling evidence indicates that, for pregnant women, the blood glucose level

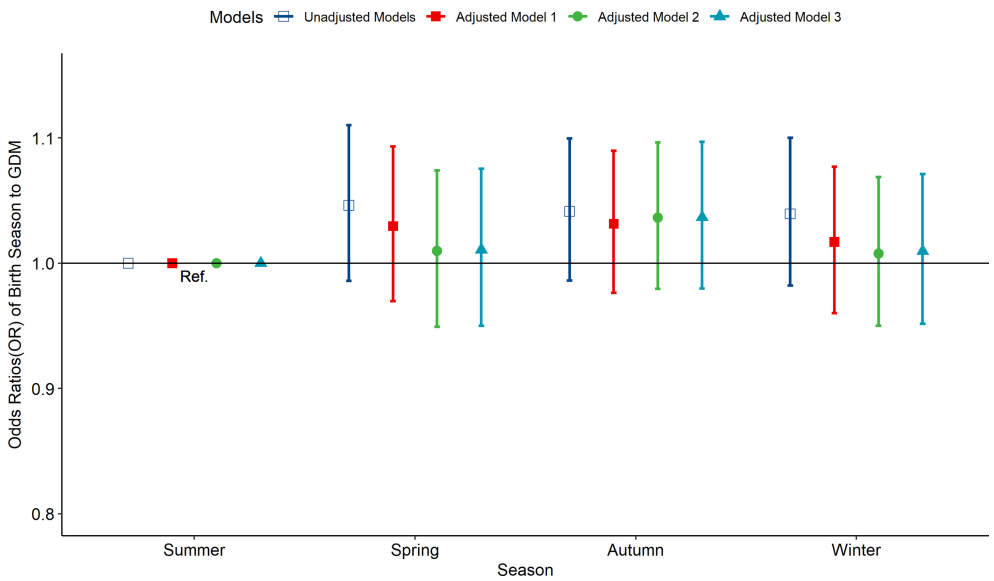

FIGURE 1 | Odds ratio (OR) and 95% confidence interval (95%CI) for GDM of pregnant women according to the season of birth. Adjusted model 1: adjusted for ethnicity, fetal sex, mother education level, ward type, insurance type, pregnant age. Adjusted model 2: in addition to the confounders in adjusted model 1, pre-pregnancy BMI was also adjusted; Adjusted model 3: in addition to the confounders in adjusted mode 2, drinking, smoking, family history of hypertension, family history of diabetes, parity and gravidity were also adjusted. Reference category is born in summer.

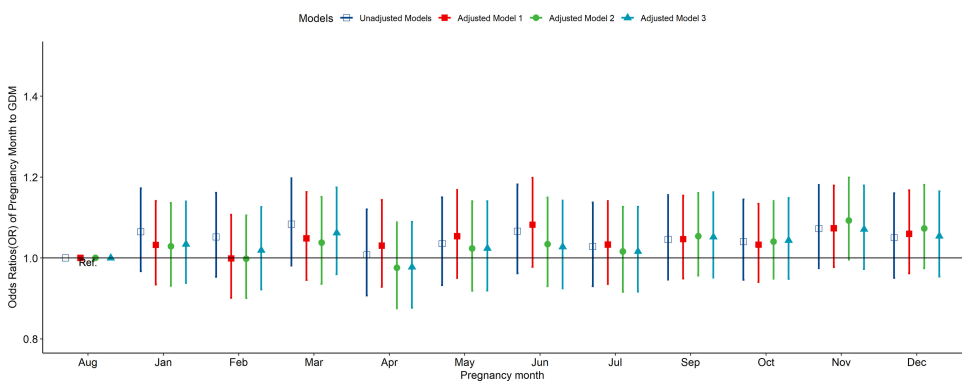

FIGURE 2 | Odds ratio (OR) and 95% confidence interval (95%CI) for GDM of pregnant women according to the month of birth. Adjusted model 1: adjusted for ethnicity, fetal sex, mother education level, ward type, insurance type, pregnant age. Adjusted model 2: in addition to the confounders in adjusted model 1, pre-pregnancy BMI was also adjusted; Adjusted model 3: in addition to the confounders in adjusted mode 2, drinking, smoking, family history of hypertension, family history of diabetes, parity and gravidity were also adjusted. Reference category is born in august.

increases compensatory during pregnancy to meet the requirement of the developing fetus (20–22). The stability of glucose metabolism is more fragile for an organism exhibiting impaired pancreatic islets and glucose metabolism in early life (23). The present work demonstrated that, compared to pregnant women born in summer, those born in autumn are not associated with a significantly high risk of GDM but their blood glucose levels significantly increased after meals. Studies have shown the association of permanent changes in pancreatic β-cell function or tissue sensitivity to insulin early in life and nutritional changes with insulin resistance and the risk of future diabetes (24, 25). In addition, the effects of pregnancy season on the GDM and blood glucose level, and the effects of subsequent GDM and elevated blood glucose level on offspring glucose metabolism may also be the potential mechanisms. Previous studies (26, 27) have shown the effect of pregnancy season on GDM. Furthermore, seasonal changes in food types, food nutritional value, and seasonal changes in eating habits may increase the risk of type 2 diabetes in adulthood in food-deficit areas or years (16, 28–30). However, herein, pregnant women

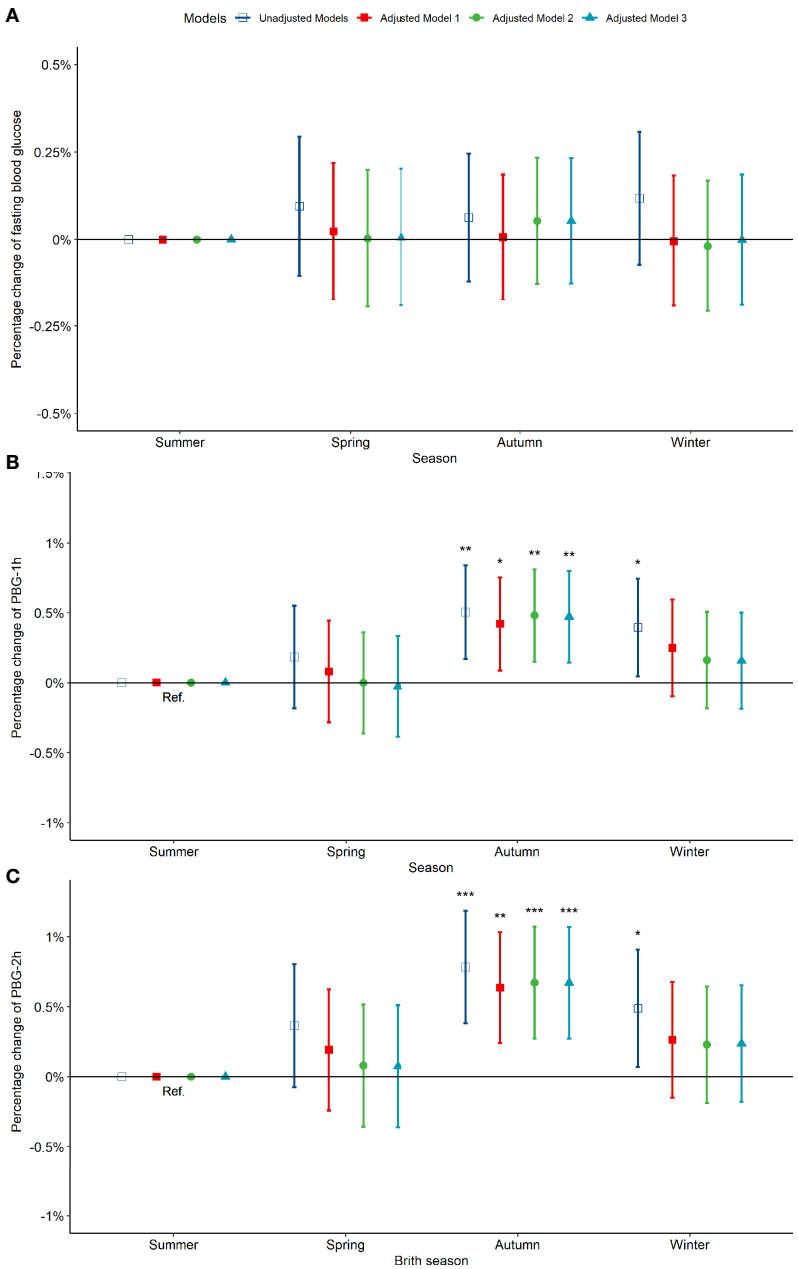

FIGURE 3 | Percentage changes of blood glucose levels [FBG **(A)**, PBG-1h **(B)**, PBG-2h **(C)**] at 24-28 weeks of pregnancy among pregnant women in difference birth month. Adjusted model 1: adjusted for ethnicity, fetal sex, mother education level, ward type, insurance type, pregnant age. Adjusted model 2: in addition to the confounders in adjusted model 1, pre-pregnancy BMI was also adjusted; Adjusted model 3: in addition to the confounders in adjusted mode 2, drinking, smoking, family history of hypertension, family history of diabetes, parity and gravidity were also adjusted. Reference category is born in summer. *p < 0.05; **p < 0.01; ***p < 0.001.

were, in most cases, born in areas with better economic development after 1975. Although the changes in early life glucose metabolism caused by nutritional deficiencies are not so obvious, they are likely to influence postprandial blood glucose levels because they impact insulin sensitivity. In addition, the year of birth of pregnant women in this study includes the era of China's rapid economic development, and the early nutritional supply of pregnant women born in different years is also very different. As such, further investigation is warranted to explore the underlying mechanism of association between birth season and GDM.

An interesting finding of this work is that after birth year stratification, pregnant women born in spring after 1985 have a higher risk of GDM than those born in summer. After 1985, Eastern China was experiencing rapid economic development (31, 32), therefore, issues with food shortage were rare.

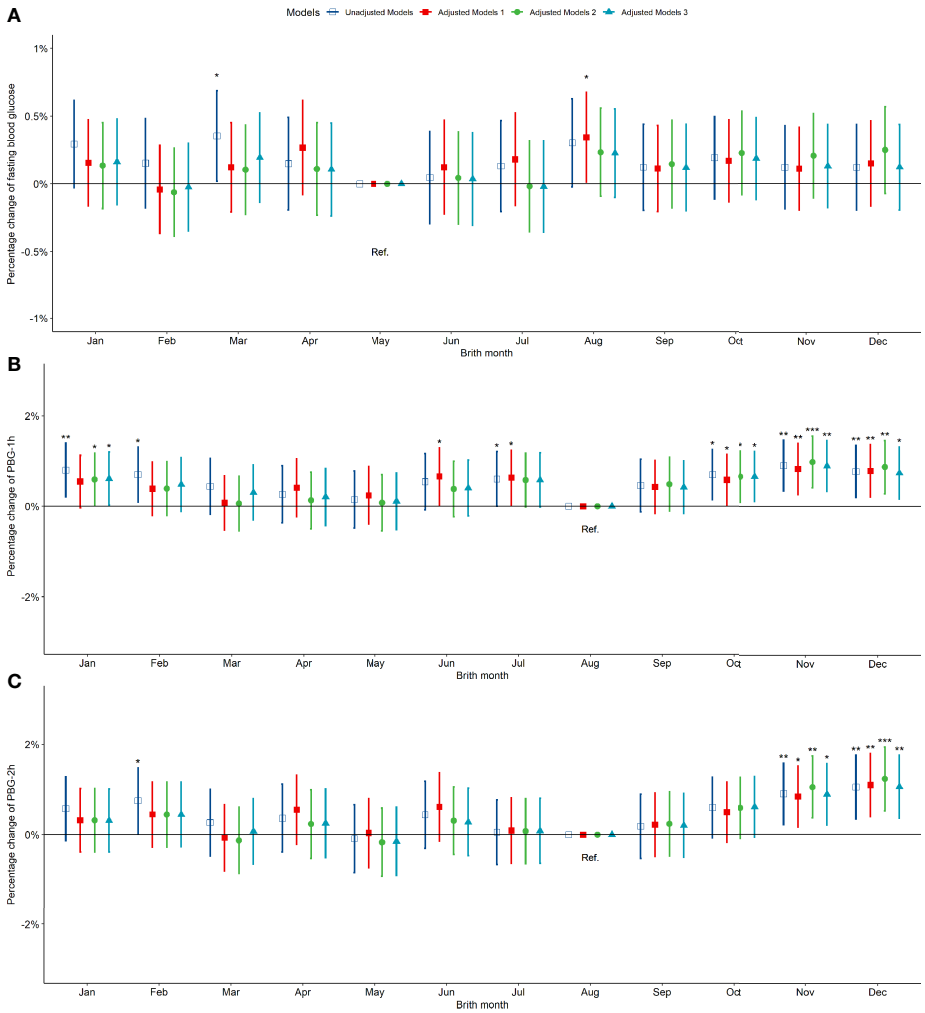

FIGURE 4 | Percentage changes of blood glucose levels [FBG **(A)**, PBG-1h **(B)**, PBG-2h **(C)**] at 24-28 weeks of pregnancy among pregnant women in different birth months. Adjusted model 1: adjusted for ethnicity, fetal sex, mother education level, ward type, insurance type, pregnant age. Adjusted model 2: in addition to the confounders in adjusted model 1, pre-pregnancy BMI was also adjusted; Adjusted model 3: in addition to the confounders in adjusted mode 2, drinking, smoking, family history of hypertension, family history of diabetes, parity and gravidity were also adjusted. Reference category of FBG is born in May; Reference category of PBG-1h and PBG-2h is born in August. *p < 0.05; **p < 0.01; ***p < 0.001.

Compared to pregnant women born in summer, those born in spring experienced cold weather during the late pregnancy and newborn period and were exposed to environmental pollution during the Chinese Spring Festival (33–35). These events may also have impacted glucose metabolism function in their early life (36, 37), but these conclusions need further exploration.

Although this research conducted in East China provides some intriguing findings, some limitations must be acknowledged. First, we did not explore factors, including the lifestyle of the participants, and therefore could not correct for the impact of lifestyle. Second, the study lacks information on exposure and material characteristics at birth; such as birth weight, maternal nutrition during pregnancy, parental socioeconomic status, and breastfeeding. Third, the division of birth season is based on the date of birth, and some information may be inaccurate. For instance, a few people in the analyzed regions habitually use the date of the lunar calendar as their date of birth. Lastly, a proportion of the explored population is small which may influence participants' birth season classification. Also, subjects who had previously suffered from GDM were excluded as we could not obtain information on previous GDM. This may underestimate the effect of birth season on GDM, except that the part of the excluded population is less than 1% of the total population.

CONCLUSION

This large retrospective cohort study demonstrates that compared to pregnant women born in summer, those born in

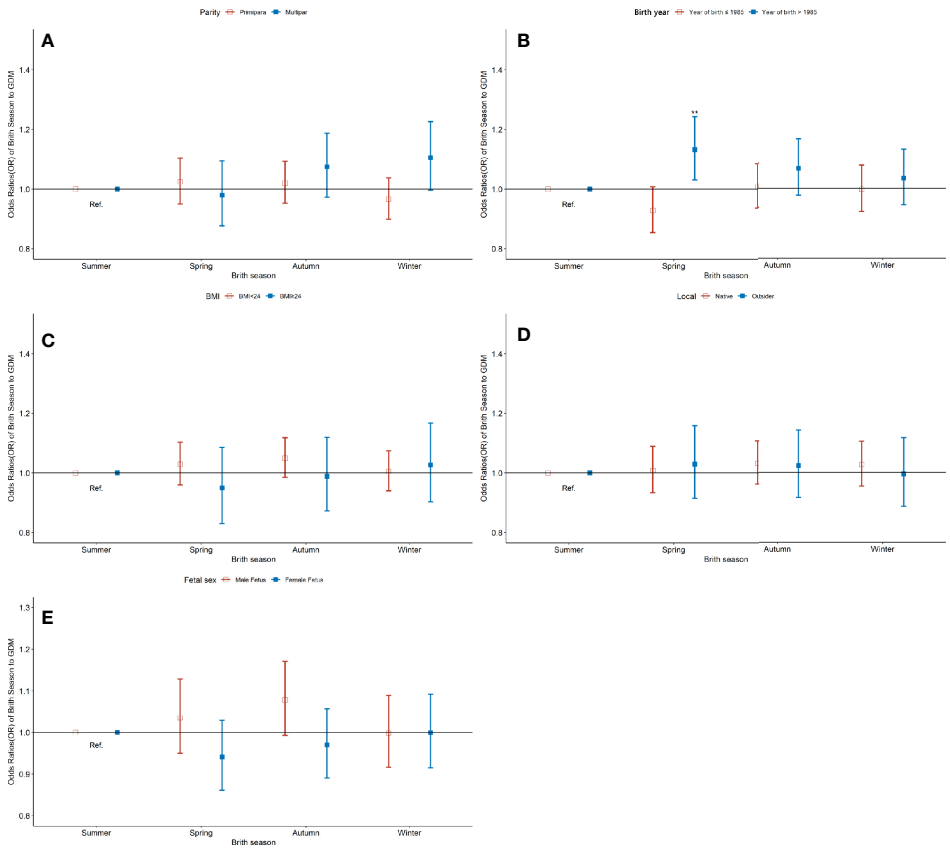

FIGURE 5 | Odds ratio (OR) and 95% confidence interval (95%CI) for GDM of pregnant women according to the season of birth, stratified by parity **(A)**, birth cohort **(B)**, pre-pregnancy BMI **(C)**, type of registration **(D)**, and fetal sex **(E)**. Model adjusted for ethnicity, fetal sex, mother education level, ward type, insurance type, pregnant age, pre-pregnancy BMI, drinking, smoking, family history of hypertension, family history of diabetes, parity and gravidity. Reference category is born in summer. **p < 0.01.

autumn and winter have significantly higher blood glucose levels at 1 hour and 2 hours after a meal in the second trimester. The findings provide strong evidence that exposure to some degree of seasonal changes early in life potentially impacts glucose metabolism during pregnancy. However, a further in-depth research is warranted to verify our findings and clarify the underlying mechanism.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

DY and YY conducted the analyses. DY and AQ wrote the manuscript. WZ, LC, and ZH contributed to data collection. DY, JBQ, and WZ contributed to study design. WZ and DY 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/fendo.2021.793489/full#supplementary-material

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Association Between Gestational Diabetes Mellitus and Future Risk of Kidney Stones

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Objective: The association between history of gestational diabetes mellitus (GDM) and risk of kidney stones has not been reported. GDM increases the risk of long-term complications including diabetes, hypertension and metabolic syndrome, which are risk factors of kidney stones. This study aimed to explore the association between previous GDM and odds of kidney stones.

Methods: Women (age $\geq$ 20 years) who had delivered at least one live birth were included from the 2007–2018 National Health and Nutrition Examination Survey cohort (N = 12,003). Patients with kidney stones and history of GDM were identified by in-home interview for all participants. Subgroup analyses were conducted by age, race/ethnicity, postpartum duration and status of hypertension, obesity, current diabetes and metabolic syndrome.

Results: Previous GDM was positively associated with odds of kidney stones [multivariate-adjusted odds ratio (95% confidence interval): 1.41 (1.13–1.77)], and the association was stronger with odds of passing 2 or more times of kidney stones [1.72 (1.31–2.26)]. In subgroup analyses, the association between previous GDM and odds of kidney stones was significant in women within 15 years of a pregnancy complicated by GDM [1.54 (1.12–2.11)], in obese participants [1.56 (1.18–2.06)], in women without hypertension [1.49 (1.07–2.08)], current diabetes [1.38 (1.02–1.87)] and metabolic syndrome [1.56 (1.10–2.19)], in women of Non-Hispanic White [1.59 (1.15–2.18)] and in women aged more than 50 year [1.45 (1.02–2.07)].

Conclusions: Previous GDM was positively associated with odds of kidney stones, and the association was independent of type 2 diabetes, hypertension and metabolic syndrome.

Keywords: kidney stones, National Health and Nutrition Examination Survey, gestational diabetes mellitus, type 2 diabetes, hypertension, metabolic syndrome

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INTRODUCTION

Gestational diabetes mellitus (GDM) is currently the most common medical complication of pregnancy (1). Globally, the prevalence of GDM is 14.7% according to the International Association of Diabetes and Pregnancy Study Groups criteria (2), and the prevalence could vary substantially depending on population characteristics such as age, race/ethnicity, obesity, and type 2 diabetes

mellitus prevalence in the background population (2). Kidney stones are the third most common urological disease with a prevalence of about 15% worldwide (3), and the prevalence and incidence of kidney stones is increasing in the United States and other parts of the world (4). In addition, the estimated 5-year recurrence rate is up to 50% (5). Patients with kidney stones have twice the risk of chronic kidney disease or end stage renal disease, and the risk is higher for females (6). The costs associated with stone disease have increased from $2 billion to over $10 billion from 2000 to 2006 in the United States alone (7).

GDM increases the risk of long-term complications including diabetes (8, 9), cardiovascular diseases (10, 11), metabolic syndromes (12) and cancer (13). However, the association between previous GDM and risk of kidney stones has not been reported. Inflammation and oxidant-antioxidant imbalance may play crucial roles in the development of kidney stones (3). Metabolic syndrome, diabetes, obesity and hypertension are established risk factors for kidney stone formation (7), and maternal obesity, type 2 diabetes, metabolic syndrome are also major risk factors for GDM development (1), supporting the potential link between GDM and development of kidney stones. A meta-analysis of prospective cohort studies showed that the summary relative risk was 1.16 (95% CI 1.03–1.31, $I^2 = 51\%$, $n = 10$) for participants with type 2 diabetes compared to participants without type 2 diabetes (14). Based on the above-mentioned findings, we hypothesized that previous GDM could be positively associated with odds of kidney stones. In addition, given the prevalence of both GDM and kidney stones varies much depending on population characteristics such as age and race/ethnicity (2, 15, 16), and the effect of GDM on long-term complications maybe differential by years after pregnancy (8), we conducted stratified analyses to explore the possible interactions between GDM and these stratified factors on kidney stones. In addition, because GDM increases the risk of long-term complications including diabetes, hypertension and metabolic syndrome which are risk factors of kidney stones (7), we also conducted stratified analyses by the presence of these chronic diseases to explore whether these chronic diseases could account for the association between previous GDM and odds of kidney stones.

MATERIALS AND METHODS

Study Populations

As a major program of the National Center for Health Statistics, the National Health and Nutrition Examination Survey (NHANES) cohort is designed to assess the health and nutritional status of a nationally representative sample of about 5,000 persons in each 2-year cycle. We used data from six cycles of the NHANES cohort (2007/2008 to 2017/2018), as these cycles specifically provided information of GDM. All women aged 20 years or older and with at least one live birth were potentially eligible for this analysis. Women who did not provide information of GDM and kidney stones, who were diagnosed with diabetes prior to a diagnosis of GDM, and women having kidney stones at the time of pregnancy complicated by GDM were excluded from this analysis.

GDM and Kidney Stones

Women who had GDM during pregnancy were identified if they answered yes to the following question: "During your pregnancy, were you ever told by a doctor or other health professional that you had diabetes, sugar diabetes or gestational diabetes?" (17). Patients with kidney stones were identified with the questions of "Have you ever had kidney stones?", and "How many times have you passed a kidney stone?" We considered any subject who reported a history of stone disease including symptomatic stone disease (16).

Covariates

According to the previous studies (14), the following covariates were included: age (in 10-year increments), race/ethnicity (Mexican–American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Races), annual family income (<$20,000, $20,000–$44,999, $45,000–$74,999, ≥$75,000), education (≤high school, Some college or AA degree, ≥College graduate), body mass index (under/normal weight: <25 kg/m^2, overweight: 25 to <30 kg/m^2, obesity: ≥30 kg/m^2), hypertension, current diabetes, physical activity (vigorous/moderate recreational activities for at least 10 min continuously per week), smoking (current smoker, former smoker, never smoker), uric acid and daily intake of total energy, total water drank, calcium, phosphate, sodium, alcohol and vitamin C. Current diabetes was defined using a self-reported diagnosis of diabetes outside pregnancy or, if diabetes was not previously diagnosed, by a hemoglobin A_{1c} level ≥ 6.5%, a fasting plasma glucose level ≥ 126 mg/dL, or 2-h plasma glucose ≥ 200 mg/dL, or taking diabetic pills to lower blood sugar (18). According to the 2017 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, hypertension was defined if they were taking antihypertensive medication, if their systolic blood pressure exceeded 130 mmHg, or if their mean diastolic blood pressure exceeded 80 mmHg (mean values of three measurements) (19).

In addition, as both GDM and kidney stones are associated with metabolic syndromes (1, 7, 12), we conducted a sensitivity analysis in which we adjusted for metabolic syndrome rather than hypertension, obesity and diabetes to determine whether metabolic syndrome could account for the association. Any 3 of the 5 following metabolic-related disorders constitute diagnosis of metabolic syndrome (20): elevated waist circumference (≥102 cm in men, ≥88 cm in women), elevated triglycerides (≥150 mg/dL), reduced HDL-C (<40 mg/dL in men, <50 mg/dL in women), elevated blood pressure (≥130 mm Hg systolic blood pressure, ≥85 mm Hg diastolic blood pressure) and elevated fasting glucose (≥100 mg/dL).

Statistical Analysis

Weighted logistic regression was used to calculate the odds ratios (95% confidence interval) [OR (95% CI)] of kidney stones for women with previous GDM compared with the control groups. We calculated three different logistic regression models. Model 1 was adjusted for age, race/ethnicity and body mass index. Model 2 included the covariates of model 1 with additional adjustment for education, family income, hypertension and

current diabetes. Model 3 included the covariates of model 2 with additional adjustment for alcohol drinking, smoking, physical activity, uric acid and dietary intakes of energy, total water, calcium, phosphate, sodium, potassium and vitamin C. New multi-year sample weight was computed by dividing the 2-year sample weights by 6. Stratified analyses were conducted by age (≤50, >50 years), race/ethnicities (Non-Hispanic White, others), postpartum duration (≤15 years, >years), hypertension (yes, no), obesity (yes, no) and current diabetes (yes, no). We also conducted a sensitivity analysis in which we adjusted for metabolic syndrome rather than hypertension, obesity and diabetes to determine whether metabolic syndrome could account for the association. Tests for interactions were performed by using cross-product terms of GDM with these stratified factors. All analyses were conducted with Stata 12.0, and $P \leq 0.05$ was considered statistically significant.

RESULTS

A total of 17,907 women aged 20 years or older were included in the 2007/2008 to 2017/2018 NHANES. After excluding those who did not have at least one live birth ($N = 5{,}692$), who were diagnosed with diabetes prior to GDM ($N = 48$), who did not answer to the question regarding history of GDM or answered "borderline" ($N = 139$), who did not response to the question of ever having kidney stones ($N = 24$), and who had kidney stones at the time of pregnancy complicated by GDM ($N = 1$), 12,003

TABLE 1 | Characteristics of the 2007–2018 NHANES adults by history of gestational diabetes mellitus (GDM).

	Patients with GDM (926)	Controls (11,077)	*P*[a]
Age [years, mean (SD)]	45.47 (12.30)	53.48 (16.76)	<0.01
Race/Hispanic origin (%)			<0.01
Mexican American	21.92	15.78	
Other Hispanic	11.34	11.67	
Non-Hispanic White	35.75	40.76	
Non-Hispanic Black	17.71	22.13	
Other Race	13.28	9.66	
Annual family income (%)			<0.01
<$20,000	20.56	26.56	
$20,000–$34,999	33.45	33.74	
$35,000–$74,999	18.87	17.58	
≥$75,000	27.12	22.09	
Education (%)			<0.01
≤High school	43.63	50.12	
Some college or AA degree	35.96	30.65	
≥College graduate	20.41	19.23	
Vigorous/moderate recreational activities for at least 10 min continuously per week (%)	14.15	13.68	0.89
Smoking			0.36
Current smoker	18.79	17.47	
Former smoker	18.03	19.66	
Never smoker	63.17	62.87	
Obesity (%)	56.07	43.06	<0.01
Hypertension (%)	48.16	56.22	<0.01
Current diabetes (%)	36.39	18.69	<0.01
Kidney stones (%)	12.96	8.81	<0.01
Metabolic syndrome (%)	45.66	37.44	<0.01
Uric acid (mg/dL)	4.94	4.93	0.79
Daily intake [M (SD)]			
Total energy (kcal)	1,883.04 (873.88)	1,757.65 (748.04)	<0.01
Total water drank (g)	1,232.69 (1,187.74)	1,039.10 (1,055.41)	<0.01
Calcium (mg)	876.67 (522.43)	810.84 (474.48)	<0.01
Phosphate (mg)	1,233.16 (590.92)	1,131.01 (515.95)	<0.01
Sodium (mg)	3,131.18 (1,576.97)	2,879.43 (1,428.66)	<0.01
Alcohol (g)	5.19 (19.10)	4.84 (16.34)	0.54
Vitamin C (mg)	73.81 (84.47)	75.55 (80.56)	0.54

M, Mean values; SD, standard deviation.

[a]*t-test was performed for continuous variables, and Chi-square test was performed for categorical variables.*

women were finally included in this analysis. The weighted prevalence of GDM and kidney stones was 7.99 and 9.91%, respectively. Women who had GDM during pregnancy tend to be younger, had higher family income and education level, and showed higher prevalence of obesity, current diabetes and kidney stones, but tend to have lower prevalence of hypertension. For the 2,412 patients with current diabetes, 48 subjects were identified to have type 1 diabetes (currently using insulin and diagnosed with diabetes under age 30) (21). The race/ethnicity also differs significantly between women who had GDM during pregnancy and the controls (**Table 1**).

The findings between previous GDM and kidney stones were similar across the three statistical models, while the magnitude of the observed association was attenuated slightly in model 2 and model 3. In model 3, previous GDM was associated with higher odds of kidney stones [OR (95% CI): 1.41 (1.13–1.77), $P < 0.01$], and the association was stronger with odds of passing 2 or more times of kidney stones [1.72 (1.31–2.26), $P < 0.01$]. In subgroup analyses, the positive association between previous GDM and kidney stones was also evident in women within 15 years of a pregnancy complicated by GDM [1.54 (1.12–2.11), $P < 0.01$], in women without hypertension [1.49 (1.07–2.08), $P < 0.05$], in obese women [1.56 (1.18–2.06), $P < 0.01$], in women without current diabetes [1.38 (1.02–1.87), $P < 0.05$], in women of Non-Hispanic White [1.59 (1.15–2.18), $P < 0.01$], and in women of age > 50 years [1.45 (1.02–2.07), $P < 0.05$]. However, the interactions between previous GDM and the above-mentioned stratified factors were not significant (all $P_{\text{forinteraction}} > 0.05$) (**Table 2**).

In sensitivity analysis in which we adjusted for metabolic syndrome rather than hypertension, obesity and diabetes, previous GDM was also associated with higher odds of kidney stones [1.57 (1.26–1.96), $P < 0.01$] in model 3. In addition, the association was evident in both women who had metabolic syndrome [1.57 (1.18–2.10), $P < 0.01$] and who did not have metabolic syndrome [1.56 (1.10–2.19), $P < 0.05$] ($P_{\text{forinteraction}}$

TABLE 2 | Odds ratios (95% confidence intervals) of kidney stones associated with previous gestational diabetes mellitus.

Groups	Odds ratios (95% confidence intervals)					$P^{a}_{\text{forinteraction}}$
	Cases with kidney stones/*N*	Model 1	Model 2	Model 3	Sensitivity analysis	
Overall	1,096/12,003	1.50 (1.22–1.85)**	1.39 (1.11–1.72)**	1.41 (1.13–1.77)**	1.57 (1.26–1.96)**	
Postpartum duration						0.53
<15 years	1,032/11,529	1.69 (1.25–2.30)**	1.63 (1.20–2.23)**	1.54 (1.12–2.11)**	1.65 (1.21–2.26)**	
≥15 years	1,040/11,551	1.36 (1.03–1.80)*	1.22 (0.92–1.64)	1.32 (0.98–1.79)	1.50 (1.12–2.02)**	
Hypertension						0.79
Yes	697/6,673	1.42 (1.07–1.88)*	1.28 (0.95–1.73)	1.33 (0.98–1.82)	1.49 (1.11–2.02)**	
No	399/5,330	1.60 (1.17–2.18)**	1.52 (1.10–2.09)*	1.49 (1.07–2.08)*	1.67 (1.20–2.31)**	
Obesity						0.62
Yes	516/6,767	1.62 (1.25–2.10)**	1.51 (1.15–1.98)**	1.56 (1.18–2.06)**	1.70 (1.29–2.23)**	
No	580/5,236	1.29 (0.90–1.85)	1.18 (0.81–1.73)	1.17 (0.78–1.74)	1.27 (0.86–1.88)	
Current diabetes						0.96
Yes	309/2,407	1.27 (0.90–1.78)	1.28 (0.91–1.81)	1.30 (0.91–1.86)	1.34 (0.94–1.92)	
No	787/9,596	1.40 (1.06–1.85)*	1.42 (1.07–1.90)*	1.38 (1.02–1.87)*	1.40 (1.04–1.89)*	
Race/ethnicities						0.81
Non-Hispanic White	549/4,846	1.57 (1.16–2.13)**	1.51 (1.10–2.06)*	1.59 (1.15–2.18)**	1.66 (1.21–2.27)**	
Others	547/7,157	1.44 (1.08–1.93)*	1.28 (0.95–1.74)	1.24 (0.90–1.72)	1.47 (1.07–2.01)*	
Age, years						0.90
≤50	432/5,458	1.61 (1.22–2.11)**	1.40 (1.05–1.86)*	1.33 (0.99–1.79)	1.50 (1.12–2.00)**	
>50	664/6,545	1.46 (1.05–2.03)*	1.41 (1.01–1.99)*	1.45 (1.02–2.07)*	1.60 (1.12–2.26)**	
Metabolic syndrome[b]						0.93
Yes	546/4,908	1.58 (1.19–2.08)**	1.60 (1.21–2.13)**	1.57 (1.18–2.10)**	—	
No	550/7,095	1.46 (1.06–2.01)*	1.50 (1.09–2.08)*	1.56 (1.10–2.19)*	—	

*$P < 0.05$.

**$P < 0.01$.

Model 1: adjusted for age, race/ethnicity and body mass index.

Model 2: adjusted for covariates in model 1 and education, family income, hypertension and current diabetes.

Model 3: adjusted for covariates in model 2 and alcohol drinking, smoking, physical activity, uric acid and dietary intakes of energy, total fluid, calcium, phosphate, sodium, potassium and vitamin C.

Sensitivity analysis: adjusted for age, race/ethnicity, education, family income, alcohol drinking, smoking, physical activity, uric acid and dietary intakes of energy, total fluid, calcium, phosphate, sodium, potassium and vitamin C, and metabolic syndrome.

[a] *P-values for interaction analyses in model 3.*

[b] *In subgroup analysis by metabolic syndrome, body mass index, hypertension and current diabetes were not included in the above models.*

= 0.93) (**Table 2**). In addition, 64 participants were defined as patients with current diabetes because they were taking diabetic pills to lower blood sugar. Some of lowering sugar pills is used not only in diabetic people, but also obese non-diabetic women. However, the results remain unchanged when these 64 participants were included in the group of non-diabetic women in model 3 [1.41 (1.12–1.77), $P < 0.01$].

DISCUSSION

To our knowledge, this is the first study to explore the association between history of GDM and kidney stones. After adjusting for other covariates, results from the national survey cohort suggested that previous GDM was independently associated with higher odds of kidney stones, and the association was independent of type 2 diabetes, hypertension and metabolic syndrome. Some differences in the association between previous GDM and kidney stones were found in stratified analyses by key population characteristics that are associated with the prevalence of GDM and kidney stones; however, these differences were not significant.

Several potential mechanisms could explain an association between history of GDM and kidney stones. GDM increases the risk of long-term complications including diabetes (8, 9). In particular, women who had GDM during pregnancy have a 7–10-fold increased risk of developing type 2 diabetes and the percentage diagnosed with type 2 diabetes was 12% higher for each additional year after pregnancy (8, 9, 22). A meta-analysis of 10 prospective cohort studies showed a 16% increase in the relative risk of kidney stones among diabetes patients compared to persons without diabetes (14). In our study, a weaker but significant association between previous GDM and kidney stones was also found after adjusting for other covariates including current diabetes. Furthermore, the magnitude of association between previous GDM and kidney stones was larger in women without current diabetes than those with current diabetes. These findings suggested that current diabetes cannot fully account for the observed association. Results from our study are consistent with those from a previous follow-up study indicating that the risk of cardiovascular disease associated with GDM was not fully dependent upon the development of type 2 diabetes (23). In addition, a retrospective cohort study showed that a history of nephrolithiasis was associated with higher risks of GDM [OR (95% CI): 3.1 (1.8–5.3)] and preeclampsia [2.2 (1.3–3.6)], suggesting that stone formation is a marker of metabolic diseases and supporting the link between GDM and kidney stones (24).

Second, in addition to diabetes, obesity, hypertension and metabolic syndrome are also risk factors for stone formation (7). Results from a recent review suggested that women with previous GDM have significantly higher blood pressure, body mass index, total cholesterol, LDL cholesterol, triglycerides, glucose and significantly lower HDL cholesterol (10). In this analysis, women with previous GDM also had significantly higher prevalence of obesity, diabetes and metabolic syndrome, while had significantly lower prevalence of hypertension. These findings suggested that the long-term effects of GDM on other components of metabolic syndrome might be much more evident that on hypertension. However, the association between previous GDM and kidney stones was stronger in sensitivity analysis adjusting for metabolic syndrome, and the association was also significant in women without metabolic syndrome. Therefore, metabolic syndrome cannot also not fully account for the observed association. As non-Hispanic White individuals, obese individuals and older subjects are much more likely to report a history of kidney stones (16), it is theoretically reasonable to find a stronger association in these population groups.

Third, kidney stones form on a foundation of calcium phosphate called Randall's plaques present on the renal papillary surface. The molecular aspect of nephrolithiasis development include inflammation, oxidant–antioxidant imbalance, angiogenesis, purine metabolism and urea cycle disorders (3). The three central features of pregnancies complicated by GDM include insulin resistance, low-grade inflammation and endothelial cell dysfunction (25). In the Diabetes and Women's Health study, women with a GDM history had significantly higher estimated glomerular filtration rate and urinary albumin-to-creatinine ratio 9–16 years postpartum, indicating early stages of glomerular hyperfiltration and renal damage (26). Women who developed type 2 diabetes after a pregnancy complicated by GDM also had an increased risk renal dialysis [hazard ratio (95% CI): 7.52 (5.24–10.81)] (23). In addition, GDM was also found as a significant risk factor for future maternal renal morbidity in a study with a mean follow-up duration of 11.2 years (27). GDM alone in the absence of subsequent diabetes was associated with microalbuminuria in the Kidney Early Evaluation Program (28). These findings suggested that GDM could be a risk factor for renal damage.

There are several limitations. First, we were unable to determine the causality in this cross-sectional study. However, the prevalence of kidney stones increases with age (16). In this study, the mean age of patients told to have GDM was 28.40 years (SD: 6.58), and the mean age of participants at the time of survey was 52.87 years (SD: 16.60). In addition, women having kidney stones at the time of pregnancy complicated by GDM were also excluded from this analysis. Second, stones composed of calcium oxalate mixed with calcium phosphate, struvite, uric acid and cystine account for ∼80, 10, 9, and 1% of stones (7), respectively. Therefore, it is necessary to determine if previous GDM is associated with the risk of certain stone types but not others in further studies. Third, history of GDM and kidney stones were self-reported, and previous medical records about GDM are not available in the NHANES. However, these data from NHANES are considered to be valid and have been widely used in epidemiological studies (16, 17, 29, 30), and misclassification of patients with undiagnosed GDM and kidney stones as controls would have biased the study results toward the null.

CONCLUSION

In conclusion, findings from this nationally representative cohort suggested that previous GDM was positively associated with odds

of kidney stones, and the association was independent of type 2 diabetes, hypertension and metabolic syndrome. These findings deserve to be confirmed by prospective cohort studies.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available in the NHANES: https://www.cdc.gov/nchs/nhanes/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Center for Health Statistics Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YM and QL designed the study. WH conducted the statistical analysis. YM, LL, and QL drafted the manuscript. QL made critical revisions. All authors have approved the final article.

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Consistently Low Levels of Osteocalcin From Late Pregnancy to Postpartum Are Related to Postpartum Abnormal Glucose Metabolism in GDM Patients

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Objective: Increasing evidence suggests that osteocalcin (OC), a marker of bone formation, plays an important role in glucose homoeostasis. Few studies have investigated the relationship between OC levels in gestational diabetes mellitus (GDM) patients and their postpartum glucose metabolism. This study evaluated the relationship between OC levels in late pregnancy, their longitudinal changes, and postpartum glucose metabolism among GDM patients.

Measures: Serum OC was measured in late pregnancy and the postpartum period for 721 GDM patients. All patients underwent a 75-g oral glucose tolerance test (OGTT) at 6–8 weeks postpartum. According to postpartum OGTT outcomes, patients were categorized into abnormal glucose metabolism (AGM) (n=255) and normal glucose tolerance (NGT) groups (n=466). Glucose metabolism-related indices were measured and calculated. Logistic regression analysis and linear mixed-effects model were used to assess the association between OC and postpartum AGM.

Results: In late pregnancy, OC levels were lower in the AGM group than in the NGT group (13.93 ± 6.90 vs 15.33 ± 7.63 ng/ml, P=0.015**).** After delivery, OC levels increased in both groups. However, OC levels remained lower in the AGM group than in the NGT group (23.48 ± 7.84 vs 25.65 ± 8.37 ng/ml, P=0.001). Higher OC levels in late pregnancy were associated with decreased risk of progressing to postpartum AGM (OR:0.96, 95% CI:0.94–0.99). Linear mixed-effects analysis showed that postpartum AGM patients exhibited consistently lower OC levels than NGT group from late pregnancy to the postpartum period after adjustment for cofactors (β=-1.70, 95% CI: -2.78– -0.62).

Conclusions: In GDM patients, consistently low levels of OC from late pregnancy to postpartum were associated with increased postpartum AGM risk. The increase in serum OC may act as a protective factor to curb the progression of AGM at postpartum for GDM patients.

Keywords: osteocalcin, gestational diabetes mellitus, abnormal glucose metabolism, risk factors, postpartum glucose metabolism

INTRODUCTION

Recently, bone has been identified as an endocrine organ involved in energy metabolism through the secretion of specific hormones (1, 2). Osteocalcin (OC), a small noncollagenous protein of 49 amino acids that is exclusively secreted by osteoblasts, participates in bone remodeling and calcium homeostasis. OC has three γ-carboxyglutamic acid residues in the 17, 21 and 24 positions of its peptide chain, which undergoes a posttranslational modification at the glutamate residue to attain a higher affinity for hydroxyapatite to integrate into the bone extracellular matrix (1, 3, 4). However, the undercarboxylated form (ucOC), as a bioactivator released into the circulation, may serve as a modulator of energy metabolism. Since ucOC levels are difficult to measure, most studies have focused on total OC (5–7).

Accumulating evidence shows that OC is vital in the cross-talk between bone remodeling and energy metabolism. Extensive animal studies have shown that OC stimulates insulin secretion directly by exerting an effect on pancreatic β-cell and indirectly *via* the secretion of glucagon-like peptide (GLP-1) by enteroendocrine L cells leading to improved insulin sensitivity (8, 9). In contrast, osteocalcin-deficient mice displayed decreased β-cell proliferation, glucose intolerance, and insulin resistance (10). To date, almost human studies have supported the findings of animal studies. In humans, serum OC was reported to be decreased in patients with type 2 diabetes compared to the levels in nondiabetic controls; inversely associated with blood glucose levels, HbA1c, BMI and insulin resistance; and positively associated with insulin secretion and insulin sensitivity (7, 11, 12).

Gestational diabetes mellitus (GDM), defined as hyperglycemia first recognized during pregnancy, is one of the most common metabolic complications in pregnancy (13, 14). Although glucose intolerance in many GDM patients usually reverts to normal after delivery, these patients and their offspring face an increased lifetime risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) in the future (15–17). As T2DM can be prevented or delayed by intensive lifestyle or metformin intervention (18, 19), it is suggested that GDM patients should be routinely screened, which is beneficial for early intervention (20).

A few studies have previously assessed the contribution of serum OC in this context. Higher OC concentrations in GDM patients than in euglycemic pregnant women and a positive association between OC and insulin resistance parameters during pregnancy had been reported (21–23), and these findings are in contrast to what has been observed in the context of diabetes. A possible explanation for the opposite results in GDM could be an early adaption to impaired glucose tolerance.

Although a few studies have explored the effects of OC on glucose metabolism in GDM patients, the role of OC levels in the postpartum glucose metabolism of GDM is unclear. Therefore, we studied 721 GDM patients and evaluated OC levels both in late pregnancy and postpartum. The associations of OC levels and their longitudinal trajectory changes with postpartum glucose metabolism of GDM were explored in our study.

MATERIALS AND METHODS

Patient Population

This retrospective study was performed at the Department of Endocrinology and Metabolism of Shanghai General Hospital from December 2015 to December 2020. Pregnant women underwent a 75-g OGTT test at 24-28 weeks of gestation and the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria was used for the diagnosis of GDM (24): fasting plasma glucose (FPG) value ≥5.1 mmol/L and/or 1-h postprandial glucose (1h-PG) value ≥10.0 mmol/L and/or 2-h postprandial glucose (2h-PG) value ≥8.5 mmol/L. After delivery, all individuals with GDM were invited to undergo a 75-g OGTT test again at 6–8 weeks postpartum. Subjects with a history of diabetes mellitus (DM) or impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) before pregnancy or lack of OC either in late gestation or at postpartum were excluded. Finally, a total of 721 subjects were included in this study.

Subjects were categorized into two groups according to 75-g OGTT results at 6–8 weeks postpartum based on 1999 WHO criteria (25): 1. Abnormal glucose metabolism (AGM) group: IFG (6.1 mmol/L ≤ FPG <7.0 mmol/L and 2h-PG <7.8 mmol/L) or IGT (FPG < 7.0 mmol/L and 7.8 mmol/L ≤ 2h-PG <11.1 mmol/L) or DM (FPG ≥7.0 mmol/L or/and 2h-PG ≥11.1 mmol/L); 2. Normal glucose tolerance (NGT) group: FPG <6.1 mmol/L and 2h-PG <7.8 mmol/L.

This study was approved by the institutional ethics committee of Shanghai General Hospital.

Study Protocol and Methods

Clinical data including age at present pregnancy, family history of diabetes, parity, pregestational body mass index (pre-BMI), BMI at 6–8 weeks postpartum, OC levels and other clinical indexes of glucose and lipid metabolism were recorded. BMI was calculated as the weight in kilograms divided by the square of the

height in meters (kg/m^2). Homeostasis model assessment was used to estimate insulin resistance (HOMA-IR) which was defined as [fasting insulin (μU/ml) * fasting glucose (mmol/l)]/22.5, and HOMA of β-cell (HOMA-β) index was used to assess β-cell function, which was calculated as [20*fasting insulin (μU/ml)]/[fasting glucose (mmol/l) – 3.5].

All blood samples were obtained in the morning after an overnight fast of 8–10 h. In our study, we used N-terminal mid-fragment of OC (N-MID OC), the largest proteolytic fragment with a relatively long half-life, to reflect serum OC levels (26). N-MID OC was measured using electrochemiluminescent immunoanalysis (Roche Cobas e601, Germany). HbA1c was measured with an autoanalyzer (Lifotronic H8, Japan). Serum insulin was measured using an automated chemiluminescence systems (Abbott i2000, United States). Serum glucose and lipid profiles including serum total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), were measured with an automatic biochemistry analyzer (Siemens ADVIA2400, Germany). During the study period, instruments or testing methodologies unchanged.

Statistical Analysis

Data are presented as the mean ± standard deviation (SD) or median (interquartile range, 25–75%) for continuous variables and proportion for categorical variables, respectively. Normally distributed continuous variables were compared by Student's t test, while nonnormally distributed continuous variables were analyzed by the Mann-Whitney U test. Categorical variables were analyzed byχ^2 test. The log-transformed levels of HOMA-β were parameterized as a continuous variable. The Pearson correlation coefficients were calculated to assess the strength of the correlation of OC in late gestation and glucose related indicators, insulin resistance and β-cell function. Multivariate linear regression was performed to determine the associations between OC levels and insulin resistance, and β-cell function.

Multiple logistic regression models were used to calculate the odds ratio (OR) and 95% CIs for the risk of postpartum AGM for OC levels in late gestation. *A priori* selection of conventional postpartum AGM risk factors, including age, postpartum BMI, parity, family history of diabetes and HbA1c in late pregnancy, was assessed at study enrollment. A linear mixed-effects model was performed to compare the longitudinal trajectories of OC in late gestation and postpartum in individuals with different postpartum glucose status according to 75-g OGTT results by using restricted maximum likelihood estimation. The model included serum OC in late pregnancy and postpartum, groups of different postpartum OGTT outcomes and time in late pregnancy and at postpartum. OC levels were adjusted for maternal age, prepregnancy BMI, family history of diabetes, parity and HbA1c in late gestation *via* covariate adjustment (fixed effects in the mixed model).

All statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY), and a P value<0.05 was considered statistically significant.

RESULTS

The mean age in the cohort was 31.98 ± 4.4 years. All GDM patients received lifestyle modification and 174 (24%) women received additionally insulin therapy during pregnancy. According to the results of the postpartum OGTT, 255 individuals were diagnosed with AGM, of whom 221 had IFG and/or IGT and 34 had diabetes. The remaining 466 women had normal glucose tolerance.

The baseline characteristics of the GDM subjects stratified by the outcomes of postpartum 75-g OGTT were shown in **Table 1**. Compared with the NGT group, subjects in the AGM group were older and had higher BMI and HbA1c both before and after delivery. Meanwhile, postpartum FBG, 2h-PG, 2h-INS, TC, TGs and LDL-C were significantly higher in the AGM group. Indices of insulin resistance (HOMA-IR) indicated that postpartum AGM women were more insulin resistant than NGT women. The OC levels of the AGM group were lower both in late pregnancy (NGT vs AGM: 15.33 ± 7.63 ng/ml vs 13.93 ± 6.90 ng/ml, P=0.015) and postpartum (NGT vs AGM: 25.65 ± 8.37 ng/ml vs 23.48 ± 7.84 ng/ml, P=0.001) (**Table 1**).

The correlation analysis showed that OC levels were positively associated with postpartum FINS (r=0.109, P=0.003), HOMA-IR (r=0.098, P=0.008) and lg (HOMA-β) (r=0.132, P<0.001) (**Figure 1**), but had no relationship with postpartum FBG and HbA1c (data not shown). In order to further explore the relationship between OC levels and insulin resistance and β-cell function, multivariate linear regression was used. We found that lg (HOMA-β) was positively associated with OC levels after adjusted for age, postpartum BMI, parity, family history of diabetes and HbA1c in late pregnancy (β=0.003, P=0.015), while HOMA-IR was not associated with OC after adjusted covariates above (β=0.002, P=0.783).

Logistic regression analysis revealed that the risk of developing AGM at postpartum was decreased by 3% after adjusting for age and parity (OR=0.97, 95%CI: 0.95-0.99). This association remained significant after further adjustment for postpartum BMI, family history of diabetes and HbA1c in late pregnancy (OR=0.96, 95%CI: 0.94-0.99) (**Table 2**).

OC levels increased significantly after delivery in both the NGT (from 15.33 ± 7.63 in late gestation to 25.65 ± 8.37 at postpartum, P<0.001) and AGM (from 13.93 ± 6.90 in late gestation to 23.49 ± 7.84 at postpartum, P<0.001) groups (**Figure 2**). Meanwhile, the linear mixed-effects model showed that the OC levels from late pregnancy to postpartum were consistently lower in AGM group than in NGT group, adjusted for parity, age, time points (late pregnancy and postpartum), pre-pregnancy BMI, HbA1c and family history of diabetes (β=-1.70, 95% CI: -2.78– -0.62) (**Supplementary Table 1**).

DISCUSSION

In the current study, we investigated the association between serum OC levels and the postpartum glucose metabolism of GDM. We found that low serum OC in late pregnancy was

TABLE 1 | Characteristics and metabolic parameters of GDM women with different glucose outcomes according to the 75-g OGTT at 6–8 weeks postpartum.

	75-g OGTT results at 6–8 weeks postpartum		P value
	NGT (n=466)	AGM (n=255)	
Age (years)	31.62 ± 4.17	32.64 ± 4.74	0.004
Family history of diabetes	101 (21.7%)	52 (20.6%)	0.715
Primiparity	245 (53.0%)	128 (50.6%)	0.533
Pre-BMI (kg/m^2)	22.50 ± 3.43	23.25 ± 3.56	0.006
Postpartum BMI (kg/m^2)	23.72 ± 3.21	24.22 ± 3.32	0.046
HbA1c in late pregnancy (%)	5.45 ± 0.44	5.56 ± 0.51	0.005
OC level in late pregnancy (ng/ml)	15.33 ± 7.63	13.93 ± 6.90	0.015
Laboratory values at postpartum			
FBG (mmol/L)	4.91 ± 0.52	5.24 ± 0.85	<0.001
2h-PG (mmol/L)	6.33 ± 0.90	9.20 ± 1.52	<0.001
TCH (mmol/L)	5.30 ± 0.96	5.48 ± 0.95	0.017
TGs (mmol/L)	1.19 ± 0.78	1.37 ± 0.97	0.01
HDL-C (mmol/L)	1.49 ± 0.38	1.47 ± 0.34	0.535
LDL-C (mmol/L)	3.01 ± 0.81	3.15 ± 0.85	0.027
FINS (mU/L)	6.65 ± 4.30	7.33 ± 4.90	0.064
2h-INS (mU/L)	22.44 (15.47, 32.85)	37.96 (24.47, 56.64)	<0.001
HOMA-IR	1.47 ± 1.00	1.77 ± 1.35	0.002
HOMA-β	84.48 (57.47, 130.43)	78.29 (53.54, 115.03)	0.070
HbA1c (%)	5.36 ± 0.43	5.55 ± 0.52	<0.001
OC at postpartum (ng/ml)	25.65 ± 8.37	23.48 ± 7.84	0.001

Data are presented as the mean ± SD, median (interquartile range), or n (%) as appropriate.
OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; AGM, abnormal glucose metabolism; Pre-BMI, body mass index before pregnancy; HbA1c, glycated haemoglobin; OC, osteocalcin; FBG, fasting blood glucose; 2h-PG, 2-h postprandial glucose; TCH, total cholesterol; TGs, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FINS, fasting insulin; 2h-INS, 2-h postprandial insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of beta-cell function.

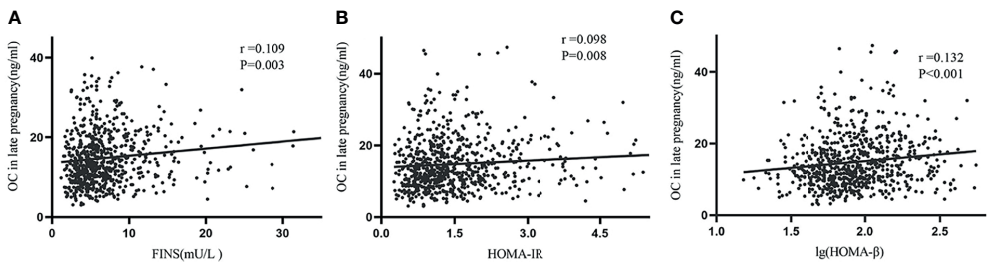

FIGURE 1 | Simple correlations between late pregnancy OC and postpartum FINS, HOMA-IR, and lg (HOMA-β). Serum OC in late pregnancy was positively associated with FINS **(A)**, HOMA-IR **(B)** and lg (HOMA-β) **(C)**.

TABLE 2 | Logistic regression analysis showing the association between OC in late pregnancy and postpartum AGM.

Factors	OR	95%CI	P value
Age (years)	1.05	1.01-1.1	0.018
Postpartum BMI (kg/m^2)	1.04	0.99-1.1	0.126
Family history of diabetes: no (reference)	0.89	0.6-1.33	0.573
Parity: 1 (reference)	0.80	0.55-1.16	0.243
OC level in late pregnancy (ng/ml)	0.96	0.94-0.99	0.004
HbA1c in late pregnancy (%)	1.61	1.11-2.34	0.012

BMI, body mass index; OC, osteocalcin; HbA1c, glycated haemoglobin.

associated with increased risk of developing postpartum AGM. After delivery OC levels increased significantly in both groups, however, the OC levels were consistently low from late pregnancy to postpartum in the AGM group than in the NGT group. To the best of our knowledge, this is the first study exploring the relationship between longitudinal changes in OC and the postpartum glucose metabolism of GDM.

In animal and clinical investigations, OC, a traditional bone formation marker, has been found to participate in the regulation of glucose metabolism. Some evidence from animal studies suggested that higher OC concentrations are protective against diet-induced obesity and type 2 diabetes. Mice lacking the *Esp* gene, which encoded osteotesticular protein tyrosine phosphatase (OST-PTP), a receptor-like protein that inhibited the bioactivity of osteocalcin, exhibited hypoglycemia and were protected from glucose intolerance due to increases in pancreatic β-cell proliferation, insulin secretion and insulin sensitivity (10). In contrast, *Osteocalcin-* knockout mice had the opposite phenotypes, namely glucose intolerance and obesity (10). On

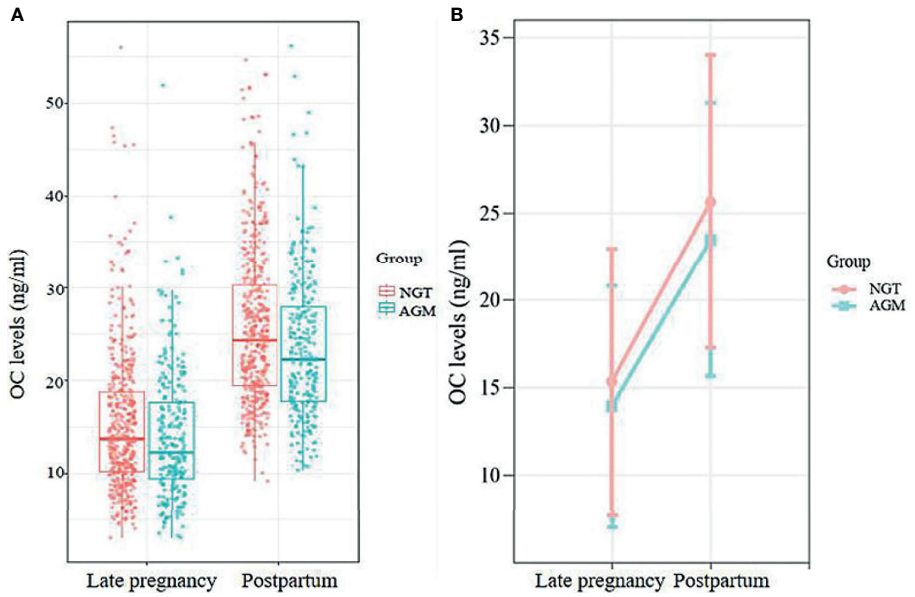

FIGURE 2 | **(A)** The distributions of OC levels at late pregnancy and postpartum in the NGT and AGM group. **(B)** Longitudinal change in OC levels in postpartum AGM individuals (orange line) and NGT individuals (blue line), adjusted for maternal age, parity, family history of DM, pre-BMI, and HbA1c in late pregnancy.

the other hand, infusion *via* subcutaneous minipump or daily injections or oral administration of recombinant OC significantly improved glucose tolerance and insulin sensitivity in mice fed a normal diet, which was possibly attributed to an increase in both β-cell mass and insulin secretion (27–29). In addition, OC stimulates pancreatic β-cell proliferation in cultured human islets (30). In accordance with previous animal studies, two meta-analyses confirmed that lower OC levels were observed in patients with type 2 diabetes than in normal controls (7, 31) and acknowledged that OC was negatively associated with fasting plasma glucose levels, HbA1c, insulin resistance and body mass index (BMI) but positively correlated with improved glycemic control, weight loss and regular exercise (11, 12).

Pregnancy itself was an insulin-resistant physiological state, and by the end of pregnancy, insulin sensitivity decreased by roughly 50% (32). To maintain euglycemia, insulin secretion increased 3 to 3.5-fold to protect against insulin resistance (33). After delivery, women's insulin sensitivity increased rapidly by 120% compared with that during late pregnancy. However, women with previous GDM remained in a state of chronic inflammation and insulin sensitivity did not significantly improve (34). In the long run, individuals with a history of GDM seemed to have an approximately 10 times higher risk of developing T2DM than those with NGT during pregnancy (35). An increasing number of studies have explored the role of OC in GDM previously, but many of them focused on the difference in OC levels between GDM patients and normal controls (21, 23). There were limited studies on the relationship between OC changes and postpartum glucose metabolism in GDM patients.

Winhofer et al. (21) found that OC levels increased in all women at 12 weeks postpartum, which was confirmed in Saucedo et al. research (36). However, fewer than 100 women with GDM underwent postpartum follow-up in their studies. In our study, we included more than 700 GDM patients. We found a 35.4% incidence of AGM; among the individuals with AGM, 13.3% were diagnosed with diabetes at 6–8 weeks postpartum. Consistent with the previous research by Saucedo et al. (36), our study showed that in the GDM group, subjects who progressed to AGM at postpartum had lower OC concentrations than individuals in the NGT group. Furthermore, we found that the OC levels from late pregnancy to postpartum were consistently lower in AGM group than in NGT group. Considering that OC can stimulate insulin secretion and has been shown to have a beneficial effect on glucose metabolism in animal and human studies, we speculated that the consistently lower levels in OC in the postpartum AGM group was an insufficient compensation for insulin resistance.

To test this hypothesis, we conducted simple correlations and found that serum OC was positively related with HOMA-β and the positive association was still robust after adjusting for age, postpartum BMI, parity, family history of diabetes and HbA1c in late pregnancy. Multivariate regression models further revealed that the risk of progressing to postpartum AGM decreased by 3.6% with per 1ng/ml increment of serum OC in late pregnancy (OR:0.964, 95%CI:0.940-0.988). Therefore, it is likely that in GDM patients, OC increases as a protective compensation mechanism to stimulate insulin secretion to cope with increased insulin demand and to further prevent developing of AGM.

There are several limitations in our study. First, we measured only the N-MID OC not ucOC, the bioactive form of OC, which is difficult to measure (37, 38). However, N-MID OC is the most

stable form of OC in serum (26). Second, we observed the relationship between OC and postpartum AGM in only a short period. Therefore, it is necessary to conduct prospective and mechanistic studies in the future.

In conclusion, consistently low levels of osteocalcin from late pregnancy to postpartum in GDM patients were at high risk of postpartum AGM. Increasing serum OC levels may become a potential preventive indicator to curb the progression to postpartum IFG/IGT or even T2DM.

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 institutional ethics committee of Shanghai General Hospital. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

YG and NL conceived of the design of the study and drafted the manuscript. ML, FF, and JY contributed to the data collection. MK and TS participated in the data analysis. YW and YP critically reviewed the data and the manuscript. All authors have reviewed and approved the final manuscript, contributed to the design of the study and interpretation of the data.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.803624/full#supplementary-material

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Low Birth Weight, β-Cell Function and Insulin Resistance in Adults: The Brazilian Longitudinal Study of Adult Health

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Background: Adverse intrauterine environment—reflected by low birth weight (LBW)—has been linked to insulin resistance and type 2 diabetes later in life. Whether β-cell function reduction and insulin resistance could be detected even in middle-aged adults without overt diabetes is less investigated. We examined the association of LBW with β-cell function and insulin sensitivity in non-diabetic middle-aged adults from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

Methods: This is a cross-sectional analysis of 2,634 ELSA-Brasil participants aged between 34 and 59 years, without diabetes. Participants were stratified according to LBW defined as <2.5 kg and their clinical data were compared. HOMA-IR, HOMA-β, HOMA-adiponectin, TyG index, QUICKI and TG/HDL were calculated and their association with LBW were tested using multiple linear regression including adjustments suggested by Directed Acyclic Graphs and propensity score matching was applied.

Results: The sample (47.4 ± 6.3 years) was composed of 57.5% of women and 9% had LBW. Subjects with LBW and normal-weight reported similar BMI values at the age of 20 years and current BMI was slightly lower in the LBW group. In average, cardiometabolic risk profile and also indexes of β-cell function and insulin sensitivity were within normal ranges. In regression analysis, log-transformed HOMA-β—but not with the other indexes—was associated with LBW (p = 0.014) independent of sex, skin color, prematurity, and family history of diabetes. After applying propensity-score matching in a well-balanced sample, HOMA-AD and TG/HDL indexes were associated with LBW.

Conclusion: The association between LBW and insulin sensitivity markers may occur in healthy middle-aged adults before overt glucose metabolism disturbances. Our data are coherent with the detection of early life events consequent with insulin resistance markers that could contribute to the risk of glucose metabolism disturbances.

Keywords: low birth weight, early life events, beta cell function, insulin sensitivity, prediabetes

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INTRODUCTION

Diabetes mellitus remains one of the most relevant public health concerns worldwide due to its micro and macrovascular complications (1). The etiology of type 2 diabetes mellitus (T2DM) is multifactorial, involving genetic, environmental, and lifestyle factors (2) and is commonly accompanied by excess body adiposity.

Based on the Developmental Origins of Health and Disease (DOHaD) theory, cardiometabolic disorders in adulthood might have their origins early in life stemming from intrauterine insults, namely, maternal and fetal undernutrition (3), maternal smoking, alcohol consumption or health conditions in perinatal life (4). As an adaptation to survive under adverse gestational conditions, fetal programming occurs, resulting in structural and functional changes in body organs and systems (5, 6).

Low birth weight (LBW), a proxy of intrauterine adversity, has been associated with adult-onset diseases, namely, obesity, T2DM and the metabolic syndrome (7, 8). It has been reported that LBW is associated with decreased β-cell mass and reduced function, resulting in a low insulin response to glucose levels (9, 10). Additional underlying mechanisms have been related to evidence of decreased insulin sensitivity in the genesis of glucose metabolism disturbance, concomitant with progressive β-cell dysfunction during adulthood (11, 12). Studies show that perinatal stress may affect insulin action in peripheral organs with reduced glucose uptake, and decreased expression of GLUT4 glucose transport by muscle and adipose cells (13–15). This condition becomes particularly worrisome considering the tendency of weight gain associated with our current environment and lifestyle. In this context, greater awareness of glucose metabolism abnormalities is important for early identification of risk later in adult life.

A number of studies have associated LBW with T2DM (16, 17), although identifying an association of birth weight with impaired insulin sensitivity and β-cell function before the onset of diabetes, the focus of interest of the present study, would be more opportune for preventive measures.

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a large cohort study of adult health in Brazil, designed to investigate risk factors associated with diabetes and cardiovascular disease (18, 19). Therefore, the ELSA-Brasil represents an opportunity to investigate associations of early life events with outcomes in adulthood. The present study examined the association of LBW with parameters of β-cell function and insulin sensitivity in non-diabetic participants of the ELSA-Brasil.

METHODS

Study Design and Population

A cross-sectional analysis was carried out of baseline data from the multicenter ELSA-Brasil study, whose methodological details have been reported elsewhere (18, 19). The baseline assessment was conducted from August 2008 to December 2010 and included 15,105 employees aged 35–74 years from six Brazilian universities and research institutions. The present analysis drew on the baseline data of 5,061 participants of both sexes, aged 35–74 years from the São Paulo center. The study was approved by the local Ethics Committee and informed consent was obtained from all participants.

Eligibility Criteria

To be eligible for the present study, participants had to be aged <60 years (to reduce recall bias), non-diabetic and have preserved renal function. Of the 5,061 participants, the following subjects were excluded: 1,036 with diabetes (self-reported or in use of antidiabetic medications or newly diagnosed), 210 with glomerular filtration rate <60 mL/min/1.73 m^2 or macroproteinuria, and 623 aged ≥60 years (20). Thirty-nine participants were subsequently excluded for being underweight (BMI <18.5 kg/m^2) and 186 because they were born with macrosomia (birth weight >4.0 kg). A further 333 participants were excluded for missing data on exposure (birth weight) or outcome (plasma glucose, insulin and lipids) variables. Therefore, a total of 2,634 participants were included in the present study (**Figure 1**).

Clinical and Laboratory Data

Participants were interviewed using standardized questionnaires (21). Self-reported data regarding demographics, socioeconomic status and health conditions were obtained. Variables of interest were age (years), sex (male, female), skin color (black, white, brown, yellow or indigenous, further stratified into white and non-white categories), family history of diabetes and hypertension (yes or no) and maternal educational level of participant.

Prematurity (yes or no) and birth weight (kg) were self-reported when possible. Birth weight was also categorized into "<2.5 kg", "2.5–4.0 kg", ">4.0 kg" or "unknown". All participants were also asked to provide their body weight at 20 years of age.

Weight and height were measured and body mass index (BMI) then calculated as weight in kilograms divided by height in meters squared to express nutritional status. Waist circumference was measured at the midpoint between the last rib and the iliac crest using an inelastic tape. Blood pressure was measured using an Omron HEM 705CPINT device (Omron Co, Kyoto, Japan) after a 5-minute rest in a sitting position. Three measurements were taken at 1-min intervals and mean values calculated. After overnight fasting, blood samples were collected and participants then underwent a 2-hour 75 g oral glucose tolerance test. Fasting and 2-hour plasma glucose and insulin were determined. Aliquots were frozen at −80°C for further determinations (22, 23).

Plasma glucose was measured by the hexokinase method (ADVIA Chemistry; Siemens, Deerfield, Illinois, USA), and glycated hemoglobin determined by high-pressure liquid chromatography (Bio-Rad Laboratories, Hercules, California, USA) according to the National Glycohemoglobin Standardization Program certified method. Insulin (Siemens, Tarrytown, USA) and adiponectin (Enzo Life Sciences,

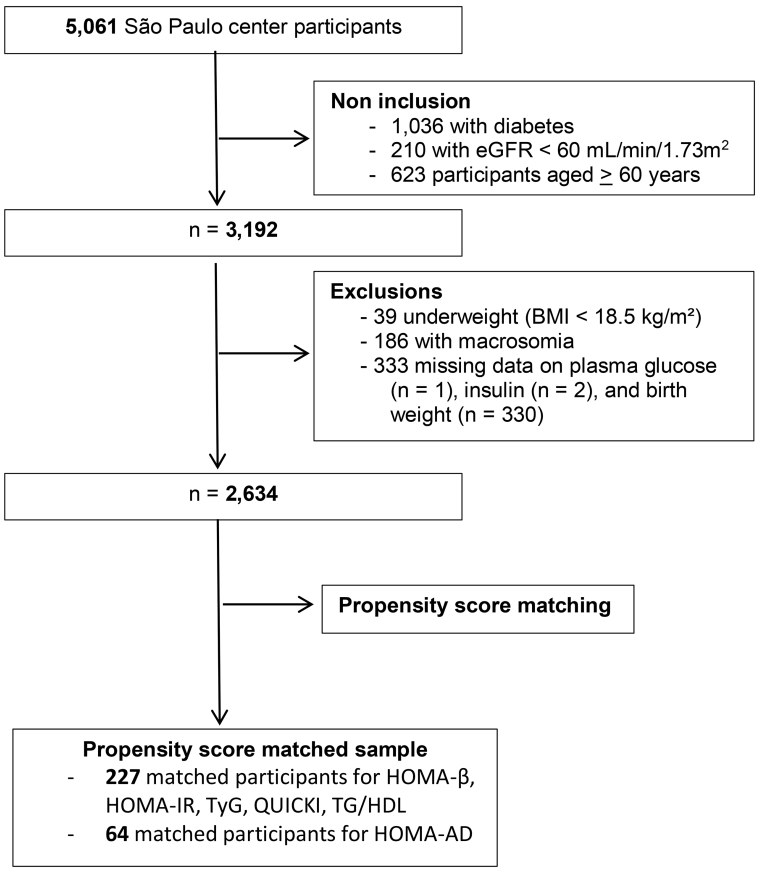

FIGURE 1 | Flowchart of selection of ELSA-Brasil participants for study inclusion.

Farmingdale, NY, USA) were determined using enzyme-linked immunoenzymatic assays.

The HOMA-β and HOMA-IR indexes were used to assess β-cell function and insulin sensitivity, respectively, and were calculated using the equations:

$$\text{HOMA-}\beta = [20 \times \text{fasting insulin (}\mu\text{UI/ml)}]/[\text{fasting glucose (mmol/L)} - 3.5]$$

$$\text{HOMA-IR} = [\text{fasting insulin (}\mu\text{UI/ml)} \times \text{fasting glucose (mmol/L)}]/22.5$$

Additionally, insulin sensitivity was evaluated by HOMA-adiponectin (HOMA-AD), the Triglycerides–glucose index (TyG index), QUICKI (Quantitative Insulin Sensitivity Check Index) and the Triglyceride-to-HDL-c ratio (TG/HDL-c), using the following equations: HOMA-AD = fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5 × adiponectin (μg/ml); TyG index = log [(fasting triglycerides (mg/dl) × fasting glucose (mg/dl)]/2; QUICKI = 1/(log insulin (μUI/ml) + (log fasting glucose (mg/dl) and TG/HDL-c.

Adiponectin was measured in a sub-sample of 1,000 participants. After applying exclusion criteria, 742 participants were included with available adiponectin data.

Total cholesterol was assessed using the enzymatic colorimetric method (ADVIA Chemistry; Siemens, Deerfield, Illinois, USA). HDL-c was determined by the homogeneous colorimetric method without precipitation, and triglycerides by the glycerophosphate peroxidase method according to the Trinder assay (ADVIA Chemistry; Siemens, Deerfield, Illinois, USA). LDL-c concentrations were calculated using the Friedewald equation.

Definitions for Analyses

Birth weight (exposure variable) was classified into three categories: low birth weight (<2.5 kg), normal birth weight (2.5–4.0 kg) and macrosomia (>4.0 kg). Prematurity was defined by an affirmative answer to the question: "*Were you a premature baby, in other words, were you born earlier than expected*?". Outcomes were HOMA-β, HOMA-IR, HOMA-AD, TyG index, QUICKI and TG/HDL-c, analyzed as continuous variables.

Nutritional status was classified into underweight (BMI <18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obesity (>30.0 kg/m^2). Hypertension was diagnosed when systolic or diastolic blood pressure levels were ≥140 or 90 mmHg, respectively, or when participant was in use of antihypertensive drugs.

Diabetes was diagnosed according to the American Diabetes Association criteria (24), as follows: fasting plasma glucose ≥126

mg/dl or 2-hour post challenge >200 mg/dl or glycated hemoglobin ≥6.5%. Prediabetes (yes or no) was defined as fasting plasma glucose between 100 and 125 mg/dl or 2-hour post challenge between 140 and 199 mg/dl or glycated hemoglobin 5.7–6.4%.

Statistical Analysis

Distribution normality was tested for continuous variables and those with non-normal distribution (HOMA-β, HOMA-IR, HOMA-AD, QUICKI, and TG/HDL-c) were log-transformed before analysis to achieve normality. Continuous variables with a normal distribution were expressed as mean ± standard deviation (SD) and compared using Student´s *t*-test. Non-normally distributed variables were expressed as median and interquartile range and compared using the Wilcoxon rank test. Categorical variables were expressed as absolute and relative frequencies and compared by the chi-squared test.

Associations of exposure (LBW) and outcome (HOMA-β, HOMA-IR, HOMA-AD, TyG index, QUICKI, and TG/HDL-c) variables were initially analyzed by simple linear regression. Directed Acyclic Graphs (DAG) were used to build theoretical models and analyze independent associations of exposure with outcomes in multiple linear regression analyses. The DAG is a causal diagram which allows scientific evidence regarding the relationships among variables to be incorporated in graphics software to reach the ideal set of covariables (minimum sufficient adjustment) for the model to prevent biases and overadjustments (25, 26). Figures were created by DAGitty software, version 3.0 (www.dagitty.net) included in the **Supplementary Material** (**Figures S1A, B**).

Based on the DAGs, the association of LBW with HOMA-β and parameters of insulin sensitivity were adjusted for sex, skin color, family history of diabetes, and prematurity.

Considering the difference in sample size between groups with normal birth weight and LBW, and potential selection bias due to the nature of the study, propensity score matching was employed to create more comparable groups (27, 28). The nearest neighbor-matching algorithm within a caliper of 0.1 SD of logit function of propensity score was used. First, for the propensity score matching, a multiple logistic regression model was used, adjusted for DAG-based covariates (sex, skin color, family history of diabetes, and prematurity), and the probability of each participant having LBW *versus* normal birth weight was estimated. Balance between the groups was assessed by comparing each covariate. When standardized mean difference fell in the −0.1 to 0.1 range, groups were considered balanced. This matching reduced all covariate imbalance in the sample. The matched sample was then submitted to multiple linear regression in order to analyze associations of LBW (exposure as independent variable) with β-cell function and insulin sensitivity markers (outcomes as dependent variables) adjusted for the same DAG-based covariates. Tests were performed using "MatchIt", "rbounds", "Matching", "twang" and "survey" packages in the R statistical environment.

All analyses were performed using the R Project for Statistical Computing software (R version 3.5.2) and statistical significance was set at a p-value of 0.05.

RESULTS

For the study sample of 2,634 participants, mean age was 47.4 ± 6.3 years, 57.5% were women and 59.3% reported white skin color. In general, the cardiometabolic parameters of the sample were within normal ranges (systolic and diastolic blood pressures of 116.6 ± 14.9 and 74.2 ± 10.4 mmHg, respectively), except for overweight (26.8 ± 4.6 kg/m^2) and prediabetic (plasma glucose of 102.0 ± 7.7 mg/dl) status.

A total of 238 (9.0%) participants reported LBW and 145 (5.5%) were born preterm. LBW participants were predominantly women (61.7%), had white skin color (52.2%), and reported low maternal educational level (62.0%).

Participants with LBW had a higher rate of low educational level compared to those reporting normal birth weight (16.1% *versus* 10.8%, p = 0.007). LBW and normal-weight groups reported similar BMI values at the age of 20 years and current BMI was slightly lower in the LBW group, with borderline significance (p = 0.075, **Table 1**). Mean values of waist circumference were higher in the normal birth weight than the LBW group (88.2 ± 11.6 *versus* 86.0 ± 11.7 cm, p = 0.008), but both values were, on average, within normal ranges. Blood pressure levels and lipid metabolism variables were similar for the two groups. No differences in beta-cell secretion and insulin sensitivity indexes were found between the groups.

On multiple linear regression analyses, associations of LBW with markers of beta-cell function and insulin sensitivity were tested. LBW was associated with log-transformed HOMA-β values (p = 0.014), but not with the other indexes of insulin sensitivity (**Table 2**).

Propensity-Score Matching—Variable Balance

Initially, the sample contained 238 participants with LBW. After applying the propensity-score matching, the final samples included 227 matched participants for HOMA-β, HOMA-IR, TyG, QUICKI and TG/HDL analysis and 64 matched participants for HOMA-AD analysis. The matching approach made all covariates appropriately balanced (standardized mean difference of between −0.1 and 0.1) for further analyses. Variable balance was compared before and after matching to assess the improvement of pairing (**Supplementary Table S1**).

Associations of LBW With β-Cell Function

After propensity-score matching, the multiple linear regression model, adjusted for sex, skin color, family history of diabetes and prematurity, showed no association between LBW and HOMA-β (ß 0.003, 95%CI −0.038–0.045 p = 0.107) (**Table 3**).

Associations of LBW With Insulin Sensitivity

The fully adjusted multiple linear regression model showed that being born with LBW was directly associated with HOMA-AD (ß 0.046, 95% CI 0.015–0.078, p = 0.005) and TG/HDL index (ß 0.021, 95% CI 0.013–0.036, p <0.001). There was no association of LBW with HOMA-IR, TyG or QUICKI (**Table 3**).

TABLE 1 | Clinical characteristics of participants born with normal and low birth weight.

	Normal Birth Weight n = 2,582	Low Birth Weight n = 238	*P*-value
Age (years)	47.4 (6.3)	47.5 (6.4)	0.657
Body mass index at age 20 (kg/m^2)	21.8 (3.4)	20.9 (3.0)	0.125
Body mass index (kg/m^2)	26.9 (4.6)	26.3 (4.5)	0.075
Waist circumference (cm)	88.2 (11.6)	86.0 (11.7)	0.008
Systolic blood pressure (mmHg)	116.5 (14.9)	117.4 (15.3)	0.417
Diastolic blood pressure (mmHg)	74.2 (10.4)	74.7 (10.6)	0.507
LDL-cholesterol (mg/dl)	129.7 (33.0)	132.5 (33.1)	0.224
HDL-cholesterol (mg/dl)	56.7 (14.4)	57.0 (13.4)	0.328
Triglycerides (mg/dl)	130.2 (91.9)	126.5 (71.3)	0.449
Fasting plasma glucose (mg/dl)	102.6 (8.4)	102.7 (7.9)	0.832
Glycated hemoglobin (%)	5.2 (0.54)	5.3 (0.57)	0.963
Fasting insulin (mg/dl)	6.0 (3.5–10.0)	5.9 (3.2–8.9)	0.181
2-h plasma glucose (mg/dl)	122.0 (24.0)	122.9 (27.5)	0.610
2-h insulinemia	43 (26.7–69.1)	41.2 (26.0–64.6)	0.434
HOMA-IR*	2.5 (1.66–3.5)	2.4 (1.58–3.4)	0.187
HOMA-β*	56.0 (32.9–91.9)	53.9 (30.8–83.8)	0.189
HOMA-AD*	0.43 (0.22–0.96)	0.42 (0.19–1.10)	0.776
TyG	2.0 (0.12)	2.1 (0.11)	0.959
QUICKI*	0.36 (0.33–0.39)	0.37 (0.34–0.40)	0.186
TG/HDL*	1.9 (1.3–3.2)	2.0 (1.4–2.9)	0.824

*HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; AD, Adiponectin; TyG, Triglycerides glucose index; QUICKI, Quantitative Insulin Sensitivity Check Index; TG/HDL, Triglycerides HDL-cholesterol index, Data are expressed as mean (SD) or median (interquartile range). Student t or *Wilcoxon test was used.*

TABLE 2 | Association of low birth weight with parameters of β-cell function and insulin sensitivity.

	β	95% CI	*P*-value
HOMA-β#			
Model 1	−0.03	−0.054–0.003	0.080
Model 2	−0.03	−0.054–0.003	0.082
Model 3	−0.04	−0.072–0.008	0.014
HOMA-IR#			
Model 1	−0.02	−0.051–0.011	0.198
Model 2	−0.02	−0.050–0.012	0.233
Model 3	−0.03	−0.065–0.005	0.089
HOMA-AD#			
Model 1	0.000	−0.110–0.110	0.997
Model 2	0.006	−0.106–0.117	0.922
Model 3	0.027	−0.100–0.155	0.667
TyG			
Model 1	0.002	−0.013–0.017	0.754
Model 2	0.004	−0.012–0.019	0.636
Model 3	−0.001	−0.018–0.016	0.899
QUICKI#			
Model 1	0.003	−0.001–0.008	0.184
Model 2	0.003	−0.002–0.007	0.215
Model 3	0.005	−0.000–0.009	0.077
TG/HDL#			
Model 1	−0.001	−0.036–0.033	0.945
Model 2	0.002	−0.033–0.037	0.898
Model 3	−0.007	−0.045–0.032	0.725

Model 1: adjusted for sex and skin color.

Model 2: adjusted for sex, skin color and family history of diabetes.

Model 3: adjusted for sex, skin color, family history of diabetes and prematurity.

#*Log-transformed values of outcomes for analyses.*

DISCUSSION

We found evidence further supporting the hypothesis that LBW is associated with decreased β-cell function and with insulin resistance in middle-aged non-diabetic participants from the ELSA-Brasil (18, 19). The study findings are strengthened by the facts that several indexes of insulin secretion and sensitivity were used and DAG applied for adjustments and propensity-score matching analysis. An association was found of LBW with HOMA-AD and TG/HDL indexes, after adjustment and

TABLE 3 | Estimates of associations of LBW with parameters of β-cell function and insulin sensitivity after propensity-score matching in ELSA-Brasil participants.

	Propensity-score pairing		
	Coefficient (ß)	**95% CI**	***P*-value**
HOMA-β[#]	0.003	–0.038–0.045	0.107
HOMA-IR[#]	0.0004	–0.00037–0.003	0.818
HOMA-AD[#]	0.046	0.015–0.078	0.005
TyG	0.009	–0.017–0.018	0.991
QUICKI[#]	0.0008	–0.0009–0.0092	0.986
TG/HDL[#]	0.021	0.013–0.036	<0.001

HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; AD, Adiponectin; QUICKI, Quantitative Insulin Sensitivity Check Index; TG/HDL, Triglycerides HDL-c; CI, confidence interval.

[#]*Log-transformed values for analyses.*

propensity-score matching. No association between low birth weight and HOMA-β was found. The results reinforced the possible role of early life events in insulin sensitivity, even with marker values within the normal range in adults born with LBW.

Considering the magnitude of T2DM as a public health concern, causing morbidity and mortality worldwide (29, 30), initiatives to improve prediction and prevention are timely. The present study was prompted by evidence that population-attributable risk of T2DM is associated with increased mortality in adults born with LBW compared to those with normal birth weight (16). Additionally, LBW has been associated with hyperinsulinemia and increased risk of diabetes later in childhood (31, 32). We hypothesized that these abnormalities can affect pancreatic function during the life course, justifying the assessment of beta cell secretion capacity, and peripheral insulin sensitivity before glucose metabolism disturbances emerged. In this context, our study evaluated traditional and novel indexes of β-cell function and insulin sensitivity/resistance.

HOMA-β and HOMA-IR are the most common indexes for estimating insulin secretion and resistance (33). In the present study, HOMA-AD was also calculated to assess insulin sensitivity. This index is a modified version of HOMA-β which incorporates the total serum adiponectin level in the denominator to indirectly adjust to degree of body adiposity. Adiponectin is a protein involved in the pathophysiology of obesity and low levels tend to be observed in obese individuals with ectopic adipose tissue deposition (34). Hypoadiponectinemia has been considered an independent risk factor for the development of T2DM (35). To the best of our knowledge, the present study is the first to assess insulin sensitivity in overweight adults with LBW. HOMA-AD has been evaluated in the pediatric population, individuals with chronic kidney disease and chronic liver disease (36–38). We also calculated TG/HDL ratio, an alternative, low-cost, useful index for clinical practice. These lipid parameters are typically altered in individuals with the metabolic syndrome, in which insulin resistance is the main pathophysiological event. Both HOMA-AD and TG/HDL were associated with LBW in the well-balanced sample after applying propensity-score matching. Considering that most people are born with normal birth weight, as was the case in the present sample, this analysis was valid for improving the reliability of comparisons of subgroups stratified according to birth weight. Several studies have shown that HOMA-AD offers greater accuracy than HOMA-IR for assessing insulin resistance in overweight non-diabetic individuals (39, 40). Given that diabetic individuals were excluded from the study sample, the findings regarding the HOMA-AD and TG/HDL indexes suggest their utility for early detection of insulin resistance in middle-aged adults.

In the natural history of T2DM, insulin resistance precedes the decline of β cell function and is associated with ectopic fat deposition in the liver, muscles and pancreas (41). In turn, weight loss can prevent this condition by improving insulin sensitivity. Our results are consistent with insulin resistance preceding β-cell dysfunction in overweight adults who have not developed a glucose metabolism disturbance. LBW was initially associated with HOMA-β on multiple linear regression. However, after applying propensity-score matching in a well-balanced sample, including for the adiposity parameter (BMI), this association no longer persisted. Therefore, these results revealed an association of LBW with insulin sensitivity markers in middle-aged adults, where an association with HOMA-β can be expected in the long term if a weight loss intervention is not pursued. To our knowledge, no previous studies have reported the use of HOMA-AD and TG/HDL indexes as early markers of insulin sensitivity in adults who still have preserved β-cell function.

Explanations for these findings are based on the reported associations of LBW and glucose metabolism dysfunction, and particularly when these infants also experience catch-up growth in childhood. These individuals are prone to developing obesity, increased visceral adiposity and insulin resistance (42, 43). An elevated number of insulin receptors in their adipocytes and abnormal signaling by phosphorylation of insulin-receptor substrate 1 may result in an anti-lipolysis state (44, 45). Also, it has been shown that each tertile decrease in birth weight was associated with a 1.72 times greater risk of insulin resistance in adults (46). Concordantly, our data favor the hypothesis that once insulin resistance is installed, insulin production will increase and can progress to β-cell failure over time. Other studies support the possibility that decreased β-*cell function can occur without insulin resistance. This was observed in individuals with intrauterine growth restriction who had a marked reduction in number of β cells (47–49). Another study confirmed that adults born with LBW had a 30% reduction in

insulin secretion (10). Animal models involving intrauterine energy restriction showed similar results, with a reduction in β cell mass of up to 35% (48). Despite uncertainties over the underlying mechanisms, the present results support the occurrence of early onset of insulin resistance in adults without diabetes.

Other indexes could have been useful to assess β cell function such as the OGIS (50) and Matsuda index (51) that require several determinations of plasma glucose and insulin during glucose tolerance tests. More recently, insulin clearance was raised as an important aspect of glucose metabolism and its impairment has been related to the risk of developing T2DM (52–54). Although this method would enhance the β cell function evaluation, measurements for its estimation were not available in the ELSA-Brasil.

The present study has limitations related to recall bias, given that retrospective data were collected regarding early life events. This bias can be reduced by using a sample of middle-aged participants, under 60 years of age. Some studies have shown that perinatal-related events are reliably reported during adult life (55–57). We also use the exposure (LBW) as a categorical variable, possibly reducing the statistical power of the analysis. This approach was chosen to minimize information inaccuracy from participants who were unable to accurately recall their birth weight in kilograms. The use of the propensity-score method decreased the sample size, limiting the ability to find valid associations. Therefore, future studies investigating the association between LBW and HOMA-β and other indexes in larger samples are needed. A cross-sectional analysis of the ELSA-Brasil data was conducted. Further analyses of the follow-up of the sample can allow causality between LBW and the occurrence of glucose metabolism disturbances to be explored.

A strength of this study was the methodological approach employed, including the Directed Acyclic Graph method to identify confounding variables, avoiding over adjustments in the regression models constructed (25, 26). Although a variety of covariates were controlled for, other exposures which occurred during the life course of participants were not included. However, we collected body weight at age 20 in an attempt to define participant body weight trajectory. Another strength was the use of propensity-score matching to reduce potential selection confounders seen in observational studies (27, 28), achieving sufficiently balanced groups in the analysis. Furthermore, the frequency of self-reported LBW found in the sample was comparable to that reported in the Brazilian population at large (58).

In conclusion, LBW was found to be associated with insulin sensitivity markers in adulthood before overt glucose metabolism disturbances emerged. HOMA-AD and TG/HDL indexes appeared to be useful for detecting insulin resistance in overweight adults who had LBW. These findings are relevant in reinforcing the hypothesis that early life events affect glucose metabolism during the life course. Thus, identifying the subset of individuals at risk may be important to allow early implementation of preventive measures.

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.

ETHICS STATEMENT

The study was approved by the National Commission on Ethics Research (CONEP) and the local ethics committee, the Research Ethics Committee (CEP) under registration number 76 of the University of São Paulo (HU-USP). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Study design, analysis, interpretation and preparation of the manuscript: JB, BA-P and SF. Acquisition of data and critical revision for the manuscript content: PL and IB. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.842233/full#supplementary-material

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Application Value of Predictive Model Based on Maternal Coagulation Function and Glycolipid Metabolism Indicators in Early Diagnosis of Gestational Diabetes Mellitus

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Objective: To investigate whether first-trimester fasting plasma glucose (FPG), blood coagulation function and lipid metabolism could predict gestational diabetes mellitus (GDM) risk.

Methods: From October 2020 to May 2021, a total of 584 pregnant women who took prenatal care in Shanghai Jiaotong University Affiliated Sixth People's Hospital were chosen as the observation subjects. The clinical information and serum samples of all pregnant women were collected at 10–13 weeks of gestation and the blood coagulation function, fasting blood glucose and lipid profiles of the pregnant women were detected. A 75 g oral glucose tolerance test was performed up to 24–28 weeks of gestation. One hundred forty-two pregnant women with GDM and 442 pregnant women without GDM were detected. Data were expressed by x ± s or median (interquartile range) and were analyzed using student's *t*-test, Wilcoxon rank sum test and Logistic regression analysis. The area under the curve (AUC) was calculated by receiver operating characteristic curve (ROC) to analyze the predictive values.

Results: Compared with non-GDM group, age, pre-pregnancy BMI, FPG, FIB, D-Dimer, FDP, FPG, TC, TG, LDL-C, sdLDL-C, APOB and APOE in GDM group were significantly higher than those in non-GDM group, while PT, INR, APTT and TT were significantly lower than those in non-GDM group. Univariate logistic regression analysis was used to explore the risk factors of GDM. Gestational age, pre-pregnancy BMI, FPG, PT, INR, APTT, FIB, TT, D-Dimer, TC, TG, LDL-C, sdLDL-C, APOB and APOE were all independent predictors of GDM. Multivariatelogistic regression showed that pre-pregnancy BMI, FPG, APTT, TT, TG, LDL-C, sdLDL-C and APOB were risk factors for GDM. The AUC of the established GDM risk prediction model was 0.892 (0.858–0.927), and the sensitivity and specificity were 80.71 and 86.85%, respectively; which were greater than that of pre-pregnancy BMI, FPG, APTT, TT,TG, LDL-C, sdLDL-C, APOB alone, and the diffffference was statistically signifificant ($P < 0.05$).

Conclusions: FPG, APTT, TT, TG, LDL-C, sdLDL-C, APOB and pre-pregnancy BMI in early pregnancy has important clinical value for the prediction of GDM, We combined these laboratory indicators and established a GDM risk prediction model, which is conducive to the early identification, intervention and treatment of GDM, so as to reduce the morbidity of maternal and infant complications.

Keywords: gestation, diabetes mellitus, fasting plasma glucose, coagulation function, lipid metabolism, prediction

INTRODUCTION

Gestational diabetes mellitus (GDM) is a kind of impaired glucose metabolism that arises or is diagnosed during pregnancy, and it is one of the most prevalent pregnancy problems. The prevalence of GDM has risen steadily in recent years (1, 2). GDM has a number of negative consequences for both moms and their children. With the continuous progress in knowledge of GDM, most industrialized nations now test for GDM at 24–28 weeks of gestation (3). Early detection and treatment of GDM has been demonstrated in studies to enhance pregnancy outcomes (4, 5). However, the current unequivocal diagnosis of GDM is generally in the second trimester, thus the potential for early intervention and treatment may be missed. Now there is strong evidence that early diagnosis of GDM will allow for timely treatment, such as dietary counseling or lifestyle interventions, which has been shown to be effective for the improvement of perinatal outcomes (6). As a result, identifying risk variables and developing a simple and effective GDM risk prediction model, particularly in early pregnancy, has significant therapeutic application value.

Pregnant women's clotting function and lipid metabolism alter significantly as their pregnancy continues. The production of coagulation factors VII, VIII, IX, X, XII, and fibrinogen increase dramatically, peaking during a full-term pregnancy. The body's blood coagulation capability is strengthened, and it is in a particular physiological hypercoagulable condition, which might be lower the risk of postpartum hemorrhage (7). To maintain normal pregnancy needs and fetal growth and development, pregnant women's fat synthesis and blood lipid levels rise in the early stages of pregnancy owing to excessive phagocytosis and increased insulin sensitivity (8). But whether this increase is natural or pathological, few studies have been conducted to determine if it may be utilized as a possible clinical signal to predict the risk of later GDM.

Previous research demonstrated that a comparative proteomic study of plasma proteins from pregnant women with GDM and normoglycemia revealed that the differences were mostly connected to the coagulation and complement pathways (9). Some researchers have discovered that hyperlipidemia increases coagulation activity and shortens prothrombin time in patients with high total cholesterol or triglycerides (10), and that poor blood glucose control negatively affects lipid metabolism and coagulation function in patients with diabetes-complicated pregnancy (11). As a result of the intertwined relationship between pregnancy, diabetes, the blood coagulation cascade, and lipid metabolism, it is worth further discussion whether it can be combined with commonly used clinical laboratory indicators such as coagulation function, blood sugar, and blood lipids to predict GDM in the early stage. This study intends to establish a prospective follow-up cohort to collect general data such as pregnant women's ages, pre-pregnancy BMI, as well as early pregnancy coagulation function and glycolipid metabolism indicators, and then use logistic regression to establish a GDM prediction model and evaluate its effectiveness. The goal of this project is to make it feasible to recognize, diagnose, and intervene in GDM in the clinic as early as possible.

MATERIALS AND METHODS

Patients

As the observation objects for prospective cohort research, we chose 584 pregnant women who had their first birth check-up card at Shanghai Jiaotong University Affiliated Sixth People's Hospital between October 2020 and May 2021. When the card was formed at 10–13 weeks of pregnancy, clinical information and peripheral blood samples were obtained from all pregnant women. The 75 g oral glucose tolerance test was performed during 24–28 weeks of pregnancy. There were 142 instances of GDM pregnant women and 442 cases of non-GDM pregnant women found. GDM diagnosis criteria include: Adopt the IADPSG-recommended GDM diagnostic approach, which is to test for GDM between 24 and 28 weeks of gestation. Pregnant women are given an oral glucose tolerance test of 75 g. If you have fasting blood glucose $\geq$5.1 mmol/L or oral glucose 1 h later, blood glucose $\geq$10.0 mmol/L or oral glucose 2 h after fasting blood glucose $\geq$8.5 mmol/L, might be diagnosed with GDM (12). Excluding numerous pregnancies, diabetes during pregnancy, hypertension, thyroid illness, cardiovascular disease, liver and kidney disease, autoimmune disease, and any other medical history of conditions impacting glucose and lipid metabolism. The Ethics Committee of Shanghai Sixth People's Hospital accepted an informed consent form completed by all observation subjects (Approval No. 2016-003).

Clinical Information and Laboratory Examination

Baseline clinical data from 584 enrolled individuals' medical records were obtained, including age, and Body Mass Index (BMI) before pregnancy. The enrolled patients fasted after 22 p.m. in the evening of the day before the blood draw, and peripheral venous whole blood was drawn at 8 a.m. in the morning of the following day, centrifuged at 3,000 rpm for 10 min, and serum or plasma was obtained.

Automated coagulation function analyzers (Siemens, Germany) and automated biochemical analyzers (Beckman, USA) were used to investigate and statistically analyze these laboratory data. The biochemical parameters from coagulation function, fasting plasma glucose, blood lipid and lipoprotein profiles examinations were collected by Automated coagulation function analyzers (Siemens, Germany) and automated biochemical analyzers (Beckman, USA), as shown in **Table 1**.

Statistical Analysis

SPSS 25.0 was used to do statistical analysis on the data that matched the criteria, and the Kolmogorov–Smirnov test was utilized to perform normal test analyses on the measurement data. The standard deviation of normally distributed data is given as x ± standard deviation (SD). The *t*-test (data conforms to a normal distribution and variance homogeneity) or Wilcoxon rank-sum test (not conforms to normal distribution and homogeneity of variance) was performed to compare the two groups. The skewed distribution measurement data are displayed as the median (M) and interquartile range (IQR). Independent sampling was used to compare skewed distribution measurement data using the Kruskal–Wallis H test.

The GraphPad Prism 8.0 software was used to create the receiver operating characteristic (ROC) curves for each indicator and combined test to determine the sensitivity, specificity, optimal cutoff value, Youden index, negative predictive value (NPV), and positive predictive value (PPV) of each index in GDM and non-GDM patients. The area under the curve (AUC) was used to evaluate the test's accuracy. A Univariate logistic regression analysis was used to screen GDM risk variables, and multivariate logistic regression analysis was utilized to develop a GDM prediction model. The *Z*-test was used to compare the area under the ROC curve of each marker and binary logistic regression analysis was used to establish the joint predictors of each index.

A nomogram based on the logistic regression model was constructed with R software (version 4.1.2). To assess the ability of the nomogram model to discriminate GDM patients, the area of ROC and 95% CIs were calculated. To analyze the agreement between nomogram predictions and actual observations, the Hosmer-Lemeshow tests were performed and calibration curves were created. Ten-Fold Cross-validation, Leave-one-out cross-validation, and Bootstraps of 1,000 resamples (with replacement) were applied to internally validate the stability of the model. Models were evaluated using discrimination and calibration, and discrimination was assessed by calculating the area under the receiver operating characteristic (ROC) curve (AUC) result for the predicted probability. The calibration degree of the prediction model refers to the consistency between the predicted probability and the actual observed value, and the calibration degree is displayed by the Hosmer-Lemeshow test and the calibration curve results.

The optimal cut-off value for each index was selected according to ROC curve, and binary logistic regression analysis was used to assess the risk of each index in GDM and non-GDM. Factors with statistical significance in the univariate analysis ($P < 0.01$) were included in the multivariate logistic regression analysis, and binary logistic regression analysis was performed to calculate the single factor, multivariate-adjusted odds ratio, and 95% confidence interval (CI) values based on maximum likelihood estimation. The difference was considered statistically significant when *P*-value was <0.05.

TABLE 1 | List of variables collected from coagulation function, fasting plasma glucose, blood lipid and lipoprotein profiles examinations.

Measured variables (abbreviation, SI)	Range of reference values
Prothrombin time (PT, s)	11–14
International standardized ratio (INR)	0.82–1.15
Activated partial thromboplastin time (APTT, s)	23.3–32.5
Fibrinogen (FIB, g/L)	2–4
Thrombin time (TT, s)	13–21
D-Dimer measurement (D-Dimer, mg/L)	0–0.8
Fibrin degradation product (FDP, mg/L)	0–5
Fasting blood glucose (FPG, mmol/L)	4.1–5.9
Total cholesterol (TC, mmol/L)	2.8–5.9
Triglycerides (TG, mmol/L)	0.45–1.81
High-density lipoprotein cholesterol (HDL-C, mmol/L)	>1.03
Low-density lipoprotein cholesterol (LDL-C, mmol/L)	<4.10
Small and dense low-density lipoprotein cholesterol (sdLDL-C, mg/L)	94–428
Apolipoprotein A1 (APOA-1, g/L)	1.04–2.02
Apolipoprotein B (APOB, g/L)	0.66–1.33
Apolipoprotein E (APOE, mg/L)	29–53
Lipoprotein (a) (LPa, mg/dL)	0–30

RESULTS

Characteristics of the Enrolled Pregnant Women Between GDM Group and Non-GDM Group

One hundred forty-two Pregnant Women Were Diagnosed With GDM in the second Trimester Among the 584 Pregnant Women Recruited in the Observation Group, and the Incidence of GDM Was 24.31%. The GDM Group's age, pre-Pregnancy BMI, FPG, FIB, D-D Dimer, FDP, FPG, TC, TG, LDL-C, sd LDL-C, APOB, and APOE Levels Were Considerably Greater Than Those of the non-GDM Group. While the PT, INR, APTT, and TT Indicators of the GDM Group Were Much Lower Than Those of the non-GDM Group, and the Difference Was Statistically Significant

TABLE 2 | Comparison of basic clinical data of the two groups in pregnant women.

Indicators	GDM group (n = 142)	Normal group (n = 442)	t/Z value	P-value
Age (y)*	30.38 ± 4.33	29.08 ± 4.31	3.130	0.002
Pre-pregnancy BMI (kg/m^2)	23.29 (21.38, 27.1)	20.1 (19.2, 21.2)	11.37	0.000
PT (s)	11.7 (11.2, 12.1)	11.9 (11.6, 12.2)	3.186	0.001
INR	0.99 (0.95, 1.03)	1.01 (0.98, 1.04)	3.269	0.001
APTT (s)*	26.92 ± 1.75	28.12 ± 1.86	−6.767	0.000
FIB (g/L)	3.933 (3.588, 4.421)	3.784 (3.362, 4.202)	3.583	0.000
TT (s)	15.5 (15.125, 15.9)	15.8 (15.4, 16.2)	5.153	0.000
D-Dimer (mg/L)	0.54 (0.40, 0.77)	0.50 (0.36, 0.70)	2.109	0.035
FDP (mg/L)	2.5 (2.5, 3.09)	2.5 (2.5, 2.72)	2.850	0.004
FPG (mmol/L)	4.965 (4.675, 5.218)	4.7 (4.5, 4.93)	7.237	0.000
TC (mmol/L)	5.31 (4.58, 5.85)	4.85 (4.35, 5.487)	3.655	0.000
TG (mmol/L)	1.91 (1.54, 2.31)	1.55 (1.25, 1.89)	6.403	0.000
HDL- (mmol/L)	1.7 (1.51, 1.92)	1.73 (1.53, 1.928)	0.477	0.634
LDL-C (mmol/L)	2.85 (2.49, 3.34)	2.61 (2.31, 3.018)	4.831	0.000
sdLDL-C (mg/L)	418.3 (346.75, 485.975)	344.15 (291.85, 392.1)	7.492	0.000
APOA-1 (g/L)*	1.73 ± 0.25	1.71 ± 0.23	0.909	0.364
APOB (g/L)	0.95 (0.82, 1.08)	0.88 (0.79, 0.987)	3.693	0.000
APOE (mg/L)	44 (38, 52)	40 (34, 49)	4.445	0.000
LPa (mg/dL)	14.3 (8.9, 29.6)	13.9 (8.67, 25.72)	0.970	0.332

*BMI, body mass index; PT, prothrombin time; INR, international standardized ratio; APTT, activated partial thromboplastin time; FIB, fibrinogen; TT, thrombin time; D-Dimer, D-dimer determination; FDP, fibrin degradation products; FPG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; sdLDL-C, small and low density Density lipoprotein cholesterol; APOA-1, Apolipoprotein A1; APOB, Apolipoprotein B; APOE, Apolipoprotein E; LPa, Lipoprotein (a); *The results of normality test showed that the observed variables were close to normal distribution in each group.*

($P < 0.05$), There Was no Significant Difference in the HDL-C, APOA-1, and LPa Between These two Groups (**Table 2**; **Figures 1**, **2**).

Univariate Logistic Regression Analysis of Risk Factors for GDM

An investigation of the risk variables for GDM was carried out using univariate logistic regression analysis. As shown in **Table 3**, age, pre-pregnancy BMI, FPG, PT, INR, APTT, FIB, TT, D-Dimer, TC, TG, LDL-C, sdLDL-C, APOB, and APOE were all predictors of gestational diabetes in the study population ($P < 0.05$).

Construction of a Multivariate Logistic Regression Model for GDM Early Detection

The pregnant women group logit (P) (GDM group = 1, Non GDM group = 0) was regarded the dependent variable, with variables having $P < 0.01$ in the univariate logistic regression analysis, indicating that the pre-pregnancy BMI (X1), FPG (X2), APTT (X3), TT (X4), TG (X5), LDL-C (X6), sdLDL-C (X7), APOB (X8) were considered self variables. The predictive parameters that integrate these indicators were calculated using multivariate logistic regression analysis (**Table 4**). The regression equation was logit (P) = −7.101+0.401X1+1.596X2-0.233X3-0.387X4+0.553X5+ 1.814X6+0.010X7-8.715X8, with the joint predictor being the analysis result of numerous joint test indicators.

The Diagnostic Value of Laboratory Indicators and the Established GDM Risk Prediction Model for GDM

The ROC curves for each indication and combination test were created using the GraphPad Prism program, as illustrated in **Figures 3A–O**. Pre-pregnancy BMI, FPG, and sdLDL-C were the single markers with the highest diagnostic value. When the threshold was 21.84 kg/m^2, the AUC of pre-pregnancy BMI was 0.817, and the sensitivity, specificity, NPV, and PPV were 70.42, 83.94, 58.48, and 89.83 %, respectively. When the threshold was 4.825 mmol/L, the AUC of FPG was 0.702, and the sensitivity, specificity, NPV, and PPV were 65.49, 66.29, 38.42, and 85.67%, respectively. When the threshold was 393.8 mg/L, the AUC of sdLDL-C was 0.71, and the sensitivity, specificity, NPV, and PPV were 58.57, 76.24, 44.19, and 85.14%, respectively. When the threshold was 0.238, the AUC of the combined detection was 0.892. The combined detection's sensitivity, specificity, NPV, and PPV were 80.71, 86.85, 66.43, and 93.34%, respectively (In **Table 5**).

According to the findings in **Table 4**, the AUC values of combined detection were higher, and the diagnostic performance was greater. The AUC values of pre-pregnancy BMI, FPG, APTT, TT,TG, LDL-C, sdLDL-C, APOB, and pre-pregnancy BMI +FPG + APTT + TT + TG + LDL-C + sdLDL-C + APOB were compared using MedCalc software. The combined detection AUC was larger than that of pre-pregnancy BMI, FPG, APTT, TT, TG, LDL-C, sdLDL-C, and APOB alone, and the difference was statistically significant ($P < 0.05$; **Table 6**).

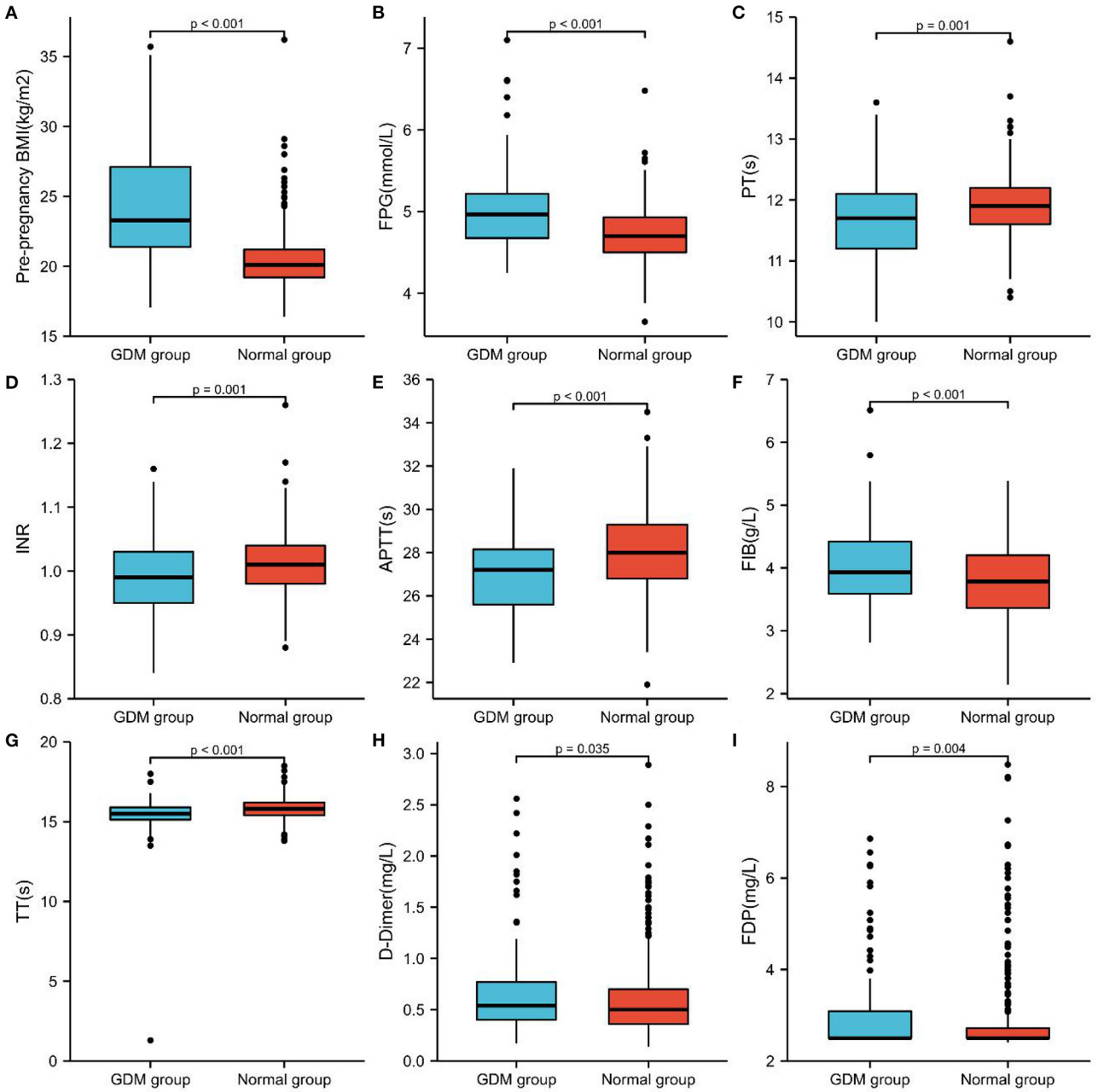

FIGURE 1 | Comparison of Pre-pregnancy BMI, FPG and coagulation function of the two groups in pregnant women with GDM and non-GDM. **(A)** Pre-pregnancy BMI, **(B)** FPG, **(C)** PT, **(D)** INR, **(E)** APTT, **(F)** FIB, **(G)** TT, **(H)** D-D dimer, and **(I)** FDP.

Establishment a Nomogram for Predicting GDM Based on Multivariable Logistic Regression Model

Based on the multivariable model, a nomogram was generated. According to the data of pregnant women, read the corresponding points of pregnant women in this variable on the horizontal axis of each variable in the figure, and the value of the corresponding point of each variable perpendicular to the point on the axis marked with "score" is the score of this variable, The sum of the scores for each variable is the total score. Find the corresponding point of the total score on the "Total Score" axis, and the value of the point perpendicular to the "GDM" axis is the predicted probability of GDM. For example, using the developed nomogram, a pregnancy woman with pre-pregnant BMI of 26.4 kg/m2 (31 points), FPG of 4.87 mmol/L (16 points), APTT of 25.6S (15 points), TT of 15.2s (13 points),TG of 2.17 mmol/L (8 points), LDL of 2.45 mmol/L (17 points), sdLDL of 345 mg/L (25

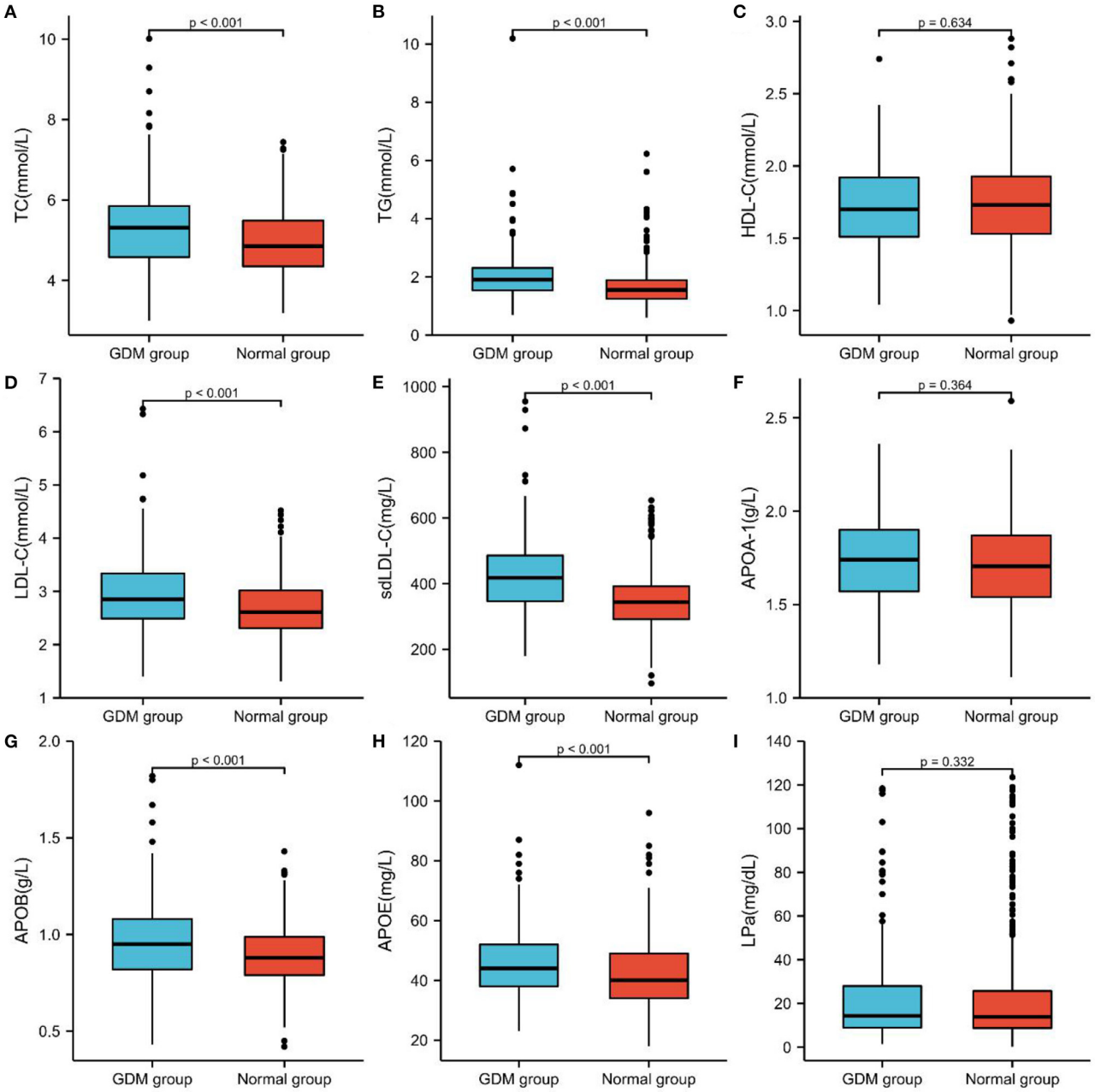

FIGURE 2 | Comparison of blood lipid and lipoprotein profiles of the two groups in pregnant women with GDM and non-GDM. **(A)** TC, **(B)** TG, **(C)** HDL-C, **(D)** LDL-C, **(E)** sd LDL-C, **(F)** APOA-1, **(G)** APOB, **(H)** APOE, **(I)** LPa.

points), APOB of 0.81 g/L (75 points), receives a total score of 200 points. The nomogram indicates that this pregnant woman may have a predictive probability of GDM of 0.81(**Figure 4**).

Discrimination, Calibration Evaluation and Internal Validation of GDM Risk Prediction Model

Model was evaluated using discrimination and calibration, and discrimination was assessed by calculating the area under the receiver operating characteristic (ROC) curve (AUC) result for the predicted probability. The AUC value of the model was 0.892 (95% CI: 0.858–0.927), indicating that the prediction model had a good degree of discrimination (**Figure 3O**). The Hosmer-Lemeshow test results showed that there was no statistical significance difference between the predicted risk value of the model and the actual observed value (χ^2 = 6.022, P = 0.645). The Calibration curve showed that the predicted probability of the model was in good agreement

TABLE 3 | Univariate logistic regression analysis results of predictors of GDM.

Indicators	*B* value	*SEM*	*Wald*	*P*-value	*OR*	95% *CI* lower	95% *CI* higher
Age	0.070	0.023	9.499	0.002	1.073	1.026	1.122
Pre-pregnancy BMI	0.459	0.047	95.923	0.000	1.583	1.444	1.736
FPG	2.176	0.301	52.342	0.000	8.814	4.888	15.894
PT	−0.569	0.183	9.614	0.002	0.566	0.395	0.811
INR	−6.424	2.035	9.970	0.002	0.002	0.000	0.087
APTT	−0.367	0.059	39.416	0.000	0.693	0.618	0.777
FIB	0.666	0.167	15.851	0.000	1.946	1.402	2.702
TT	−0.768	0.163	22.284	0.000	0.464	0.337	0.638
D-Dimer	0.468	0.233	4.057	0.044	1.597	1.013	2.520
TC	0.477	0.107	19.838	0.000	1.611	1.306	1.987
TG	0.764	0.140	29.878	0.000	2.147	1.633	2.824
LDL-C	0.890	0.165	29.220	0.000	2.434	1.763	3.360
sdLDL-C	0.007	0.001	49.810	0.000	1.007	1.005	1.009
APOB	2.366	0.539	19.253	0.000	10.656	3.703	30.661
APOE	0.033	0.008	17.433	0.000	1.034	1.018	1.050

TABLE 4 | Multivariate logistic regression analysis results of predictors of GDM.

Indicators	*B* value	*SEM*	*Wald*	*P*-value	*OR*	95% *CI* lower	95% *CI* higher
Pre-pregnancy BMI	0.401	0.054	54.778	0.000	1.494	1.343	1.662
FPG	1.596	0.384	17.289	0.000	4.934	2.325	10.471
APTT	−0.233	0.077	9.245	0.002	0.792	0.682	0.921
TT	−0.387	0.171	5.140	0.023	0.679	0.486	0.949
TG	0.553	0.190	8.439	0.004	1.739	1.197	2.526
LDL-C	1.814	0.699	6.731	0.009	6.136	1.558	24.161
sdLDL-C	0.010	0.003	12.967	0.000	1.010	1.005	1.016
APOB	−8.715	2.457	12.578	0.000	0.000	0.000	0.020

with the actual probability, as shown in **Figure 5**. Cross-validation, Jackknife validation (cross-validation) and bootstrap sampling method (repetitive sampling 1,000 times) were used to conduct internal validation on the model data, and the C-statistics were 0.884, 0.882, and 0.892, respectively. The results are stable in the validation method, indicating that the model has good predictive performance in the modeling population.

Pre-pregnancy BMI, FPG, APTT, TT,TG, LDL-C, sdLDL-C, and APOB Risk Assessment in Predicting GDM

We employed binary logistic regression analysis to assess the risk predictive value of pre-pregnancy BMI, FPG, APTT, TT, TG, LDL-C, sdLDL-C, and APOB levels in pregnant women with GDM. The cut-off value for each index was selected according to ROC curve. First, patients were split into two groups based on their pre-pregnancy BMI (21.84 kg/m^2), FPG (4.825 mmol/L), APTT (27.75s), TT (15.65s), TG (1.735 mmol/L), LDL-C (2.965 mmol/L), sdLDL-C (393.8 mg/L), and APOB(0.975 g/L). Compared with low pre-pregnancy BMI, the risk of GDM in pregnant women with high pre- pregnancy BMI was 12.441 (95% CI = 8.006–19.334, $p < 0.01$), and the adjusted OR was 12.45 (95% CI = 7.385–20.99); Similarly, compared with low FPG, the risk of GDM in pregnant women with high FPG was 3.732 (95% CI = 2.506–5.558, $p < 0.01$), and the adjusted OR was 2.984 (95% CI = 1.783–4.994); Compared with prolonged APTT, the risk of GDM in pregnant women with shortened APTT was 2.826 (95% CI = 1.886–4.233, $p < 0.01$), and the adjusted OR was 2.216 (95% CI = 1.319–3.723); Compared with prolonged TT, the risk of GDM in pregnant women with shortened TT was 2.431 (95% CI = 1.4642–3.599, $p < 0.01$), and the adjusted OR was 2.457 (95% CI = 1.468–4.113); Compared with low TG, the risk of GDM in pregnant women with high TG was 3.201 (95% CI = 12.158–4.747, $p < 0.01$), and the adjusted OR was 2.072 (95% CI = 1.223–3.508); Compared with low LDL-C, the risk of GDM in pregnant women with high LDL-C was 2.295 (95% CI = 1.551–3.396, $p < 0.01$), and the adjusted OR was 4.386 (95% CI = 2.081–9.243); Compared with low sdLDL-C, the risk of GDM in pregnant women with high sdLDL-C was 4.538 (95% CI = 3.038–6.778, $p < 0.01$), and the adjusted OR was 0.649 (95% CI = 0.284–1.482); Compared with low APOB, the risk of GDM in pregnant women with high APOB was 2.376 (95% CI = 1.604–3.519, $p < 0.01$), and the adjusted OR was 1.206 (95% CI = 0.518–2.804) ($P < 0.05$, **Figures 6**, **7**).

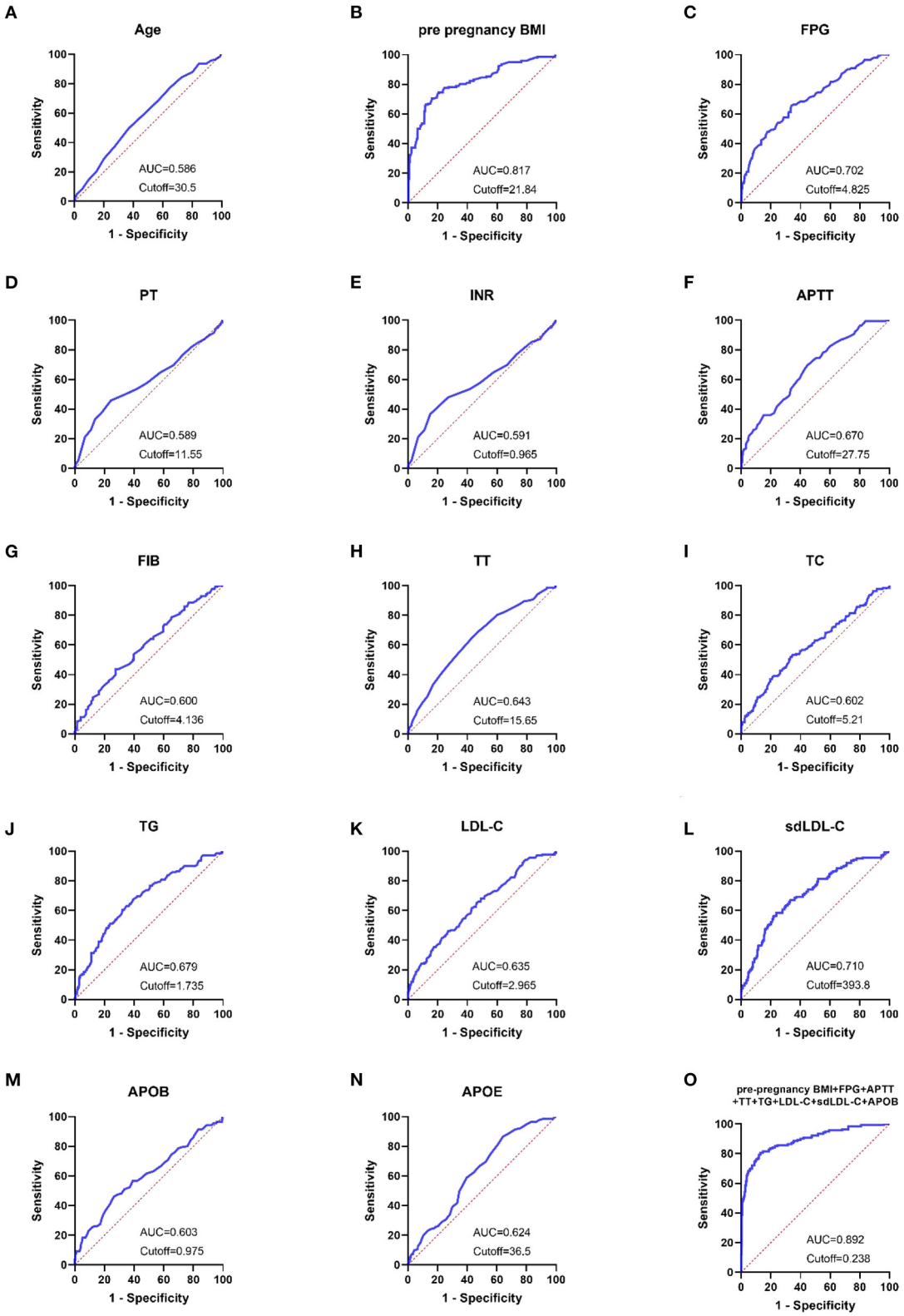

FIGURE 3 | (A–O) ROC curves showed the diagnostic value of laboratory-related indicators for pregnant women with GDM.

TABLE 5 | Diagnostic performance of laboratory-related indicators in pregnant women with GDM.

Indicators	Youden index	Cutoff	AUC	AUC 95% CI	Sensitivity	Specificity	PPV (%)	NPV (%)
Age	0.1277	30.5	0.586	0.5332–0.6394	49.65	63.12	30.19	79.61
Pre-pregnancy BMI	0.5436	21.84	0.817	0.7734–0.8604	70.42	83.94	58.48	89.83
FPG	0.3178	4.825	0.702	0.6510–0.7524	65.49	66.29	38.42	85.67
PT	0.2151	11.55	0.589	0.5300–0.6473	45.77	75.74	37.73	81.30
INR	0.2165	0.965	0.591	0.5322–0.6496	36.62	85.03	44.00	80.68
APTT	0.2482	27.75	0.670	0.6195–0.7187	69.72	55.1	33.28	85.00
FIB	0.16	4.136	0.600	0.5464–0.6533	43.66	72.34	33.64	79.99
TT	0.2171	15.65	0.643	0.5914–0.6954	64.79	56.92	32.57	83.43
TC	0.1857	5.21	0.602	0.5469–0.6574	53.19	65.38	33.04	81.30
TG	0.2828	1.735	0.679	0.6280–0.7299	63.12	65.16	36.78	84.62
LDL-C	0.1895	2.965	0.635	0.5823–0.6877	46.1	72.85	35.29	80.80
sdLDL-C	0.3481	393.8	0.710	0.6605–0.7594	58.57	76.24	44.19	85.14
APOB	0.1963	0.975	0.603	0.5472–0.6592	46.1	73.53	35.87	80.94
APOE	0.2249	36.5	0.624	0.5747–0.6736	86.52	35.97	30.26	89.26
Combined test	0.6756	0.238	0.892	0.8581–0.9268	80.71	86.85	66.43	93.34

TABLE 6 | Comparison of AUC areas for pre pregnancy BMI, FPG, APTT, TT, TG, LDL-C, sdLDL-C, APOB and combined test in GDM and non-GDM group.

Detection indicators	*Z* value	*P*-value
Combined test and pre-pregnancy BMI	3.950	0.0001
Combined test and FPG	7.940	<0.0001
Combined test and APTT	8.749	<0.0001
Combined test and TT	8.876	<0.0001
Combined test and TG	7.440	<0.0001
Combined test and LDL-C	8.761	<0.0001
Combined test and sdLDL-C	6.762	<0.0001
Combined test and APOB	8.972	<0.0001

DISCUSSION

As a pregnancy complication, GDM is associated with glucose intolerance and insulin resistance (13). GDM is identified when an OGTT test is conducted at 24–28 weeks of pregnancy in women who do not have a history of GDM or diabetes mellitus before pregnancy. The blood glucose metabolism of most GDM patients will recover to normal after delivery, however, some GDM patients may acquire type 2 diabetes as a result of their condition (T2DM) (14). In a short time, gestational diabetes mellitus (GDM) might raise the risk of preeclampsia, polyhydramnios, preterm labor, and ketoacidosis in expecting mothers (15). Diabetes, cardiovascular disease, and metabolic syndrome are long-term consequences for the mother (16). As a result, neonates with GDM have a higher risk of problems, such as birth damage, respiratory distress syndrome, hyperbilirubinemia, and hypoglycemia. Fetal hyperinsulinemia, and macrosomia may result from inadequate blood glucose management in pregnant women with GDM (15). GDM has long-term negative impacts on children, including an increased incidence of Type 2 diabetes and obesity (17).

Recent years have seen an increase in the number of research attempting to develop risk prediction models for gestational diabetes mellitus (GDM). Predicting GDM based on clinical and biological signs is the subject of many investigations, and various mathematical models have been developed (18–20). However, the majority of GDM risk prediction models described in the literature relied only on the fundamental characteristics of pregnant women, such as age, nationality, and pre-pregnancy body mass index (Pre-pregnancy BMI). Most studies that were described were also retrospective, which limits the clinical value of the findings. Pregnant women's age, pre-pregnancy BMI, and various coagulation and blood glucose and blood lipid indicators in early pregnancy were integrated into our research to predict the likelihood of GDM and identify the associated risk factors. Increased pre-pregnancy body mass index (BMI), FPG, TG, LDL-C, sdLDL-C, APOB, and shorter APTT, TT was observed to be associated with an increased risk of gestational diabetes. GDM risk prediction model was built using the receiver operating characteristic curve (ROC) as a measure of model efficacy. As a consequence, this model has a high diagnostic value. It is possible to predict gestational diabetes (GDM) based on the combination of these clinical signs.

Endothelial damage caused by high blood glucose activates the internal coagulation system in pregnant women with GDM (21, 22), and some studies have also shown that the level of coagulation factor XII in pregnant women with GDM was significantly higher than healthy pregnant women (23). The reason might be that endothelial damage caused by high blood glucose activates the internal coagulation system in pregnant women with GDM. We also found that among pregnant women with GDM, the PT and APTT were shorter and the FPG was higher in the first trimester, suggesting that the variations in blood coagulation and blood glucose between the two groups did not begin in the second trimester. First-trimester pregnancy blood glucose and

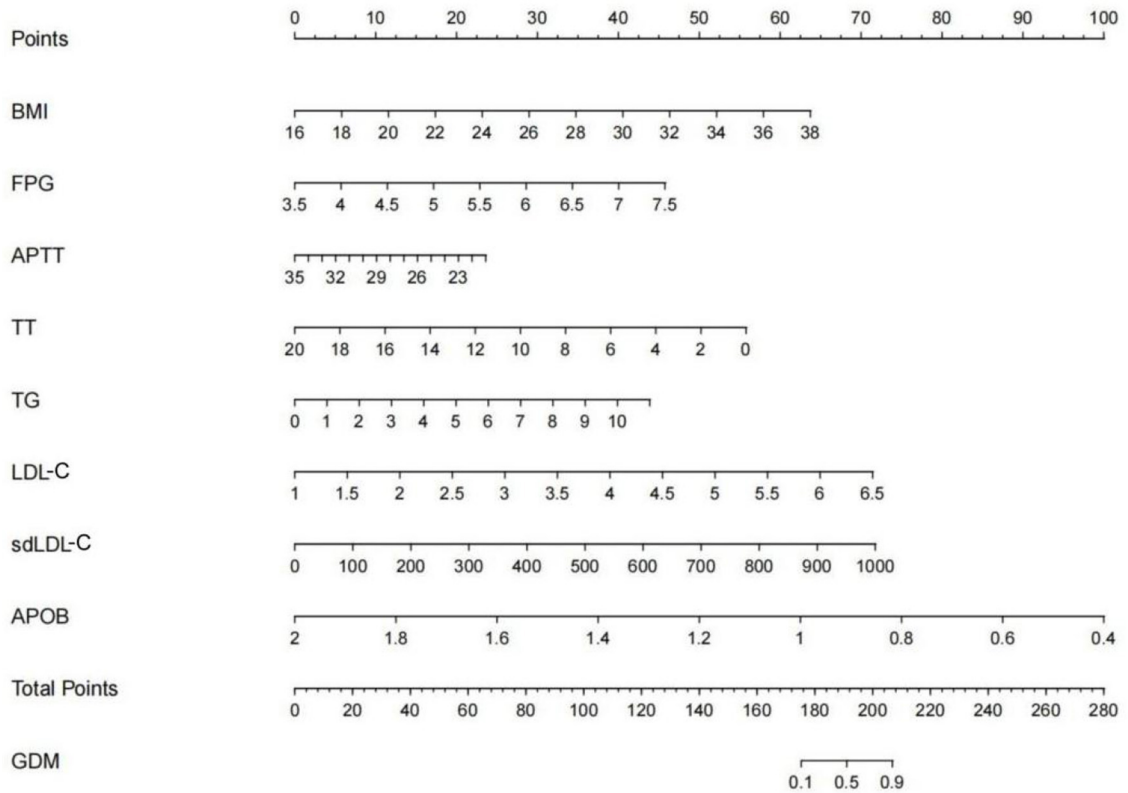

FIGURE 4 | The nomogram of predictive model for GDM. Patient prognostic values were located on the axis of each variable. A vertical line was then drawn from that value to the top points scale to determine the number of points for that particular variable. The sum of these numbers was located on the total score axis, and a line was drawn at a 90° angle downward to the GDM risk axis to determine the risk of GDM.

coagulation function monitoring may be useful in predicting and diagnosing GDM.

Pregnant women with elevated lipid levels have a higher chance of developing GDM. When it comes to TC, TG, and LDL-C, pregnant women with GDM had higher levels than pregnant women without the condition (24). But the findings of the meta-analysis suggested that in addition to a rise in TG, cholesterol variations across various groups were not consistent. Insulin resistance was caused by hypertriglyceridemia, not hypercholesterolemia (25). This research demonstrated that in the early stages of pregnancy, the GDM group had substantially higher levels of TC, TG, LDL-C, sdLDL-C, APOB, and APOE than the control group. HDL-C, APOA-1, and LPa levels were not significantly different between the two groups. A substantial difference in blood lipid distribution between GDM and non-GDM groups was found in this study. Early in pregnancy, GDM pregnant women suffer from more severe dyslipidemia and insulin resistance. We studied the correlation between early pregnancy blood lipid profile and GDM to discover whether dyslipidemia in early pregnancy had clinical prognostic implications. We found that when TG >1.735 mmol/L, LDL-C >2.965 mmol/L, sdLDL-C >393.8 mg/L, APOB >0.975 g/L, the incidence of GDM in pregnant women rose by 3.201, 2.295, 4.538, and 2.376 times, respectively. After adjustment OR the incidence of GDM in pregnant women rose by 2.072, 0.649, 4.386, 1.206 times, respectively. In the first trimester, TG, LDL-C, sdLDL-C and APOB may be excellent risk predictors of GDM.

By analyzing numerous coagulation, blood glucose, and blood lipid indicators in the early stages of pregnancy, it is possible to accurately predict the risk of GDM. This method and model of multiple indicators improves the sensitivity and specificity of prediction, helps to identify GDM early, and promotes early prevention, intervention, and treatment of GDM, thus improving pregnancy outcomes and reducing the risk of long-term metabolic diseases in pregnant women and their infants. However, there are several limitations to our research. First, it should be noted that the model needs external validation in an independent study. Second, this study is a single-center study with a relatively small sample size, which cannot yet represent the general significance in a large-scale clinical population. In addition, some clinical indicators found in the latest research were not included. therefore, larger sample sizes and joint survey studies from

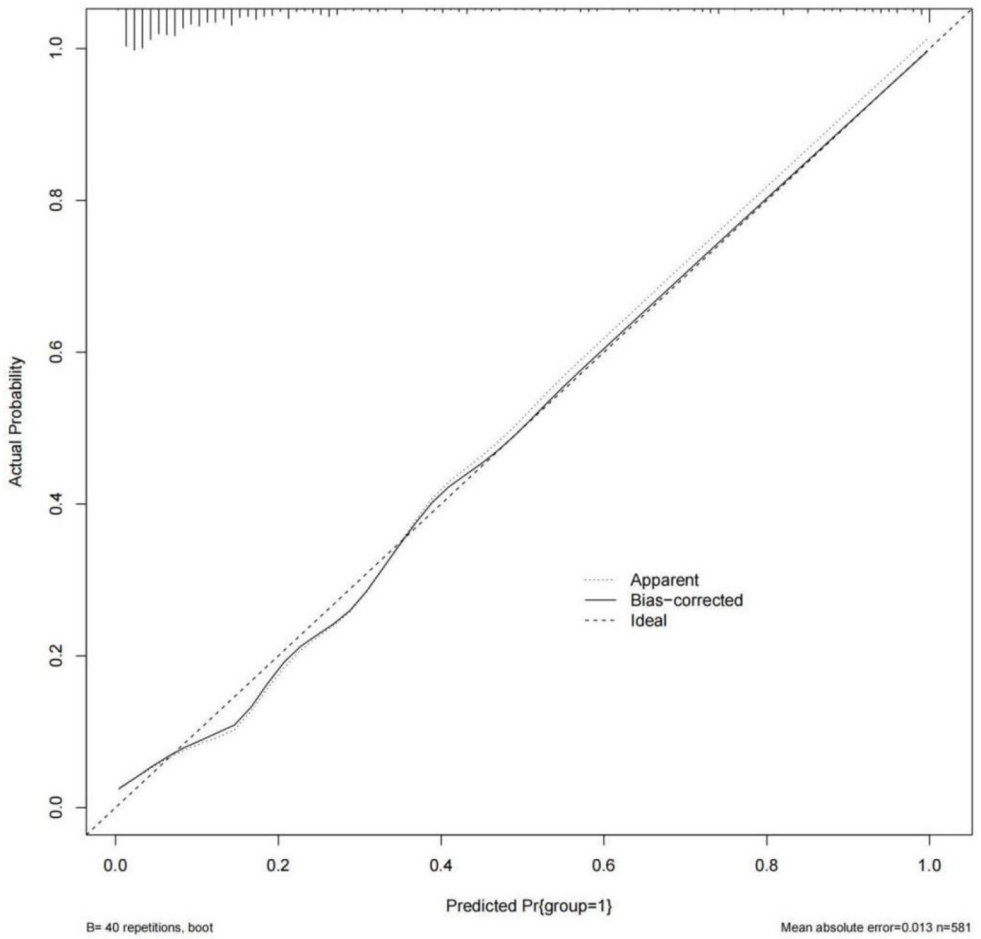

FIGURE 5 | Calibration curve of GDM observation probability and prediction probability.

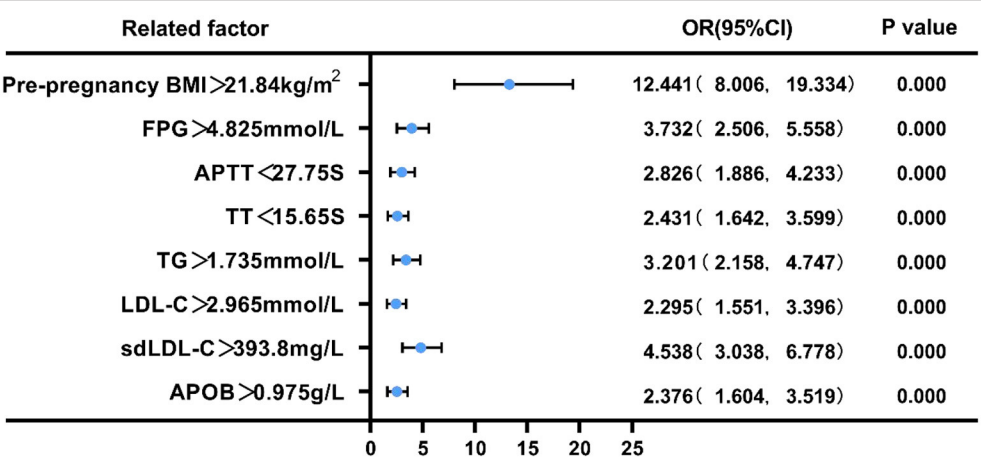

FIGURE 6 | Forest plot of the univariate logistic regression analysis of pre-pregnancy BMI, FPG, APTT, TT,TG, LDL-C, sdLDL-C, APOB in pregnant women with GDM.

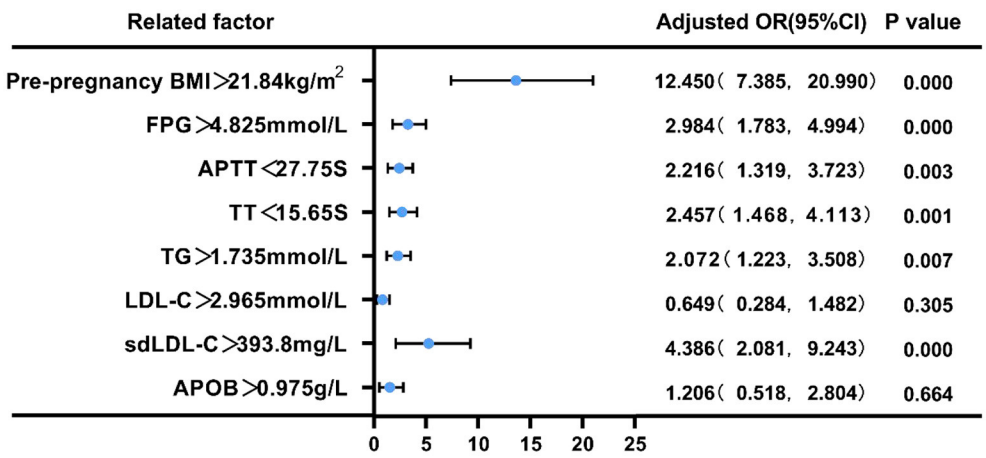

FIGURE 7 | Forest plot of the multivariate logistic regression analysis of pre-pregnancy BMI, FPG, APTT, TT,TG, LDL-C, sdLDL-C, APOB in pregnant women with GDM.

multiple centers may provide better clinical research value in the future.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai Sixth People's Hospital (Approval No. 2016-003). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YZ, WH, WQ, and YC contributed to study concept and design, acquisition of the data, analysis and interpretation of the data, and drafting of the manuscript. WQ and YC contributed to statistical analysis and contributed to funding acquisition. YZ and JX contributed to sample collections. WH and HH contributed to study supervision and critical revision of the manuscript. YC contributed to project administration. All authors have read and agreed to the published version of the manuscript.

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Annual Body Mass Index Gain and Risk of Gestational Diabetes Mellitus in a Subsequent Pregnancy

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Introduction: Weight change during the interpregnancy is related to gestational diabetes mellitus (GDM) in the subsequent pregnancy. In interpregnancy care/counseling, the timeframe for goal setting is important, while the timing of the next conception is unpredictable and preventing age-related body weight gain is difficult. This study aimed to investigate the association between annual weight gain during the interpregnancy, which provide clearer timeframe, and GDM in subsequent pregnancies.

Methods: This multicenter retrospective study was conducted by collecting data on two pregnancies of the same women in 2009–2019. The association between annual BMI gain and GDM during the subsequent pregnancy was examined.

Results: This study included 1,640 pregnant women. A history of GDM [adjusted odds ratio (aOR), 26.22; 95% confidence interval (CI), 14.93–46.07] and annual BMI gain (aOR, 1.48; 95% CI, 1.22–1.81) were related to GDM during the subsequent pregnancy. In the women with a pre-pregnant BMI of <25.0 kg/m^2 and without GDM during the index pregnancy, an annual BMI gain of ≥0.6 kg/m^2/year during the interpregnancy were associated with GDM in subsequent pregnancies; however, in the other subgroups, it was not associated with GDM in subsequent pregnancies.

Conclusions: For women with a pre-pregnant BMI of <25.0 kg/m^2 and without GDM during the index pregnancy, maintaining an annual BMI gain of <0.6 kg/m^2/year may prevent GDM during the subsequent pregnancy.

Keywords: GDM, BMI gain, interpregnancy care, previous history, recurrence

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as a diabetes diagnosed in the 2nd or 3rd trimester of pregnancy that was not clearly overt diabetes prior to gestation (1). The incidence is reported to be 12-18% of all pregnancies (2), and the recurrence rate of GDM is as high as 30–70% in a subsequent pregnancy (3–5). Women with a history of GDM have an increased risk of type 2 diabetes mellitus (T2DM) (6–9), metabolic syndrome (10, 11), and cardiovascular disease later in life (12–14). Women with recurrent GDM are reported to have a higher risk of developing T2DM than those with a single event (15). In addition to adverse maternal effects, children of women with GDM are at an increased risk of abnormal glucose metabolism and adiposity (16–18), as well as attention-deficit/hyperactivity disorder (19, 20). Thus, there is an urgent need to establish strategies to prevent GDM; however, there are currently no concrete recommendations for the prevention of GDM.

Interpregnancy care/counseling is well known for its beneficial role in the women's health and subsequent pregnancy outcomes (21–23). In addition to a history of GDM, being overweight/obese (body mass index [BMI] ≥25.0 kg/m^2) is a risk factor for developing GDM in a subsequent pregnancy (3, 24–27). Evidence suggests that BMI changes between the index and subsequent pregnancy is also a risk factor for GDM during the subsequent pregnancy (3, 28). Previous meta-analyses and systematic reviews have suggested that interpregnancy BMI gain is associated with higher risk of GDM during the subsequent pregnancies (29–31). The overall interpregnancy BMI gain is certainly a valuable indicator for detecting high-risk for GDM at the first visit for subsequent pregnancy; however, a total interpregnancy BMI change is not a suitable indicator for the prevention of GDM in a subsequent pregnancy. First reason why the total BMI gain is not suitable for prevention is the difficulty in preventing age-related weight gain, as reported previously (32). Recent longitudinal studies have reported that the mean age-related annual weight gain in women younger than 50 years is approximately 0.5 kg/year (33–35). For Japanese women of average height (157.9 cm), the implied age-related annual BMI gain is 0.2 kg/m^2/year. Second reason is most women do not plan and expect when they will have another baby just after childbirth in the index pregnancy. Considering the difficulties in compensating for this age-related weight gain and unpredictability of the next conception, goal-setting based on total BMI changes during the interpregnancy period can be ambiguous.

One of the most commonly recommended frameworks for goal-setting is the SMART goal model, which is an acronym for Specific, Measurable, Attainable, Relevant, and Time-related (36). While formulating SMART goals, it is important to assess attainability and the timeframes. The concept of "annual BMI change" can provide a more realistic goal-setting process and clearer timeframes. It has already been reported in many medical fields, including oncology (37, 38), diabetes mellitus (39, 40), obstructive sleep apnea (41), and cardiovascular disease (42). Recently, we have also reported that it would be helpful in the interpregnancy care/counseling for hypertensive disorders of pregnancy (HDP) (43); however, no reports have focused on the association between annual BMI changes and GDM.

Thus, this study aimed to evaluate whether an annual BMI gain of ≥0.2 kg/m^2/year (natural gain) during the interpregnancy period was associated with the risk of GDM during the subsequent pregnancy.

MATERIALS AND METHODS

Study Population

This multicenter retrospective study used electronic medical record data of pregnant women aged ≥15 years who delivered at two tertiary centers in Aichi Prefecture (Nagoya University Hospital and TOYOTA Memorial Hospital) or 12 private maternity facilities (Kishokai Medical Corporation located in Aichi and Gifu Prefectures) from 2009 to 2019. Women who had medical records available for both the index and subsequent pregnancies were included. We assessed the medical records directly and ascertained the data, including laboratory tests, if necessary. The exclusion criteria were as follows: pre-pregnancy diabetes mellitus (overt DM), multiple pregnancies, stillbirth before 22 weeks of gestation, and missing data on maternal pre-pregnancy BMI and GDM status (**Figure 1**). Women who developed GDM in a subsequent pregnancy were allocated into the GDM group, while those who did not were allocated into the non-GDM group.

Definitions of the Variables

Women with pre-pregnancy DM, a hemoglobin $A1_C$ (HbA1c) level of ≥6.5% (48 mmol/mol), or a fasting plasma glucose level of ≥126 mg/dL during pregnancy were defined as having overt DM. Based on the clinical recommendation by the Japan Society of Obstetrics and Gynecology (44, 45), GDM was diagnosed based on a two-step approach. First, the casual blood glucose test or a non-fasting 50-g blood glucose challenge test was performed between 24 and 28 weeks of gestation with a cutoff value of 100 mg/dL or a cutoff value of 140 mg/dL, respectively. Second, a 75g oral glucose tolerance test (OGTT) was performed for the women with a positive screening test. Third, GDM was diagnosed when any of the following plasma glucose values were met (1): the 75g OGTT result was a fasting plasma glucose level of ≥92 mg/dL or the 1-h and 2-h plasma glucose levels were ≥180 mg/dL or ≥153 mg/dL, respectively. Assisted reproductive technology (ART) was defined as conception after *in vitro* fertilization or intracytoplasmic sperm injection. Gestational age (GA) was routinely estimated by expected date of delivery (EDD) determined based on the last menstruation cycle and the measurement of the crown–rump length by ultrasonography. In ART pregnancies, EDD was determined using the age of the embryo and the date of transfer. Light-for-date and heavy-for-date were diagnosed using the Japanese standards for birth weight according to the pregnancy durations (≥90th percentile and <10th percentile, respectively) (46, 47). Macrosomia is defined as newborns whose weighs exceed 4,000 g regardless of his or her gestational age (47).

We used the self-reported maternal pre-pregnancy body weight and height obtained during routine practice to calculate

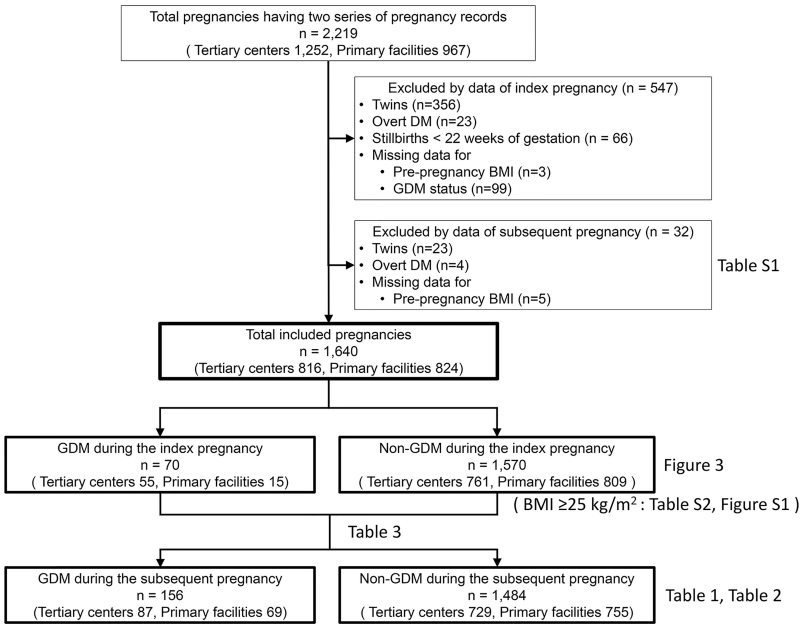

FIGURE 1 | Flow chart of the study participants. Clinical data of 2,219 patients who delivered at two tertiary care centers and 12 primary maternity care units and had available medical records on the index and subsequent pregnancies. A total of 1,640 patients were eligible for this study after excluding 547 and 32 women based on the index and subsequent pregnancy status, respectively. DM, diabetes mellitus; BMI, body mass index; GDM, gestational diabetes mellitus.

the BMI (kg/m^2) (weight in kg divided by square of the height in m^2). The calculated BMIs were categorized as <25.0 or ≥25.0 kg/m^2 according to the World Health Organization's classifications and previous study (28, 48). As shown in **Figure 2**, we defined interpregnancy BMI change (ΔBMI) as a change in pre-pregnancy BMI from the index pregnancy to the subsequent pregnancy, as previously reported (28). The pregnancy interval was defined as the interval between the two gestations, which is equal to the interval from EDD of the index pregnancy (EDD^{index}) to that of the subsequent pregnancy (EDD^{subsequent}): (EDD^{subsequent} – 280 days) – (EDD^{index} – 280 days). The annual BMI change was calculated as follows: ΔBMI/pregnancy interval.

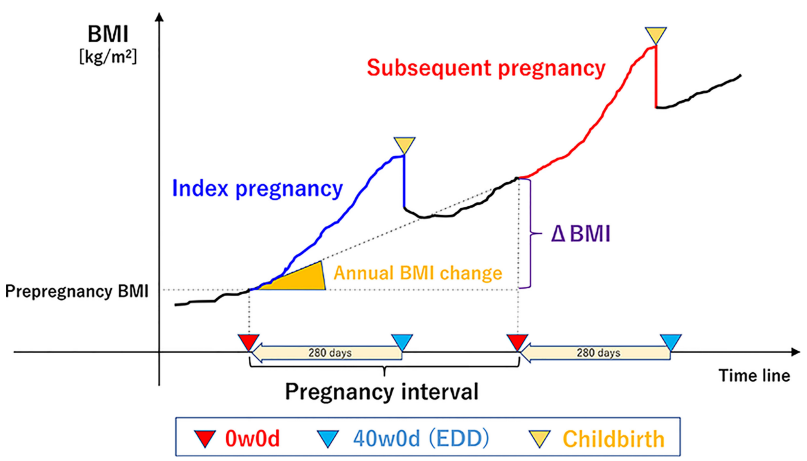

FIGURE 2 | Overview of the definitions of terms. (the reference 43, Tano S et al. Sci Rep,11(1), 22519,2021, Springer Nature). We defined inter-pregnancy BMI change (ΔBMI) as a pre-pregnancy BMI change between the index pregnancy and the subsequent pregnancy. The pregnancy interval was defined as the interval from the EDD of the index pregnancy to that of the subsequent pregnancy, which is equal to the interval between the two gestations. The annual BMI change was calculated as follows: ΔBMI/pregnancy interval. BMI, body mass index; 0w0d, $0^{0/7}$ weeks of gestation; 40w0d, $40^{0/7}$ weeks of gestation; EDD, expected date of delivery.

The annual BMI change during the interpregnancy period was categorized into 5 groups: <0.0 kg/m^2/year [weight loss], ≥0.0–<0.2 kg/m^2/year [natural gain, reference], ≥0.2–<0.6 kg/m^2/year, ≥0.6–<1.0 kg/m^2/year, and ≥1.0 kg/m^2/year (43). A gain of 0.2 kg/m^2/year has been considered a natural annual BMI change (34, 35); gains of 0.6 and 1.0 kg/m^2/year are equivalent to increments of approximately 1.5 and 2.5 kg/year in the weights of women of average height (157.9 cm), respectively. Gestational weight gain was defined as the change between pre-pregnancy body weight and that before delivery.

Statistical Analysis

The clinical characteristics and parameters (**Table 1**) of the GDM and non-GDM groups were compared using the Fisher's exact test, χ^2 test, Student's *t*-test, Welch's *t*-test, or Mann–Whitney U test as appropriate. Crude and adjusted odds ratios (aORs) for GDM during the subsequent pregnancy were calculated using univariable and multivariable logistic regression analyses. Variables used in the univariable and multivariable analyses were selected based on previous studies (26–28, 49–52): maternal age of ≥35 years, pre-pregnancy BMI of ≥25.0 kg/m^2, the presence of GDM, macrosomia during the index pregnancy, and a parity of ≥2 in the subsequent pregnancy. In addition, insulin use during the index pregnancy was added as a variable for the subgroup analysis of GDM recurrence (26). The annual BMI gains were classified into five categories based on their distributions, as mentioned above, and a multivariable analysis was performed to determine how the aOR changed with specific annual BMI changes.

Data are presented as means ± standard deviations or medians [p25, p75] for continuous variables and numbers (percentages) for categorical variables. Statistical significance was set at a *p*-value of <0.05. The statistical analyses were conducted using SPSS version 28.0 for Windows software (SPSS, Inc., Chicago, IL, USA).

RESULTS

Participants

A total of 2,219 pregnant women (tertiary centers, n=1,252; primary maternity care units, n=967) were included. Among them, 579 were excluded because of multiple pregnancies (n=379), overt DM (n=27), stillbirth before 22 weeks of gestation (n=66), and missing data on the pre-pregnancy BMI (n=8) and GDM status (n=99) during the index and subsequent pregnancy (**Figure 1**). The remaining 1,640 pregnant women (tertiary centers, n=816; primary maternity care units, n=824) were finally included.

Four women who developed GDM during the index pregnancy developed postpartum DM, and their subsequent pregnancies were treated as overt DM. They were excluded from the study population; their clinical data are listed in **Supplementary Table 1**. Two women needed insulin use during their index pregnancies (cases 2 and 3). One patient did not need insulin for GDM, and her pre-pregnancy BMI was within the normal range (case 1).

Comparison of Clinical Parameters Between the GDM and Non-GDM Groups

GDM occurred in 70/1,640 women (4.3%) during the index pregnancy and 156/1,640 women (9.5%) during the subsequent pregnancy; 55.8% of the patients with GDM during the subsequent pregnancy were treated at tertiary centers (**Table 1**).

Regarding the index pregnancy characteristics, the following factors were significantly different between the GDM during the subsequent pregnancy and non-GDM during the subsequent pregnancy groups: maternal age (31.9 ± 4.4 *vs.* 30.5 ± 4.8 years, respectively; $p<0.001$), pre-pregnancy BMI (23.0 ± 5.1 *vs.* 20.7 ± 3.1 kg/m^2, respectively; $p<0.001$), placental weight (593.0 ± 111.7 *vs.* 567.5 ± 114.6 g, respectively; $p=0.008$), incidence of ART conception (13.5% *vs.* 8.1%, respectively; $p=0.022$), hypertensive disorders of pregnancy (HDP) (22.4% *vs.* 11.1%, respectively; $p<0.001$), GDM (30.8% *vs.* 1.5%, respectively; $p<0.001$), having a heavy-for-date infant (19.2% *vs.* 9.8%, respectively; $p<0.001$), and macrosomia (3.2% *vs.* 0.9%, respectively; $p=0.012$). Additionally, the proportion of patients with GDM who used insulin during the index pregnancy was also higher in the GDM during the subsequent pregnancy group than in the non-GDM group (39.6% *vs.* 9.1%, respectively; $p=0.010$).

The median pregnancy interval did not differ significantly between the GDM and non-GDM groups (both 2.1 years, $p=0.497$). In contrast, the ΔBMI and annual BMI change were significantly higher in the GDM group than in the non-GDM group (0.86 ± 1.73 *vs.* 0.40 ± 1.35 kg/m^2, $p=0.001$; and 0.44 ± 1.04 *vs.* 0.19 ± 0.76 kg/m^2/year, $p=0.004$, respectively).

Risk Factors for GDM During the Subsequent Pregnancy

According to the multivariable analysis (**Table 2**), three variables (pre-pregnancy BMI of ≥25.0 kg/m^2, GDM during the index pregnancy, and an annual BMI change during the pregnancy interval) were significantly associated with GDM during the subsequent pregnancy after adjusting for known risk factors. GDM during the index pregnancy showed the highest aOR for GDM during the subsequent pregnancy [aOR, 26.22; 95% confidence interval (CI), 14.93–46.07]. Therefore, further analysis was performed by stratifying by the presence or absence of GDM during the index pregnancy.

The aOR for GDM recurrence during the subsequent pregnancy was calculated in patients who had GDM during the index pregnancy (n=70) (**Table 3**, subgroup 1). In this subgroup, the recurrence rate of GDM was 68.6% (48/70). The annual BMI change and pregnancy interval were not significantly associated with GDM recurrence (aOR, 1.16; 95% CI, 0.75–1.79; and aOR, 1.10; 95% CI, 0.60–2.01; respectively); however, a pre-pregnancy BMI of ≥25.0 kg/m^2 and insulin use during the index pregnancy were significant (aOR, 5.83; 95% CI, 1.33–25.52; and aOR, 6.98; 95% CI, 1.38–35.38; respectively).

TABLE 1 | Baseline characteristics and perinatal outcomes.

	GDM during the subsequent pregnancy n = 156	Non-GDM during the subsequent pregnancy n = 1,484	p-value
Index pregnancy			
Tertiary center	87 (55.8)	729 (49.1)	0.114
Maternal age, years old	31.9 ± 4.4	30.5 ± 4.8	<0.001*
Maternal age ≥ 35 years	34 (21.8)	273 (18.4)	0.301
Pre-pregnancy BMI, kg/m^2	23.0 ± 5.1	20.7 ± 3.1	<0.001*
Pre-pregnancy BMI ≥ 25.0 kg/m^2	37 (23.7)	102 (6.9)	<0.001*
Smokers	2 (1.3)	15 (1.0)	0.354
Hypertension	4 (2.6)	17 (1.1)	0.137
Hyperthyroidism	1 (0.6)	13 (0.9)	1.000
Hypothyroidism	6 (3.8)	25 (1.7)	0.124
Primiparity	118 (75.6)	1,184 (79.8)	0.224
ART	21 (13.5)	120 (8.1)	0.022*
Gestational body weight gain, kg	10.7 ± 4.2	11.0 ± 3.8	0.387
HDP	35 (22.4)	164 (11.1)	<0.001*
GDM	48 (30.8)	22 (1.5)	<0.001*
Insulin	19/48 (39.6)	2/22 (9.1)	0.010*
Stillbirth ≥ 22 weeks	1 (0.6)	7 (0.5)	0.568
GA at delivery, weeks	39.3 ± 2.0	39.1 ± 2.1	0.333
Preterm birth (<37 weeks)	9 (5.8)	122 (8.2)	0.283
Cesarean section	37 (23.7)	367 (24.7)	0.780
Neonatal sex, male	85 (54.5)	806 (54.3)	0.967
Neonatal height, cm	49.7 ± 3.4	49.3 ± 3.0	0.101
Birthweight, g	3,059 ± 509	2,956 ± 506	0.016*
Heavy for date infant	30 (19.2)	146 (9.8)	<0.001*
Light for date infant	10 (6.4)	141 (9.5)	0.204
Macrosomia (Birthweight ≥ 4 kg)	5 (3.2)	14 (0.9)	0.012*
Placental weight, g	593.0 ± 111.7	567.5 ± 114.6	0.008*
Pregnancy interval			
Pregnancy interval, years, median [p25, p75]	2.1 [1.8, 2.7]	2.1 [1.7, 2.5]	0.497
ΔBMI, kg/m^2	0.86 ± 1.73	0.40 ± 1.35	0.001*
Anuual BMI change, kg/m^2/year	0.44 ± 1.04	0.19 ± 0.76	0.004*
Annual BMI change			
Weight loss (< 0 kg/m^2/year)	42 (26.9)	441 (29.7)	<0.001*
0 to < 0.2 kg/m^2/year	21 (13.5)	388 (26.1)	
0.2 to < 0.6 kg/m^2/year	41 (26.3)	375 (25.3)	
0.6 to < 1.0 kg/m^2/year	24 (15.4)	153 (10.3)	
≥1.0 kg/m^2/year	28 (17.9)	127 (8.6)	
Subsequent pregnancy			
Maternal age, years old	34.3 ± 3.6	32.7 ± 5.0	<0.001*
Pre-pregnancy BMI, kg/m^2	23.8 ± 5.0	21.1 ± 3.3	<0.001*
Pre-pregnancy BMI ≥ 25.0 kg/m^2	50 (32.1)	138 (9.3)	<0.001*
High parity (Parity ≥ 2)	38 (24.4)	327 (22.0)	0.507
ART	19 (12.2)	120 (8.1)	0.093
Gestational body weight gain, kg	8.5 ± 3.9	10.3 ± 3.6	<0.001*
HDP	23 (14.7)	112 (7.5)	0.002*
GDM	156 (100)	0 (0.0)	–
Insulin	30/156 (19.2)	–	–
Stillbirth ≥ 22 weeks	0 (0.0)	1 (0.1)	1.000
GA at delivery, weeks	39.0 ± 1.5	39.0 ± 1.6	0.879
Preterm birth (<37 weeks)	9 (5.8)	77 (5.2)	0.757
Cesarean section	44 (28.2)	354 (23.9)	0.228
Neonatal sex, male	86 (55.1)	756 (50.9)	0.398
Neonatal height, cm	49.9 ± 2.2	49.7 ± 2.3	0.167
Birthweight, g	3,135 ± 482	3,032 ± 429	0.011*
Heavy for date infant	29 (18.6)	154 (10.4)	0.004*
Light for date infant	5 (3.2)	56 (3.8)	0.646
Macrosomia (Birthweight ≥ 4 kg)	3 (1.9)	16 (1.1)	0.416
Placental weight, g	607.7 ± 113.8	578.4 ± 109.7	0.002*

*GDM, gestational diabetes mellitus; BMI, body mass index; DM, diabetes mellitus; ART, assisted reproductive technology; GA, gestational age; HDP, hypertensive disorders of pregnancy. Data are presented as means ± standard deviation or median [p25, p75] for continuous variables and n (%) for discrete variables. *Statistically significant.*

In the subgroup of patients without a history of GDM during the index pregnancy (n=1,570) (**Table 3**, subgroup 2), 108 women (6.9%) developed GDM during the subsequent pregnancy. The annual BMI change was associated with GDM during the subsequent pregnancy (aOR, 1.57; 95% CI, 1.27–1.95; **Table 3**), and a pre-pregnancy BMI of ≥25.0 kg/m^2 during the index pregnancy was also associated with GDM during the subsequent pregnancy (aOR, 2.28; 95% CI, 1.28–4.04; **Table 3**). In this subgroup, the aORs for GDM during the subsequent pregnancy were calculated using the five categories of annual BMI changes, with the reference category being 0.0–0.2 kg/m^2/year (**Figure 3**). Among women with a pre-pregnancy BMI of <25.0 kg/m^2 during the index pregnancy, those with BMI gains of ≥0.6–<1.0 units/year and ≥1.0 kg/m^2/year had a 2.82

TABLE 2 | Univariable and multivariable logistic regression analysis of variables potentially associated with GDM during the subsequent pregnancy.

	n/N (%)	Crude OR	95%CI	p-value	Adjusted OR	95%CI	p-value
Maternal age ≥ 35 years†	34/307 (11.1)	1.24	(0.83-1.85)	0.301	1.12	(0.70-1.78)	0.643
Pre-pregnancy BMI ≥ 25.0†	37/139 (26.6)	4.21	(2.76-6.41)	<0.001*	2.65	(1.61-4.36)	<0.001*
GDM†	48/70 (68.6)	29.54	(17.19-50.74)	<0.001*	26.22	(14.93-46.07)	<0.001*
Macrosomia†	5/19 (26.3)	3.48	(1.24-9.79)	0.018*	2.08	(0.60-7.22)	0.249
Pregnancy interval, years	–	1.13	(0.96-1.33)	0.131	1.10	(0.92-1.32)	0.276
Anuual BMI change, kg/m^2/year	–	1.42	(1.18-1.71)	<0.001*	1.48	(1.22-1.81)	<0.001*
High parity (Parity ≥ 2)	38/365 (10.4)	1.14	(0.78-1.68)	0.507	1.18	(0.77-1.81)	0.459

n/N: The number of GDM events during the subsequent pregnancy/the number of patients for each variables; OR, odds ratio; CI, confidence interval; BMI, body mass index; GDM, gestational diabetes mellitus.

†*Variables during the index pregnancy. *Statistically significant.*

TABLE 3 | Subgroup analysis: Univariable and multivariable logistic regression analysis of factors potentially associated with GDM during the subsequent pregnancy.

	Subgroup1: GDM during the index pregnancy n = 70								Subgroup2: Non-GDM during the index pregnancy n = 1,570							
	N (%)	n/N (%)	cOR	95%CI	p-value	aOR	95%CI	p-value	N (%)	n/N (%)	cOR	95%CI	p-value	aOR	95%CI	p-value
Maternal age ≥ 35 years†	17 (24.3)	14/17 (82.4)	2.61	(0.66-10.24)	0.170	1.86	(0.41-8.41)	0.423	290 (18.5)	20/290 (6.9)	1.00	(0.61-1.66)	0.990	1.00	(0.59-1.67)	0.990
Pre-pregnancy BMI ≥ 25.0†	23 (32.9)	20/23 (87.0)	4.52	(1.18-17.38)	0.028*	5.83	(1.33-25.52)	0.019*	116 (7.4)	17/116 (14.7)	2.57	(1.47-4.49)	<0.001*	2.28	(1.28-4.04)	0.005*
Insulin use†	21 (30.0)	19/21 (90.5)	6.55	(1.37-31.32)	0.019*	6.98	(1.38-35.38)	0.019*	0 (0.0)	–	–	–	–	–	–	–
Macrosomia†§	2 (2.9)	2/2 (100)	–	–	–	–	–	–	17 (1.1)	3/17 (17.6)	2.96	(0.84-10.45)	0.093	1.99	(0.53-7.46)	0.305
Pregnancy interval, years	–	–	1.03	(0.69-1.54)	0.893	1.16	(0.75-1.79)	0.513	–	–	1.07	(0.88-1.31)	0.493	1.13	(0.92-1.37)	0.241
Anuual BMI change, kg/m^2/year	–	–	1.00	(0.64-1.58)	0.986	1.10	(0.60-2.01)	0.765	–	–	1.60	(1.30-1.98)	<0.001*	1.57	(1.27-1.95)	<0.001*
High parity (Parity ≥ 2)§	15 (21.4)	15/15 (100)	–	–	–	–	–	–	350 (22.3)	23/350 (6.6)	0.94	(0.58-1.51)	0.797	0.93	(0.57-1.50)	0.755

N: The number of patients for each variables; n/N: The number of GDM events during the subsequent pregnancy/N; cOR, clude odds ratio; aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; GDM, gestational diabetes mellitus.

†*Parameteres of the index pregnancy.* §*ORs were not calculated because there were no non-GDM during the subsequent pregnancy in subgroup1. *Statistically significant.*

(95% CI, 1.29–6.19) and 5.12 (95% CI, 2.38–11.00) higher odds of GDM during the subsequent pregnancy, respectively. On the other hand, among women with a pre-pregnancy BMI of ≥25.0 kg/m^2 during the index pregnancy, none of the five categories of annual BMI change were significantly associated with GDM during the subsequent pregnancy. Although no significant difference was detected, the weight loss category showed a trend to reduce the prevalence of GDM compared to the reference category (10.5% *vs.* 26.3%, **Figure 3**). Additionally, increasing annual BMI gain showed an inverse trend with GDM prevalence and aOR. In the further multivariable analysis of this subgroup (**Supplementary Table 2**), annual BMI was not an independent factor, but pregnancy interval was independently associated with GDM during the subsequent pregnancy (aOR 1.72, 95% CI 1.12–2.63). In this subpopulation, increasing annual BMI gain also showed a shorter trend of pregnancy interval (**Supplementary Figure 1**), similar to a trend of GDM prevalence (shown in **Figure 3**).

DISCUSSION

This was the first study to evaluate the association between GDM during the subsequent pregnancy with the annual BMI change during the interpregnancy period. Annual BMI gain during the interpregnancy period was an independently associated with GDM during subsequent pregnancies. Higher pre-pregnancy BMI, and GDM during the index pregnancy were also factors which were independently associated with GDM during the subsequent pregnancy. Among these factors, a history of GDM during the index pregnancy was the most significantly associated with the GDM during the subsequent pregnancy. The 68.6% (48/70) of women with a history of GDM experienced recurrent GDM during the subsequent pregnancy, and the recurrence rate was as high as almost 90% in patients with GDM who had a pre-pregnancy BMI of ≥25.0 kg/m^2 during the index pregnancy. However, the annual BMI change during the interpregnancy

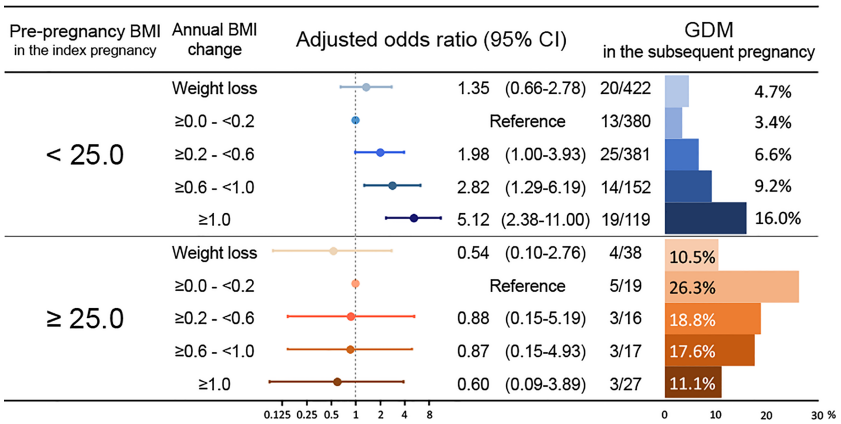

FIGURE 3 | Adjusted odds ratios for GDM during the subsequent pregnancy among women without a history of GDM according to the annual BMI change and pre-pregnancy BMI during the index pregnancy. The multivariable models were adjusted for maternal age of ≥35 years, pre-pregnancy BMI in the index pregnancy, pregnancy interval, and classified annual BMI changes. The forest plot represents the adjusted odds ratio for the classified annual BMI changes for GDM during the subsequent pregnancies. The bar chart displayed on the right shows the incidence of GDM during the subsequent pregnancy according to the degree of annual BMI change. The number of GDM events during the subsequent pregnancy/the total number is shown on the left of the bar chart. BMI, body mass index; GDM, gestational diabetes mellitus; CI, confidence interval.

period was not significantly associated with recurrent GDM. On the other hand, in women without a history of GDM, the annual BMI gain was associated with GDM during the subsequent pregnancy. Furthermore, an annual BMI gain of ≥0.6 kg/m^2/year during the interpregnancy period was associated with GDM during the subsequent pregnancy among women with a pre-pregnancy of BMI of <25.0 kg/m^2 and without development of GDM during the index pregnancy.

Previous studies have suggested that a history of GDM and insulin use were risk factors for GDM during the subsequent pregnancy (3, 4, 25, 27). The recurrence rate in this study was consistent with those of previous studies (3, 5, 53). It is important to note that patients with a history of GDM are at a high risk of developing GDM during the subsequent pregnancy. While parity is also correlated with the risk of GDM (51), approximately 70% of the patients with GDM during the subsequent pregnancy did not have GDM during the index pregnancy, suggesting that focusing only on those who had GDM during the index pregnancy would not reduce the incidence of GDM during the subsequent pregnancy. Other known risk factors for GDM development during the subsequent pregnancy that have been reported are as follows: older maternal age, higher pre-pregnancy BMI, and higher interpregnancy weight gain (4, 27, 28); these were consistent with the findings of the present study.

Using subgroup analyses, the present study identified the subgroup at risk of interpregnancy BMI gains, which in turn could increase the risk of GDM in subsequent pregnancies. In women with a pre-pregnancy BMI of <25.0 kg/m^2 and without a history of GDM during the index pregnancy, interpregnancy BMI gains were significantly correlated with the incidence of GDM during the subsequent pregnancy. The cut-off value of the annual BMI change was found to be ≥0.6 kg/m^2/year according to the multivariable analysis. In this study population, the mean annual BMI change was approximately 0.21 kg/m^2/year, which was comparable to those reported in previous studies (34, 35). Thus, maintaining an annual weight gain of <0.6 kg/m^2/year might be advisable for women with a pre-pregnancy BMI of <25.0 kg/m^2 and without a history of GDM during the index pregnancy to prevent GDM occurrence during the subsequent pregnancy; however, most clinicians have not paid much attention to those women. Additionally, weight loss during interpregnancy might not reduce GDM risk during the subsequent pregnancy for those women (**Figure 3**).

On the other hand, the annual BMI change was not significantly associated with GDM during the subsequent pregnancy in the following subgroups: women whose pre-pregnancy BMI was ≥25.0 kg/m^2 and didn't have GDM during the index pregnancy, and those who had GDM during the index pregnancy. For the former subgroup, we speculated that they might be resistant to GDM development due to BMI gain. Some specific variants might be related to this resistance, as several genetic variants have decreased GDM risk (54). The multivariable analysis in this subgroup showed pregnancy interval as an independent risk for GDM during the subsequent pregnancy. It suggested that 'aging' might be more critical than 'BMI gain'. The paradoxical trend, which was not statistically significant, that higher annual BMI gain categories had lower prevalence of GDM during the subsequent pregnancies (**Figure 3**), would depend on higher annual BMI gain categories with shorter pregnancy intervals (**Supplementary Figure 1**). Additionally, weight loss might reduce the risk of GDM in the subsequent pregnancy for these women. No significant difference was detected, but this might have been due to the low number of the weight-loss population in this present study. For the latter subgroup, it is worth noting that in this study, 87% (20/23) of the patients with GDM who had a pre-pregnancy BMI of ≥25.0

kg/m^2 during the index pregnancy experienced recurrent GDM during the subsequent pregnancy. However, the importance of interpregnancy care for these patients should not be overlooked. Another retrospective study suggested that interpregnancy weight loss might reduce the risk of GDM during the subsequent pregnancy among overweight patients who had GDM during the index pregnancy (28). Some active interventions to lose weight might be more effective for these patients, and further prospective research is needed. More evidence for interpregnancy care protocols to prevent GDM is warranted. The present study was the first to demonstrate the association between annual BMI gain during the interpregnancy period and GDM incidence during subsequent pregnancies among women with or without GDM during the index pregnancy.

STRENGTHS AND LIMITATIONS

This study had several strengths. First, this was the first study to assess the association between GDM during the subsequent pregnancy and annual BMI changes during the pregnancy interval. Second, the aOR for GDM was also stratified by several other factors, including a history of GDM and pre-pregnancy BMI during the index pregnancy. Third, as this was a multicenter study, both primary maternity care units and tertiary care centers participated in this study. The study population included pregnant women at various risk levels, which helped minimize selection bias. Recent studies on the risk of recurrent GDM have included only women who gave birth at tertiary centers (4, 26, 27). The data used in this study were detailed and reliable, as required by the national registry studies.

This study also had several limitations. First, the study population consisted only of patients who had both index and subsequent pregnancy records available. The following patients were excluded: women who delivered a subsequent baby at a non-participating institute, those who had an abortion in a subsequent pregnancy, and those who developed infertility after the index pregnancy. These populations might have other problems; however, these were outside the scope of our study. Second, we did not follow up on the postpartum weights. The annual BMI change was not measured as a part of an annual check but was calculated according to the pregnancy interval and ΔBMI. However, the mean weight change from pre-pregnancy to 1 year after delivery, which is approximately 2 years, has been reported to be 0.9 kg (55), which was comparable to the age-related weight gain (33–35). Therefore, the difference between actual annual BMI change and calculated annual BMI change would be not so significant because the mean pregnancy interval was 2.1 years. Third, only 61.3% of the patients (1,006/1,640) were verified their family history of diabetes, and most of the patients who had an unknown family history of diabetes were patients in tertiary centers (548/634 [86.4%]). Therefore, we thought its inclusion in the analysis would make a reliable assessment difficult even though it was a possible confounder (56). Additionally, the women who had systemic diseases interfering with glucose homeostasis were not excluded from the analysis in this study. The risk of developing GDM during the subsequent pregnancies was analyzed separately by stratifying according to the presence or absence of GDM during the index pregnancy, regardless of underlying disease or genetic background. We have speculated that some women with such complications might have developed GDM during the index pregnancy and treated as women with a history of GDM during the index pregnancy. These have limitations in terms of accurate risk assessment, but when considering future applications in interpregnancy care, it will be an advantage in terms of simplifying the assessment of the patients. Fourth, self-reported weight was used to calculate BMI. However, most participants measured their weights at the prenatal visit in the first trimester, so the difference between the self-reported and actual weight is likely to be minimal.

Interpregnancy health checks, including weight checks for women who hope to have subsequent pregnancies, have not been provided in clinical settings in Japan. Based on the current results, the maintenance of an appropriate annual BMI change may be advised. However, it is still unclear whether active interventions can prevent GDM in subsequent pregnancies. Thus, we plan to implement such interventions based on this study's findings. Finally, the subgroup with a history of GDM was a small population, and research with more extensive populations is warranted to confirm the results.

In conclusion, in this study, an annual weight gain of ≥0.6 kg/m^2/year was independently associated with higher incidence of GDM during the subsequent pregnancy in patients with a pre-pregnancy BMI of <25.0 kg/m^2 and without a history of GDM during the index pregnancy. Furthermore, patients with a history of GDM and insulin use during the index pregnancy had higher incidence of GDM during the subsequent pregnancy. However, the association between annual BMI change and GDM incidence during the subsequent pregnancy was not confirmed in this subgroup.

These results might help lay the foundation for further research to determine whether limiting annual BMI gains can prevent GDM during a subsequent pregnancy and establish protocols for interpregnancy care to prevent GDM. Preventing GDM will in turn help improve the health outcomes of women and their children.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request, and with the permission of Kishokai Medical Corporation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Nagoya University Hospital (approval number: 2015–0415) in accordance with the Declaration of Helsinki. The ethics committee waived the requirement for written informed consent because of the retrospective nature of the study.

AUTHOR CONTRIBUTIONS

ST, TK, and MYo conceived the study. ST, TK, and FK conducted the statistical analyses. ST, TK, TU, KI, TN-K, YM, YI, SY, MYa, YK, HO, and HK collected and interpreted the clinical data. ST and TK drafted the manuscript. All authors contributed to the interpretation of the results and approved the final 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/fendo.2022.815390/full#supplementary-material

Supplementary Table 1 | Detailed characteristics of individuals diagnosed with DM after the index pregnancy

Supplementary Table 2 | Univariable and multivariable logistic regression analysis of variables potentially associated with GDM during the subsequent pregnancy among women whose pre-pregnant BMI were ≥25.0 kg/m^2 and didn't have GDM during the index pregnancy.

Supplementary Figure 1 | Mean pregnancy interval for each annual BMI change categories.

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Conflict of Interest: Authors SY and MYa are an employee, and President and CEO of Kishokai Medical Corporation, respectively.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association of COVID-19 Lockdown With Gestational Diabetes Mellitus

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Importance: The ongoing pandemic of COVID-19 is still affecting our life, but the effects of lockdown measures on gestational diabetes mellitus (GDM) in pregnant women remain unclear.

Aim: To investigate the association between COVID-19 lockdown and GDM.

Subjects and Methods: Medical records of 140844 pregnant women during 2015-2020 were extracted from 5 hospitals in Guangdong Province, China. Pregnant women who underwent the COVID-19 Level I lockdown (1/23 - 2/24/2020) during pregnancy were defined as the exposed group (N=20472) and pregnant women who underwent the same calendar months during 2015-2019 (1/23 - 2/24) were defined as the unexposed group (N=120372). Subgroup analyses were used to explore the potential susceptible exposure window of COVID-19 lockdown on GDM. Cumulative exposure is quantitatively estimated by assigning different weights to response periods with different exposure intensities. A logistic regression model was used to estimate the association between COVID-19 lockdown exposure and GDM.

Results: The rates of GDM in the exposed and unexposed groups were 15.2% and 12.4%, respectively. The overall analyses showed positive associations (odds ratio, OR=1.22, 95%CI: 1.17, 1.27) between lockdown exposure and GDM risk in all pregnant women. More pronounced associations were found in women who underwent the COVID-19 lockdown in their first four months of pregnancy, and the adjusted OR values ranged from 1.24 (95%CI: 1.10, 1.39) in women with 5-8 gestational

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weeks (GWs) to 1.35 (95%CI: 1.20, 1.52) with < 5 GWs. In addition, we found a positive exposure-response association of cumulative lockdown exposure with the risk of GDM.

Conclusions: The COVID-19 lockdown was associated with an increased risk of GDM, and the first four months of pregnancy may be the window for sensitive exposure.

Keywords: COVID-19, lockdown, pregnant woman, gestational diabetes mellitus, China

INTRODUCTION

Gestational diabetes mellitus (GDM) is temporary hyperglycemia induced by glucose intolerance with onset or first monitor during pregnancy (1). As one of the most common complications in pregnant women, GDM is widely prevalent around the world. The median estimated prevalence of GDM in the Middle East and North Africa region is 12.9% versus 5.8% in Europe, while in the Western Pacific region, prevalence estimates vary from 4.5% in Japan to 25.1% in Singapore (2). In China, the prevalence of GDM is also not optimistic. A meta-analyses conducted by Gao et al. in 2019 found a prevalence of GDM of 14.8% across China (3). According to the data released by the International Diabetes Federation (IDF), more than 1 million Chinese women were affected by GDM in 2013, ranking second in the world after India (4).

Although the degree of blood glucose elevation is usually not as high as that of diabetes mellitus combined with pregnancy, it can still cause serious harm to both women and fetuses (4). The short-term effects of GDM on mothers and infants include increased maternal pregnancy complications, such as gestational hypertensive disease and polyhydramnios, as well as increased risk of fetal macrosomia, and neonatal respiratory distress syndrome (4). The long-term threat to maternal and child health is mainly the increased risk of long-term type 2 diabetes mellitus (T2DM) and metabolic syndrome in mothers after postpartum and offspring (2, 4, 5). Thus, reducing the prevalence of GDM is an important public health issue.

Since the early 2020, the COVID-19 pandemic and the corresponding catastrophic effect have challenged the view of public health of the world's people. At the time of the COVID-19 pandemic, a series of special measures have been adopted by governments and health-care leaders around the world to decrease the pandemic of the virus. For example, many cities and regions have fully or partially implemented lockdown measures, with large venues closed and traffic restricted. Apart from the control of pandemic, these measures during the lockdown have not only led to economic recessions, but also the strain on medical resources (6–8), which has substantially affected health in the public such as glycemic control in diabetic patients (9, 10).

Pregnant women go through huge physiological and psychological changes during pregnancy, and are more potentially affected by extreme events (11). A few epidemiological studies have reported significant associations of COVID-19 lockdown with maternal health and pregnancy outcomes, such as stillbirth, and preterm delivery (12, 13). While as a common complication of pregnancy, few studies have assessed the association of COVID-19 lockdown measure with GDM. A study had found the association between COVID-19 and blood sugar control in pregnant women (14). Moreover, there are several research issues or limitations that need to be fully addressed or investigated in future studies. First, previous studies focused on changes in glycemic control in patients with GDM and changes in GDM prevalence during COVID-19 need to be further evaluated. Second, the impact of environmental changes on maternal health is related to the stage of pregnancy (15, 16). The sensitive window exposure period when COVID-19 affects pregnant women's GDM remains unknown. Third, the intensity and duration of the lockdown varied constantly, and its impact on GDM should be considered.

Accordingly, to fill in these research gaps, we comprehensively evaluated the association between the COVID-19 lockdown and the risk of GDM by quantifying the duration and intensity of exposure among pregnant women in Guangdong Province, South China. Moreover, we considered seasonal effects and adequate follow-up time in this study.

MATERIALS AND METHODS

Subjects

Medical records of 222126 pregnant women between 2015 and 2020 were obtained from 5 hospitals [Guangzhou (n=1), Shenzhen (n=1), Dongguan (n=2), and Jiangmen (n=1)] located in Guangdong Province, China (**Figure 1**). We excluded 1318 women with missing information on important variables, and 37487 women whose gestational period did not overlap with the COVID-19 lockdown period in 2020 or the same period in 2015-2019. Because GDM is usually diagnosed during the 24th to 28th gestational week (GW) (17), we further excluded those (n=42353) pregnant women whose gestational age was larger than 28GWs at the time of COVID-19 lockdown and the corresponding period in 2015-2019, and those (n=124) preterm pregnant women with less than 28 GWs (not screened for GDM) when had their childbirth. Finally, 140844 pregnant women were included in the data analyses. None of these pregnant women was infected with SARS-CoV-2 (**Supplementary Figure 1**).

Data Collection

We extracted the following individual information from maternal medical records: maternal age, gestational weeks (GWs), marital status, parity, and gestational diabetes mellitus (GDM). For this study, the data is imported into R3.6.1 software to clean up the data information mentioned above. Unreasonable or abnormal values were either amended or defined as missing.

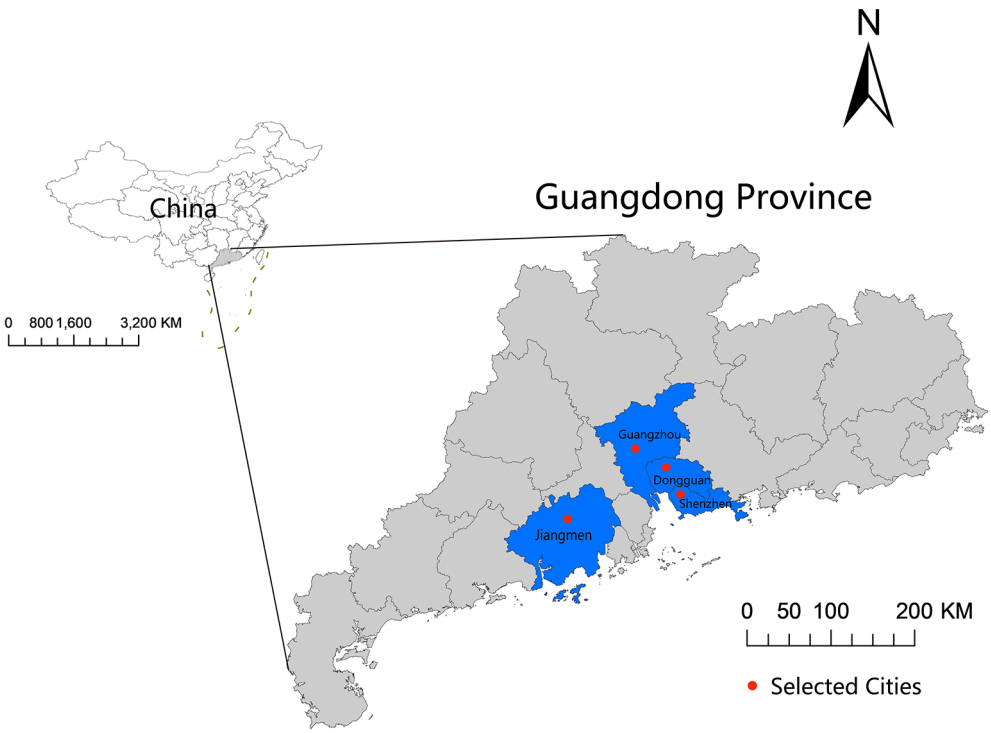

FIGURE 1 | Geographic locations of the four included study cities in Guangdong Province, China.

Exposure Assessment

According to the National Emergency Plan for Public Emergencies, the emergency response for public health emergencies is divided into four levels: Level I (especially serious), Level II (serious), Level III (relatively serious), and Level IV (general) (18). In response to the COVID-19 outbreak, Guangdong Province launched a Level I response on 1/23/2020. Then the public health emergency response level was adjusted to Level II on 2/24/2020 and Level III on 5/9/2020. During the Level I response, the government implemented control measures to minimize public gatherings and stopped public gatherings rigorously (19). Shopping malls, bars, schools, and other establishments were closed, and traffic was restricted. After the Level I response, fewer restrictions were imposed. During the Level II response, public places at risk of cross-infection were temporarily closed or disinfected. During the Level III response, except for masks and temperature checks in certain places such as hospitals and shopping malls, life is gradually returning to pre-pandemic conditions (**Supplementary Table 1**).

The days with Level I response (1/23-2/24/2020) were defined as Level I lockdown. We identified the exposure group (N=20472) based on the time of pregnancy crossed with the Level I lockdown. The unexposed group (N=120372) experienced the same calendar months as the exposed group between 2015 and 2019. This helps to control for seasonal effects, as our data suggest that the GDM rate is related to the season of pregnancy (**Supplementary Figure 2**).

To explore the potential susceptible exposure window, we divided the exposed group into 8 subgroups according to GWs and the crossover of 1/23/2020. We calculated the date of conception based on GWs and birth date. For instance, the first subgroup consisted of women who conceived during the Level I lockdown, and the second group was pregnant women in the first four GWs of gestational age at 2020/1/23 (**Supplementary Figure 3**). The grouping ended at 28 GWs. Similarly, the unexposed group was also divided into 8 subgroups (considering the same calendar month) and matched with the exposed group. For each pair of subsets (exposed vs unexposed), we calculated the associations between lockdown exposure and GDM risk.

The lockdown measures during the Level II (2/25-5/9/2020) and Level III (5/10-12/31/2020) responses might also adversely affect GDM risk. Therefore, we assigned different weights to different response times, and multiply response times with weights to quantitatively estimate the cumulative exposure: (no response, weighting=0), (Level I, weighting=3), (Level II, weighting=2), and (Level III, weighting=1). Because GDM is usually diagnosed between 24 and 28 GWs (17), we only estimated the amount of cumulative exposure before 28 GWs (**Figure 2**). **Supplementary Figure 4** shows the distribution of cumulative exposures to COVID-19 lockdown.

Outcome Measures

Individual information on GDM was extracted from each woman's medical record. Gestational diabetes was diagnosed when the blood glucose was higher than the standard at any of the three time points: fasting blood glucose 5.1 mmol/L; 1-h plasma glucose 10.0 mmol/L following a 75 g oral glucose

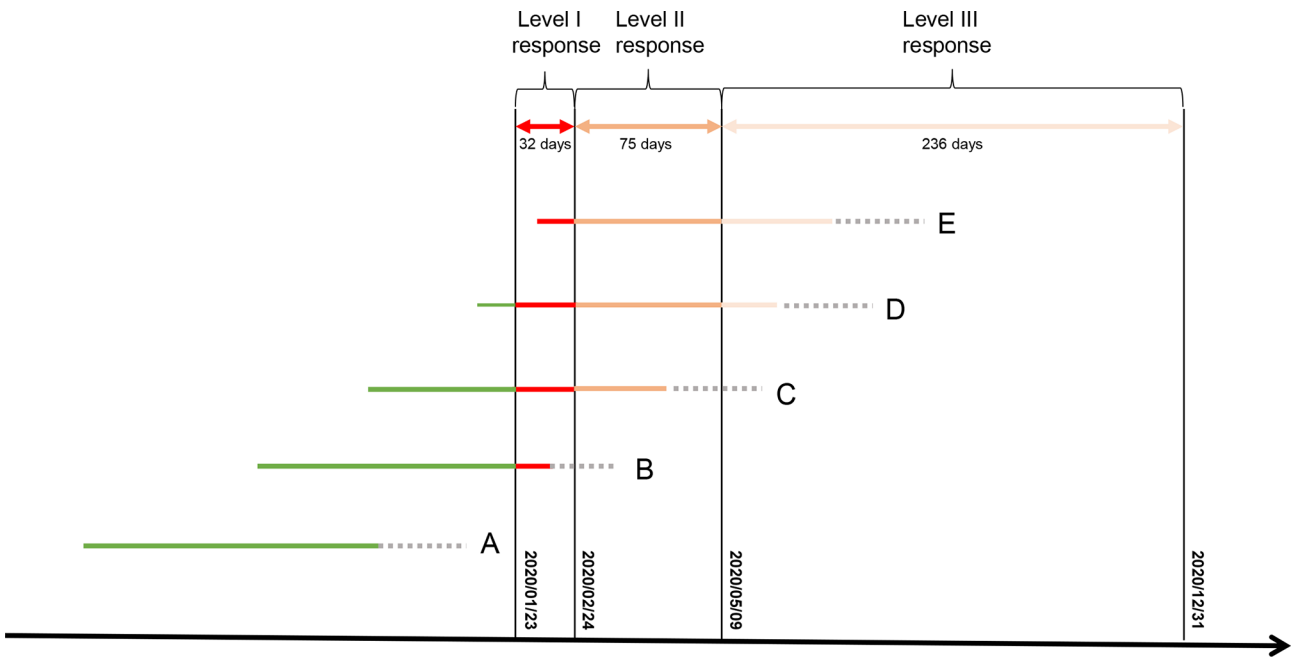

FIGURE 2 | Approach to calculating individual cumulative exposure dose to lockdown in the first 28 GWs. Weeks after 28 GWs. **(A–E)** represent subgroups of pregnant women with different GWs during the Level I lockdown; We assigned a weighting value of 3 to the days with Level I response, 2 to the days with Level II response, 1 to the days with Level III response, and 0 to days before lockdown (no exposure).

tolerance test; or 2-h plasma glucose 8.5 mmol/L following a 75 g oral glucose tolerance test (OGTT) (20).

Potential Confounders

We probe into the following confounders potentially associated with GDM based on biological plausibility, literature review, and data availability: maternal age, marital status, parity, and residential city.

Statistical Analyses

Chi-square test (for categorical variables) or *t*-test (for continuous variables) were applied to detect the difference in the distribution of maternal characteristics between exposed (n = 20472) and unexposed (n = 120372) groups. An unconditional logistic regression model was implemented to estimate the associations of lockdown exposure with GDM, after adjusting for potential confounders. The logistic regression model was also implemented to analyze the association between the cumulative exposure dose and GDM risk. The cumulative exposure was treated as a continuous variable and categorical variables in the logistical regression model. For the categorical variable, the cumulative exposure was divided into four groups [Q1 (<25% centile), Q2 (≥25% centile and <50% centile), Q3(≥50% centile and <75% centile), and Q4 (≥75% centile)] according to the quartiles. The trend test is performed by inputting the four groups as continuous variables. We employed a generalized additive model (GAM) with a binomial link function to estimate the potential nonlinear exposure-response association between cumulative lockdown exposure and the risk of GDM. A penalized smoothing spline with 3 degrees of freedom (df) was used to estimate the potential nonlinear effect of cumulative lockdown exposure.

Sensitivity Analysis

It was reported that the worldwide prevalence of GDM is constantly increasing (3). Thus, it is expected that prevalence of 2020 may be significantly higher of those of 2015, independently from lockdown. To test the potential impact of long-term trend of GDM prevalence on the association between COVID-19 lockdown and GDM risk, we selected those pregnant women only in 2019 as the control group.

'We performed all the analyses in R3.6.1 (R Development Core Team 2019). And all p values were 2-sided, and a *P*-value <0.05 was considered statistically significant.

Ethics Statement

This study was approved by the Ethics Committee of Guangdong Provincial Center for Disease Control and Prevention (No. W96-027E-2020004). Written informed consent was obtained from all participants.

RESULTS

General Characteristics of Study Subjects

Out of the total included 140844 pregnant women, 20472 were identified as exposed group and 120372 were defined as unexposed group (**Table 1**). Compared with the unexposed

TABLE 1 | General characteristics of study participants.

	Unexposed group (n = 120372) No. of participants (%)	Exposed group (n = 20472) No. of participants0 (%)	χ^2	*P*
Maternal age (years)				
<24	8670 (7.2)	1150 (5.6)	228.61	<0.001
24–26	17309 (14.4)	2596 (12.7)		
27–29	29234 (24.3)	4546 (22.2)		
30–32	26770 (22.2)	5089 (24.9)		
33–35	20511 (17.0)	3696 (18.0)		
>35	17878 (14.9)	3395 (16.6)		
Residential city				
Guangzhou	15381 (12.8)	2346 (11.5)	37.267	<0.001
Dongguan	27843 (23.1)	4624 (22.6)		
Jiangmen	15230 (12.7)	2725 (13.3)		
Shenzhen	61918 (51.4)	10777 (52.6)		
Gestational diabetes mellitus (GDM)			123.449	<0.001
No	105413 (87.6)	17352 (84.8)		
Yes	14959 (12.4)	3120 (15.2)		
Marital status			750.81	<0.001
Married	116223 (96.6)	19346 (94.5)		
Unmarried	3403 (2.8)	598 (2.9)		
Other	746 (0.6)	528 (2.6)		
Parity			2.6951	0.260
0 (Primiparas)	57293 (47.6)	9858 (48.2)		
1 (Multiparas)	50676 (42.1)	8559 (41.8)		
2-4 (Multiparas)	12403 (10.3)	2055 (10.0)		
	Mean ± SD	**Mean ± SD**	***t***	***P***
Maternal age (years)	30.31 ± 4.85	30.80 ± 4.84	13.462	<0.001

group, the exposed group had a significantly higher proportion of women aged 30 years or older (59.5% vs 54.1%) and a lower proportion of married (94.5% vs 96.6%).

Associations of COVID-19 Lockdown Exposure With GDM

We observed a greater prevalent GDM in the exposed group (15.2%) than the unexposed group (12.4%). Multivariable analyses showed a positive association [adjusted odds ratio (OR)= 1.22, 95%CI: 1.17, 1.27] of lockdown exposure with GDM in the total pregnant women, after adjustment for maternal age, marital status, parity, and residential city. Subgroup analyses showed that the significant associations were only found in pregnant women who experienced the Level I lockdown in the first four months of pregnancy. The adjusted ORs varied from 1.35 (95%CI: 1.20, 1.52) in women with less than 5 GWs to 1.24 (95%CI: 1.10, 1.39) in women with 5-8 GWs on 1/23/2020, the beginning of Level I response (**Table 2**).

Association of Cumulative Exposures to COVID-19 Lockdown With GDM

We also found significant positive associations between cumulative exposure dose and GDM risk (**Table 3**). The risk of GDM increased by 1.09 (95%CI:1.07, 1.11) times for each additional 100 units of cumulative exposure during the first 28 GWs. Compared with the unexposed group, the adjusted ORs of GDM in the Q1, Q2, Q3, and Q4 groups were 1.17 (95%CI: 1.08, 1.27), 1.10 (95%CI: 1.02, 1.20), 1.22 (95%CI: 1.13, 1.32), and 1.39 (95%CI: 1.29, 1.50), respectively. In addition, the nonlinear exposure-response relationship showed that higher cumulative lockdown exposure was associated with a higher risk of GDM (**Figure 3**).

Sensitivity Analyses

The results of sensitivity analysis suggest that the associations between COVID-19 lockdown and GDM were attenuated, and subgroup analyses suggested that the significant association was found only during the first five GWs (**Supplementary Table 2**). However, the adjusted OR of GDM in all pregnant women was also statistically significant (1.07, 95%CI: 1.02, 1.14), which indicated the solid effect of COVID-19 lockdown on the risk of GDM.

DISCUSSION

This study comprehensively investigates the effect of COVID-19 lockdown measures on GDM risks in pregnant women using a large database from South China. The results suggested that the COVID-19 lockdown measures were associated with an increased risk of GDM in pregnant women. The association was stronger in pregnant women within the first four months of pregnancy during the Level I lockdown period. In addition, we observed a significant exposure-response association between cumulative exposures to lockdown and GDM risk. These findings extend our understanding of the effects of COVID-19 lockdown measures on maternal and fetal health, and suggest taking actions to prevent the risk of GDM in pregnant women during COVID-19 lockdown periods.

TABLE 2 | Associations of exposure to the COVID-19 lockdown with gestational diabetes mellitus.

	Unexposed group (n, %)		Exposed group (n, %)[a]		OR for GDM (95%CI)	
	GDM (-)	GDM (+)	GDM (-)	GDM (+)	Crude OR(95% CI)	Adjusted OR* (95% CI)
Gestational week at the beginning of the Level I lockdown						
All	105413 (87.6)	14959 (12.4)	17352 (84.8)	3120 (15.2)	1.27 (1.22, 1.32)	1.22 (1.17, 1.27)
Conception during the lockdown	16228 (87.6)	2298 (12.4)	2271 (84.0)	432 (16.0)	1.34 (1.20, 1.50)	1.30 (1.16, 1.46)
Prior to 5th	13431 (87.6)	1905 (12.4)	2229 (83.5)	439 (16.5)	1.38 (1.24, 1.55)	1.35 (1.20, 1.52)
5th -8th	13188 (86.9)	1988 (13.1)	2293 (83.9)	441 (16.1)	1.27 (1.14, 1.43)	1.24 (1.10, 1.39)
9th -12nd	12881 (87.8)	1783 (12.2)	2159 (84.8)	387 (15.2)	1.29 (1.15, 1.46)	1.25 (1.11, 1.41)
13rd -16th	12743 (88.6)	1643 (11.4)	2332 (86.0)	379 (14.0)	1.26 (1.12, 1.42)	1.26 (1.11, 1.42)
17th -20th	12946 (87.9)	1787 (12.1)	2187 (86.6)	337 (13.4)	1.11 (0.98, 1.26)	1.04 (0.92,1.19)
21st -24th	12058 (87.3)	1760 (12.7)	2036 (85.3)	352 (14.7)	1.18 (1.05, 1.34)	1.11 (0.97, 1.26)
25th -28th	11938 (86.9)	1795 (13.1)	1845 (83.9)	353 (16.1)	1.27 (1.12, 1.44)	1.20 (1.06, 1.36)

**Adjusted for maternal age, marital status, parity, residential city.*

GDM, gestational diabetes mellitus.

[a]Pregnant women who have experienced the COVID-19 lockdown (from 1/23/2020 to 2/24/2020) during any period of their pregnancy were defined as the exposed group. We further divided the exposed group into subgroups according to their gestational weeks (GW) on 1/23/2020, the beginning of lockdown.

TABLE 3 | Associations of cumulative exposure to the COVID-19 lockdown with gestational diabetes mellitus.

	Exposure dose in Unexposed group (Mean ± SD)	Exposure dose in Exposed Group (Mean ± SD)		No. of participants (%)		OR for GDM (95%CI)	
						Crude OR (95% CI)	Adjusted OR* (95% CI)
	GDM (-) +GDM (+)	GDM (-)	GDM (+)	GDM (-)	GDM (+)		
Cumulative exposure dose in the first 28 weeks during the Level I to the Level III lockdown[a]							
Per 100 unit increase in all participants	0 ± 0	223.94 ± 90.67	227.11 ± 92.55			1.10 (1.08, 1.12)	1.09 (1.07, 1.11)
Categories of cumulative exposure dose							
Unexposed group	0 ± 0	–	–	105413 (87.6)	14959 (12.4)	Reference	Reference
Q_1 (<158)	–	89.35 ± 44.45	86.75 ± 43.89	4310 (84.9)	769 (15.1)	1.26 (1.16, 1.36)	1.17 (1.08, 1.27)
Q_2 (158-256)	–	211.19 ± 29.87	213.54 ± 30.62	4448 (86.1)	720 (13.9)	1.14 (1.05, 1.24)	1.10 (1.02, 1.20)
Q_3 (257-298)	–	279.07 ± 11.64	279.16 ± 11.48	4306 (84.9)	763 (15.1)	1.25 (1.15, 1.35)	1.22 (1.13, 1.32)
Q_4 (≥299)	–	317.10 ± 10.74	316.98 ± 10.97	4288 (83.2)	868 (16.8)	1.43 (1.32, 1.54)	1.39 (1.29, 1.50)
P for trend test							< 0.001

**Adjusted for maternal age, marital status, parity, residential city.*

GDM, gestational diabetes mellitus.

[a]The exposed group refers to the pregnant women who have experienced the COVID-19 lockdown in their first 28 GWs. The other participants were defined as the unexposed group. The individual cumulative exposure dose was calculated by combining the weightings with the overlap between their pregnancy period ≤28 GWs and the three levels of responses. Q_1-Q_4 were defined as the cumulative exposure dose of the exposed group classified by quartiles, and the unexposed group was used as reference.

-Not applicable.

A population study in Italy is consistent with our results. Zanardo et al. found a significant increase in the prevalence of GDM among pregnant women during the COVID-19 pandemic. Experiencing lockdown during the first trimester of pregnancy plays an important role in increasing the GDM risk in pregnant women (21). Moreover, several previous studies had estimated the associations of disasters or the COVID-19 pandemic with adverse human health including pregnancy complications. For example, a study in New York State reported an increased risk of GDM after massive power outages during Hurricane Sandy (22). Another study found a 42.3% (95% CI: 15.0%, 76.0%) increase in emergency department visits for diabetes or abnormal blood sugar in New York State during Hurricane Sandy (23). A study of the Great East Japan Earthquake of 2011 showed a 5% increase in the prevalence of GDM among the most affected residents compared to those who were not affected (24). On top of that, during the COVID-19 lockdown, an Indian cohort study found an increased risk of type 2 diabetes (25), and some other studies found that lockdown measures designed to avoid SARS-CoV-2 transmission may contribute to the deterioration of control in patients with diabetes (9, 10).

These previous studies suggest the plausible causal association between COVID-19 lockdown and GDM, which may relate to several reasons. First, during the COVID-19 lockdown period, most medical services were allocated to tackle the pandemic, and it is difficult for pregnant women to receive timely and adequate prenatal care (26). Pregnant women may also cut back on prenatal care for reasons such as fear of contracting

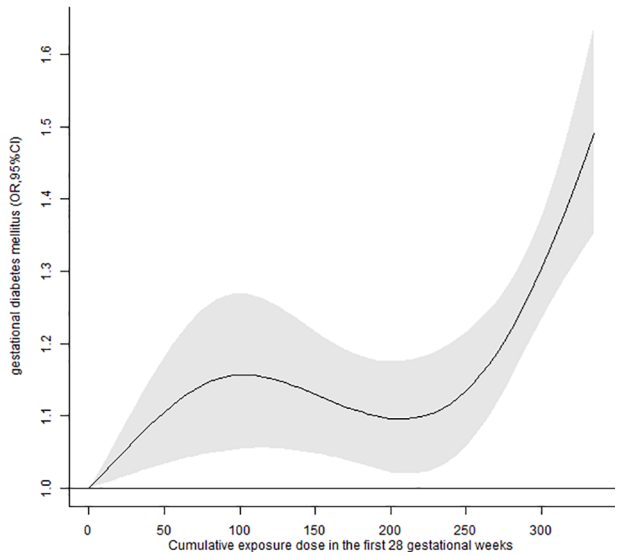

FIGURE 3 | Associations between cumulative exposure dose to lockdown in the first 28 GWs and the risk of GDM.

COVID-19 patients in the hospital, following government recommendations to stay home, and restricting transportation (27, 28). Second, social distancing and family economic stress during the lockdown may induce psychological problems in pregnant women who could not attend entertainment venues, play team sports, or meet friends to relax (7, 29). Mental disorders have been regarded as a common risk factor of GDM (30). Third, there is a lot published data, including from China (31), to show that people gain weight during the lockdown. Maternal BMI was an independent risk factor for GDM (32). During the lockdown, snacks and carbohydrates are consumed more (33, 34), and the movement range and mode were greatly restricted (14, 35), which can lead to an elevated maternal BMI.

We further observed that women in the first four months during the Level I lockdown were at a greater risk of developing GDM, which is consistent with previous studies. For instance, Abdo et al. also reported a positive association between exposure to wildfire smoke during early pregnancy and GDM (36). These findings suggest that early pregnancy might be a susceptible exposure window for environmental factors affecting GDM in pregnant women. Changes in environments, behaviors, and the psychological status during the lockdown, such as physical inactivity, low sleep levels, poor diet, and mental health problems, may disturb the normal glycometabolism, and lead to GDM (37). In addition, these women in the early pregnancy during the Level I lockdown would continue to experience lockdown measures even though the Level I lockdown was over, and therefore get more cumulative exposures to lockdown measures in the first 28 GWs. We also observed a positive exposure-response association between cumulative exposure to COVID-19 lockdown and the risk of GDM, which also suggests a higher risk of GDM in women who have experienced the most cumulative exposures to lockdown. Therefore, the government and others should consider how to provide economic, medical treatment, and psychological assistance to pregnant women to reduce the risk of GDM.

Strengths and Limitations

There are several strengths in this study. First, this is the first study to quantitatively assess the exposure to COVID-19 lockdown, and investigate the association with GDM risk in a Chinese population of pregnant women. We not only estimated the association of exposure to COVID-19 lockdown as an event with the risk of GDM but also provided the exposure-response association between cumulative exposure to lockdown and GDM risk. Second, we applied a large dataset with detailed individual information to investigate the association between lockdown and GDM risk. The dataset covered a wide enough timespan, in which GDM information of all women who have experienced the lockdown was recorded. The large sample size also provided us an adequate statistical power to implement subgroup analyses and identify the potential susceptible exposure window. Third, we used strict contemporaneous controls to reduce the impact of seasonal effects on the occurrence of GDM. To test the seasonal impacts, we estimated the difference in GDM rates between the exposed group and all pregnant women in 2015-2019 (rather than matching calendar months). After adjustment for maternal age etc., we found no statistical association between lockdown and GDM risk (**Supplementary Table 3**). These strengths could provide a stronger causal argument for our findings.

Several limitations should be considered. First, our study is a retrospective study, due to the unexpected emergence of the COVID-19 and the related lockdown measures, which limited our ability to infer the causal relationship between lockdown and GDM. Second, information of all participants was extracted from their medical recodes. Hence, several individual covariates such as maternal BMI, heredity for T2DM, smoking, alcohol consumption were not obtained in this study, and the influence of these confounding factors on the association was unknown. Third, the COVID-19 lockdown measures were implemented across countries with substantial variation in timing, content, and comprehensiveness. But this study was conducted in only four south cities, which limits the generalization of our findings. Fourth, some countries used alternative criteria for diabetes screening to avoid pregnant women staying in the hospital for long time during the COVID-19 pandemic (38, 39). However, it was not clear whether the diagnostic criteria for GDM were modified during the lockdown in this study, which may be a potential bias in this study. Some studies reported that using alternative criteria can increase the missed diagnosis rate of GDM by as much as 30-50% (40, 41). Meanwhile, a prospective study by Molina-Vega et al. found that the rate of missed diagnosis of GDM did not substantially change when comparing conventional criteria used before the pandemic with alternative diagnostic criteria used during the COVID-19 pandemic (42). Therefore, more studies are needed to examine the effects of diagnosis criteria on the association between COVID-19 lockdown and GDM. Fifth, the COVID-19 lockdown included many measures which were usually implemented simultaneously. As a result, we cannot

determine their individual impact on the risk of GDM. The COVID-19 is still ongoing throughout the world, and the lockdown measures have been implemented in many countries. Therefore, more research works are needed to demonstrate the effect of COVID-19 lockdown measures on GDM.

In conclusion, we found that the COVID-19 lockdown was associated with a moderately higher risk of GDM, and the first four months might be a susceptible exposure window. Now that the global pandemic of COVID-19 is not over, and we are also confronted with the challenge of the Delta variant B.1.617.2. A study had shown that non-pharmaceutical interventions have made a huge difference in controlling the epidemic (43), so that the lockdown measures will continue to affect our lives. Our findings suggest the critical importance of planning for strong maternal services in the future lockdown. Governments and women's health care providers must take action to reduce the risk of pregnant women developing GDM. Given the nature of this study, more investigation is needed to clarify the association between the lockdown measures and GDM, which is critical to maternal health.

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 authors.

AUTHOR CONTRIBUTIONS

TL and XS conceived study hypotheses. ZH, YL, SZ, YP, and QL conceptualized and designed the study. TL, XS, ZH, and YL edited the first draft of the manuscript. ZH, HZ, MD, JW, JF, YY, and HC did formal analyses, interpreted the results. RQ, JJ, YC, GC, GH, and SC contributed to data curation and did statistical analyses. JH, JX, and WM helped interpret and discuss the results. All authors critically revised and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Correlation Between Circulating PCSK9 Levels and Gestational Diabetes Mellitus in a Chinese Population

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Background: Previous studies reported that proprotein convertase subtilisin/kexin type 9 (PCSK9) was a key player in the regulations of lipid metabolism and glucose homeostasis. The current study aimed to detect the expression of PCSK9 in pregnant women with gestational diabetes mellitus (GDM) and investigate the possible relationships between PCSK9 and related metabolic phenotypes in GDM.

Methods: Circulating PCSK9 levels were determined by ELISA kit in a cohort of subjects with GDM (n = 170) and normal glucose tolerance (NGT; n = 130). We collected blood samples from all participants for the biochemical index determinations. Diagnosis of GDM was made according to the International Association of the Diabetes and Pregnancy Study Groups Consensus Panel. Correlation analysis and logistic regression analysis were used to study the potential associations between PCSK9 and GDM.

Results: GDM women presented significantly higher circulating PCSK9 levels than those in NGT pregnant subjects (268.07 ± 77.17 vs. 254.24 ± 74.22 ng/ml, $P < 0.05$). In the GDM group, serum PCSK9 levels were positively correlated with fasting plasma glucose (FPG) ($R = 0.251$, $P = 0.015$), glycated hemoglobin (HbA1c) ($R = 0.275$, $P = 0.009$), total cholesterol (TC) ($R = 0.273$, $P = 0.010$), and low-density lipoprotein cholesterol (LDL-C) ($R = 0.326$, $P = 0.002$) after adjustment of age and gestational age. Logistic regression found that age [odds ratio (OR) = 5.412, $P = 0.02$] and serum PCSK9 levels (OR = 4.696, $P = 0.03$) were independently associated with GDM. Compared with the lowest serum PCSK9 level quartile group, the prevalence of GDM was significantly higher in the highest quartile group, the ORs of GDM were 3.485 (95% CI 1.408–8.627, $P < 0.05$ for the trend), after adjusting for potential confounders.

Conclusions: Circulating PCSK9 levels were associated with dyslipidemia, pathoglycemia, and the risk of incident GDM, indicating a potential link between PCSK9 and GDM.

Keywords: proprotein convertase subtilisin/kexin type 9 (PCSK9), gestational (gestational diabetes), lipid, glucose–insulin, metabolism

INTRODUCTION

The American Diabetes Association (ADA) defines gestational diabetes mellitus (GDM) as any degree of glucose intolerance that was first recognized during pregnancy, regardless of the degree of hyperglycemia (1). GDM is a common metabolic complication that develops as gestation proceeds. It contributes to adverse metabolic disorders including type 2 diabetes mellitus (T2DM), obesity, and metabolic syndrome both in mother and fetus later in life (2–4). In recent decades, the incidence of GDM continued to increase worldwide (5). According to a meta-analysis, the GDM prevalence in China was reported to be 11.91% (6). It should be noted that increased insulin resistance and the following β-cell dysfunction take part in the development of GDM, but the exact pathogenesis of GDM have not been fully understood yet (7).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is the ninth member of subtilisin-like serine convertase superfamily and mainly derived from the liver (8). It is a central regulator of low-density lipoprotein (LDL) receptor (LDL-R) expression, by promoting the clearance of LDL-R, resulting in subsequent increased plasma LDL cholesterol (LDL-C) levels and hypercholesterolemia (9). Despite the previously observed close associations of PCSK9 with dyslipidemia, it was reported that PCSK9 also have effects on other metabolic diseases, but the results were controversial. Previous data observed that PCSK9 levels were increased in type 2 diabetes mellitus/metabolic syndrome patients and positive correlations of PCSK9 levels with LDL, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), fasting insulin, and insulin resistance (10, 11). Moreover, a recent population-based longitudinal study observed a positive association between serum PCSK9 levels and the incidence of T2DM in the prediabetic populations (12). In contrast, evidence from an animal study indicated that PCSK9 deficiency reduced insulin secretion and promoted glucose intolerance (13). These studies suggested a key role for PCSK9 in the progression of DM.

Unlike other cytokines, circulating levels of PCSK9 in GDM subjects have been little studied and poorly understood until now. In view of the regulation effects of PCSK9 on lipid metabolism, we sought to investigate the plasma PCSK9 levels in GDM patients and its possible relationships with GDM.

MATERIALS AND METHODS

Study Population and Design

We recruited second-trimester pregnant women (gestational weeks 24–28) who attended an antenatal outpatient clinic in the Xinhua Hospital Chongming Branch Affiliated to Shanghai Jiao Tong University School of Medicine between January and December 2020. This cross-sectional study comprised 130 newly diagnosed GDM women (GDM group, n = 130) and 170 healthy pregnant women randomly selected from normal glucose tolerance (NGT) subjects (NGT group, n = 170) according to the random number. A total of 300 participants were enrolled. The exclusion criteria were as follows: age <18 or >40 years, multiple pregnancies, preexisting diabetes or other metabolic disorders, hypertension, endocrine disease, liver or kidney disease, infections. The study protocol was in compliance with the Declaration of Helsinki and approved by the ethics committee of the hospital. Each participant has read and written the informed consent. Study design of this current trial was described in **Figure 1**.

Diagnosis of Gestational Diabetes Mellitus

All subjects underwent a 75-g oral glucose tolerance test (OGTT) screening for GDM during 24–28 gestational weeks. Using the criteria of the International Association of the Diabetes and Pregnancy Study Groups, GDM is diagnosed when any of the following plasma glucose values is met or exceeded: fasting glucose ≥5.1 mmol/L, 1-h glucose ≥10.0 mmol/L, or 2-h glucose ≥8.5 mmol/L (14).

Clinical Characteristics and Laboratory Measurements

Basic information of name, age, pre-pregnancy weight, history of gravidity and parity, and family history of diseases was obtained using self-reported questionnaire from all subjects at the first prenatal examination during 13–15 gestational weeks. Anthropometric indices including height, weight, blood pressure, and abdominal girth were measured according to international standards in the second trimester. After overnight fasting, blood samples were collected during the course of OGTT that was undertaken between the 24th and 28th week of gestation. Then, the samples were separated and frozen at -80℃ for later analysis. Blood glucose levels, HbA1c, serum insulin levels, serum creatinine (Cr), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), LDL-C, alanine aminotransferase (ALT), aspartate transaminase (AST), γ-glutamyltransferase (GGT), and white blood cell count were detected by standard laboratory methods in the clinical laboratory of our hospital. Furthermore, the plasma PCSK9 values were measured by sandwich ELISA assay (R&D Systems, Minneapolis, MN, USA) based on manufacturer's instruction. Each sample was detected in duplicate; the lowest limit of detection was 91 pg/ml with intra- and inter-assay coefficients of variation of 2.32%–8.91% and 4.54%–10.22%, respectively. Homeostasis model assessment of insulin resistance (HOMA-IR) was determined using the formula: HOMA-IR = fasting insulin (mU/L) × FPG (mmol/l)/22.5; HOMA-β assuming the pancreatic β-cells' function was calculated as [FINS × 20/(FPG-3.5)] (15); insulin sensitivity was calculated by the Matsuda and de Fronzo index (ISOGTT), defined as [10,000/sqrt (FPG × FINS × mean glucose × mean insulin)].

Statistical Analysis

We used Social Sciences software version 22.0 (SPSS, Chicago, IL, USA) for data analysis. Continuous variables were presented as mean ± SD or medians (interquartile range); for comparisons between groups, we used independent-samples t-test or Mann–Whitney U test based on different data distributions. Categorical variables were reported as rate (%), comparing by chi-square test.

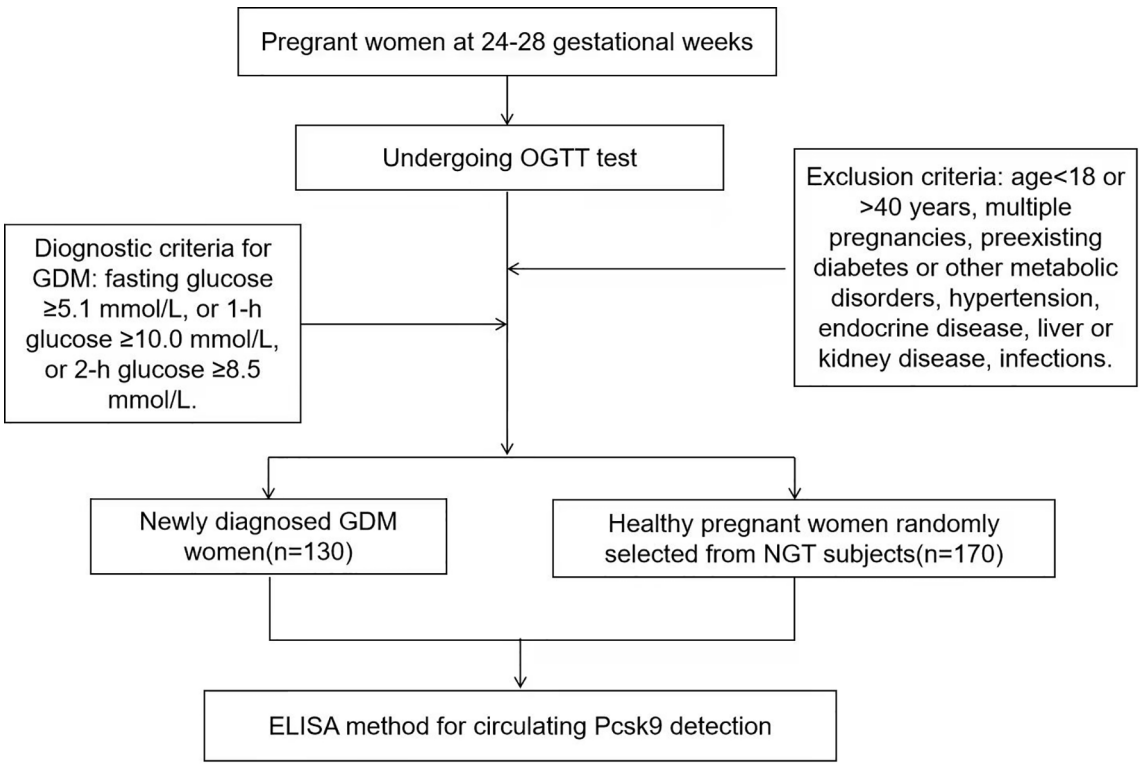

FIGURE 1 | Flow graph of study design.

The relationship between PCSK9 levels and metabolic variables were performed by partial Spearman's correlation analysis after adjusting for maternal age and gestational age. Logistic regression analysis was conducted to investigate the association between serum PCSK9 levels and the risk of incident GDM. A two-sided P value <0.05 was accepted as statistically significant. Sample size of 300 was evaluated according to a GDM prevalence of 11.91% in China (6). Referring to a recent study, the mean (SD) of PCSK9 in healthy populations was 283.68 (97.09) ng/ml (12). In our study, to detect a 50-ng/ml difference in PCSK9 values with a significance level of 0.05 between two groups, the power was 83.6% ($\alpha = 0.05$).

RESULTS

Baseline Characteristics of the Two Groups

The clinical and biochemical parameters of the groups were shown in **Table 1**. As we observed, maternal age, pre-body mass index (BMI), FPG, 1-h post-meal plasma glucose (1hPG), 2hPG, HbA1c, fasting insulin level (FINS), 1-h post-meal plasma insulin level (1hPINS), 2hPINS, HOMA-IR, obstetric history, uric acid, TG, white blood cell count, and circulating PCSK9 levels were much higher in the GDM group, while HDL and ISOGTT were significantly lower than those in the NGT group (all $P < 0.05$). There were no group differences in blood pressure, pregnancy BMI, parity times, abdominal perimeter, HOMA-β, LDL-C, TC, and Cr parameters (all $P > 0.05$) (**Table 1**).

Correlations Between PCSK9 Levels and Metabolic Indices in GDM Group

As shown in **Table 2**, by partial Spearman correlation analysis, we found that serum PCSK9 levels were positively correlated with FPG ($R = 0.251$, $P = 0.015$), HbA1c ($R = 0.275$, $P = 0.009$), TC ($R = 0.273$, $P = 0.010$), and LDL-C ($R = 0.326$, $P = 0.002$) after adjustment of age and gestational age; we failed to observe any significant correlations between PCSK9 levels and other parameters ($P > 0.05$) in the GDM group.

Associations of Circulating PCSK9 Levels With Risk of Incident Gestational Diabetes Mellitus

Binary logistic regression was carried out to assess the relationship between PCSK9 and the risk of GDM. The dependent variable was whether pregnant women were diagnosed with GDM, and the independent variables were age, gestational age, family history of diabetes, pre-BMI, abdominal girth, and PCSK9. The results were shown in **Table 3**. We observed that age [odds ratio (OR) = 5.412, $P = 0.02$] and serum PCSK9 levels (OR = 4.696, $P = 0.03$) were independently correlated with GDM.

TABLE 1 | Clinical characteristics and circulating PCSK9 level of the groups studied.

Variable	GDM (n = 130)	NGT (n = 170)	P value
Age, years	30.01 ± 4.55	28.60 ± 5.00	0.021
Week of gestation, weeks	25.46 ± 1.01	25.29 ± 1.05	0.203
Parity times	2 (1–3)	2 (1–3)	0.058
Delivery times	0 (0–1)	0 (0–1)	0.301
Pre-BMI, kg/m^2	22.82 ± 3.51	22.01 ± 2.84	0.045
BMI, kg/m^2	25.05 ± 4.11	24.58 ± 2.86	0.539
Abdominal perimeter, cm	92.31 ± 7.98	91.08 ± 7.25	0.222
SBP, mm/Hg	115.17 ± 12.14	116.94 ± 10.63	0.241
DBP, mm/Hg	74.41 ± 9.01	73.31 ± 8.88	0.353
HbA1c (%)	5.16 ± 0.81	4.88 ± 0.32	<0.001
FPG, mmol/l	4.86 ± 0.57	4.45 ± 0.30	<0.001
1hPG, mmol/l	9.71 ± 1.55	7.37 ± 1.27	<0.001
2hPG, mmol/l	8.61 ± 1.53	6.43 ± 0.95	<0.001
FINS, mU/l	8.03 (4.95–10.94)	5.68 (3.42–8.65)	<0.001
1h PINS, mU/l	56.63 (41.87–81.31)	54.84 (34.11–70.20)	0.003
2h PINS, mU/l	64.62 (41.35–95.34)	54.35 (35.25–71.06)	0.004
HOMA-IR	1.69 (0.98–2.53)	1.05 (0.68–1.74)	<0.001
HOMA-β	122.72 (92.26–165.77)	129.63 (79.05–180.26)	0.987
ISOGTT	317.67 (260.43–410.01)	392.92 (310.45–503.10)	<0.001
ALT (U/L)	10 (7–16)	9 (6–17)	0.303
Cr (mmol/L)	39.29 ± 10.34	37.47 ± 7.74	0.130
Uric acid (U/L)	0.21 ± 0.06	0.19 ± 0.04	0.008
TC (mmol/L)	5.46 ± 0.87	5.43 ± 1.10	0.777
TG (mmol/L)	1.97 ± 1.03	1.68 ± 0.81	0.020
HDL (mmol/L)	2.61 ± 0.52	2.95 ± 0.62	0.000
LDL (mmol/L)	2.93 ± 0.69	2.90 ± 0.88	0.801
Family history of DM (%)	10%	1.43%	<0.001
PCSK9, ng/ml	268.07 ± 77.17	254.24 ± 74.22	0.001

Data are means ± standard deviation (SD) or medians (interquartile range).

pre-BMI, body mass index before pregnancy; BMI, body mass index in pregnancy; DBP, diastolic blood pressure; SBP, systolic blood pressure; FPG, fasting plasma glucose; 1hPG, 1-h post-meal plasma glucose; 2hPG, 2-h post-meal plasma glucose; FINS, fasting insulin level; 1hPINS, 1-h post-meal plasma insulin level; 2hPINS, 2-h post-meal plasma insulin level; ALT, alanine aminotransferase; Cr, serum creatinine; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; PCSK9, proprotein convertase subtilisin/kexin type 9.

We used logistic regression analysis model, taking the lowest PCSK9 quartile group (PCSK9 <223.94 ng/ml) as a reference, to further assume the prevalence of GDM according to quartiles of PCSK9. As presented in **Table 4**, the ORs for GDM were higher with increasing PCSK9 quartiles. In the highest PCSK9 quartile, the OR of GDM were 3.386 (95% CI 1.668–6.874, P = 0.001 for the trend). Furthermore, the upward trend remained even after adjustment of age, gestational age, BMI, blood pressure, abdominal girth, family history of diabetes mellitus, TG, LDL-C, and HOMA-IR (model 2, model 3, model 4) compared with those in the first quartile of PCSK9 (all P < 0.05 for a linear trend).

DISCUSSION

To our knowledge, very few studies have been performed to explore the status of PCSK9 in relation to metabolic factors in GDM subjects. Our data demonstrated that serum PCSK9 values were elevated significantly in the GDM group compared with those in the NGT group and correlated positively to HbA1c, LDL, TC, and FPG significantly. Moreover, a positive association was found between PCSK9 levels and the risk of GDM; the observation remained after adjustment of LDL-C and TG.

Early studies have reported that plasma PCSK9 values were elevated in T2DM patients (16–19). Moreover, PCSK9 is also increased in T1DM among younger subjects; with glycemic control worsening, plasma PCSK9 levels increased significantly (20). While Brouwers et al. (21) demonstrated that plasma PCSK9 was not altered in subjects with impaired glucose metabolism and T2DM. The findings were inconsistent. Notably, a recent study evaluated PCSK9 in GDM, finding no differences between GDM and healthy pregnant women (22). In our research, we found that serum PCSK9 levels were raised in GDM subjects as compared to those in NGT subjects. However, the underlying mechanism behind such elevation was unclear. It is reported that nutritional status and insulinemia modulate PCSK9 expression *via* a pathway involving sterol regulatory element-binding protein 1c (SREBP-1c) (23). Also, studies in adults coupled with studies in cells and mice indicated that hyperinsulinemia in obesity/T2DM might upregulate PCSK9 expression (24). In addition, a positive association was found between PCSK9 and insulin levels in a large pediatric population research (25). In view of these reports, insulinemia was an important factor influencing serum PCSK9 levels. Nevertheless, in this paper, we failed to find this observation. Early study reported that PCSK9 was increased in placentas from hypercholesterolemic pregnancies, presenting a protective role

TABLE 2 | Partial Spearman correlations among PCSK9 and metabolic features in the GDM group.

Variable	R	P value
SBP	-0.03	0.816
DBP	0.09	0.460
Abdominal girth	0.022	0.841
BMI1	0.133	0.216
BMI2	0.04	0.724
FPG	0.251	0.015
1hPG	0.010	0.927
2hPG	0.118	0.271
HbA1c	0.275	0.009
FINS	0.021	0.827
1hPINS	0.067	0.483
2hPINS	-0.010	0.924
HOMA-IR	0.050	0.642
HOMA-β	-0.007	0.950
ISOGTT	-0.026	0.810
TC	0.273	0.010
HDL	-0.090	0.400
LDL	0.326	0.002
TG	0.121	0.260

Adjusted for age and gestational age.

pre-BMI, body mass index before pregnancy; BMI, body mass index in pregnancy; DBP, diastolic blood pressure; SBP, systolic blood pressure; FPG, fasting plasma glucose; 1hPG, 1-h post-meal plasma glucose; 2hPG, 2-h post-meal plasma glucose; FINS, fasting insulin level; 1hPINS, 1-h post-meal plasma insulin level; 2hPINS, 2-h post-meal plasma insulin level; ALT, alanine aminotransferase; Cr, serum creatinine; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; PCSK9, proprotein convertase subtilisin/kexin type 9.

to prevent so much cholesterol transport from maternal to the fetal at the third trimester (26). However, our study was conducted in the second trimester of pregnancy; serum LDL-C levels were higher in GDM women, while the difference was not significant. Therefore, we considered that the effect of placenta in GDM on the remarkably increased serum PCSK9 levels was uncertain and may be slight in this period. More profound investigations are necessary to detect the PCSK9 expression of maternal blood, fetal blood, and placenta tissue in GDM subjects.

In line with previous data, our research also confirmed the significant positive relationships between PCSK9 and TC as well as LDL-C. On the other hand, accumulating data indicated that PCSK9 was associated with multiple metabolic factors including blood glucose, insulin concentration, HbA1c, and HOMA-IR (27–30). In this current study, we also found positive associations of PCSK9 with FPG and HbA1c, presenting a metabolic relationship between PCSK9 and GDM. But the exact mechanisms behind remain unclear. Recent study reported that PCSK9 was positively correlated with BMI in women and obesity was associated with elevated PCSK9 levels (29). Among the participants of our study, most GDM patients with a normal weight before pregnancy had a gestational weight gain within normal parameters in the second trimester of pregnancy and we failed to find a significant positive relationship between BMI and PCSK9 in the GDM group. Therefore, in our research, we think that BMI in this period may not have a notable effect on PCSK9 levels. As gestation proceeds, patients with GDM may end up on

TABLE 3 | Logistic regression analysis on risk factors for gestational diabetes mellitus.

Variables	B	SE	OR value (95% CI)	P value
Age	0.064	0.030	1.066 (1.005–1.015)	0.032
Gestational age	0.153	0.140	1.165 (0.886–1.532)	0.286
Family history of diabetes	0.196	0.540	1.217 (0.423–3.503)	0.716
pre-BMI	0.043	0.067	1.044 (0.916–1.190)	0.519
Abdominal girth	0.008	0.029	1.008 (0.953–1.067)	0.773
PCSK9	0.009	0.003	1.009 (1.003–1.104)	0.003

pre-BMI, body mass index before pregnancy; CI, confidence interval; OR, odds ratio; SE, standard error; PCSK9, proprotein convertase subtilisin/kexin type 9.

TABLE 4 | Odds ratios and 95% confidence interval for GDM according to quartile of serum PCSK9 levels (n = 300).

	Q1 OR (95% CI)	Q2 OR (95% CI)	Q3 OR (95% CI)	Q4 OR (95% CI)	P value for trend
GDM					
Model 1	1	2.155 (1.071–4.337)	2.216 (1.093–4.493)	3.386 (1.668–6.874)	0.001
Model 2	1	2.517 (1.138–5.566)	2.520 (1.190–5.333)	3.818 (1.775–8.211)	0.001
Model 3	1	2.416 (1.098–5.312)	2.854 (1.241–6.564)	3.670 (1.652–8.155)	0.004
Model 4	1	2.337 (1.042–5.797)	3.068 (1.228–7.664)	3.559 (1.346–9.416)	0.009

Model 1 was not adjusted.

Model 2 was adjusted for age and gestational age.

Model 3 was adjusted for the variables in model 2 plus blood pressure, family history of diabetes mellitus, pre-BMI, and abdominal girth.

Model 4 was adjusted for the variables in model 3 plus TG, LDL-C, ALT, white blood cells, and HOMA-IR.

Subjects with a baseline circulating PCSK9 level in the lowest quartile group served as the reference group. Cutoff values in the four groups were Q1 <223.94 ng/ml, Q2 223.94–253.47 ng/ml, Q3 253.47–286.70 ng/ml, and Q4 >286.70 ng/ml.

GDM, gestational diabetes mellitus; OR, odds ratio; pre-BMI, body mass index before pregnancy; ALT, alanine aminotransferase; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; PCSK9, proprotein convertase subtilisin/kexin type 9.

the verge of obesity in cases of progressive insulin resistance (IR), worsened glycemic control, excessive fat accumulation.

It is best known that PCSK9 binds to LDL-R, leading to their intracellular degradation and then promoting plasma LDL-C levels and hyperlipidemia. Previous evidence indicated that excessive cholesterol accumulation played a direct role in pancreatic islet dysfunction and might well be a key factor underlying the progression of diabetes (31). Prolonged exposure to high levels of LDL or very low-density lipoprotein (VLDL) could damage β-cell function and induce their necrosis (32, 33). Besides, published research indicated that PCSK9 was involved in inflammation (34). Li et al. (35) found that plasma PCSK9 levels were positively associated with the white blood cell count in coronary artery disease (CAD) patients. In our study, white blood cell count was higher in the GDM group while a significant positive association was not found. Further insight investigations are needed. T2DM coupled with a frequent status of lipid abnormalities is associated with an increased risk of CAD (36). PCSK9 inhibitor is a new class of drugs that markedly reduces plasma LDL-C levels, especially in combination with other lipid-lowering drugs. Hence, targeting PCSK9 represents an efficient therapeutic approach of improving diabetic dyslipidemia (37, 38). The inhibition of PCSK9 can be achieved by several approaches. Inclisiran is a novel gene silencing therapy of PCSK9 synthesis, lowering LDL-C levels and reducing the risk for CAD events (39, 40). However, PCSK9 mediates multifarious functions instead of well-known functions of lipid metabolism regulation. The long-term safety of targeting PCSK9 is still unknown. Additionally, antibodies that inhibit PCSK9 should not be used in children and pregnant populations because of their unwarrantable safety (41).

In the present study, we discovered that serum PCSK9 levels showed a positive association with the risk of GDM from the data during the second trimester of pregnancy independent of several potential factors.

Although available data from early epidemiological and clinical trials documented that serum PCSK9 levels increased the incidence risk of DM, genetic findings were completely opposite. Therefore, the link between PCSK9 and DM was still conflicting and controversial (42). Further intensive studies are required to prove the cause-and-effect relationship between the two.

Several limitations need to be acknowledged. First, the study was unable to establish causality due to its observational nature. Second, we used HOMA-IR formula but not the standard method to precisely evaluate the degree of insulin resistance. Third, we failed to observe long-term changes of PCSK9 levels throughout pregnancy and after delivery.

CONCLUSIONS

In summary, this current study found that circulating PCSK9 levels increased significantly in the GDM group with a close relation to LDL-C, FPG, and HbA1c. Furthermore, serum PCSK9 levels were positively associated with the risk of GDM, suggesting a possible link between PCSK9 and GDM.

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 authors.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, and all participants signed an informed consent form. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LQ defined the research theme. YW, JS, and ZY performed the experiments, collected and analyzed the data, and wrote the paper. QS revised the article for important intellectual content. All authors contributed to the article and approved the submitted version.

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Association Between History of Gestational Diabetes Mellitus and the Risk of Arthritis in Women

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Objective: The association between gestational diabetes mellitus (GDM) and the risk of arthritis has not been reported. GDM increases the risk of long-term complications including diabetes and metabolic syndrome that are positively associated with the risk of arthritis. This study aimed to explore the association between GDM and the risk of arthritis.

Methods: Women (age ≥ 20 years) who had delivered at least one live birth were included from the 2007 to 2018 National Health and Nutrition Examination Survey cohort ($N = 11,997$). Patients who had a history of GDM and arthritis were identified by in-home interview. Subgroup analyses were conducted by arthritis types and status of obesity, current diabetes, metabolic syndrome, smoking, alcohol drinking, and physical activity.

Results: GDM was associated with increased odds of arthritis [multivariable-adjusted odds ratio (95% confidence interval): 1.31 (1.06–1.62)], and the result was similar in sensitivity analysis with further adjustment for metabolic syndrome [1.30 (1.05–1.60)]. In subgroup analyses, GDM was associated with increased odds of osteoarthritis [1.47 (1.05–2.06)], while no association was observed with rheumatoid arthritis [1.04 (0.69–1.57)] and other types [1.26 (0.94–1.68)]. GDM was associated with increased odds of arthritis in women without metabolic syndrome [1.34 (1.00–1.78)] and diabetes [1.35 (1.03–1.76)], in obese individuals [1.64 (1.24–2.16)], current/former smokers [1.43 (1.05–1.95)], and current drinkers [1.76 (1.00–3.14)], and in individuals engaging in higher levels of physical activity [1.53 (1.06–2.20)].

Conclusions: GDM was associated with increased odds of arthritis, and the association was independent of type 2 diabetes and metabolic syndrome.

Keywords: arthritis, National Health and Nutrition Examination Survey, type 2 diabetes, metabolic syndrome, gestational diabetes mellitus

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INTRODUCTION

Gestational diabetes mellitus (GDM) is diabetes that develops during pregnancy, and is currently the most common medical complication of pregnancy (1). The prevalence of GDM was estimated to be 7.6% in the US (2), and the overall weighted GDM prevalence in European countries was estimated at 10.9% (3). GDM increases the risk of long-term complications, including obesity, type

2 diabetes, metabolic syndrome, cancer, and cardiovascular disease (1, 4–7), and GDM provides unique opportunities for improving maternal health (8). Musculoskeletal conditions account for a significant proportion of non-communicable diseases contributing to disability adjusted life years, with osteoarthritis contributing most to this burden (9). The major arthritis-related disorders such as osteoarthritis and rheumatoid arthritis collectively make arthritis rank among the most common disabling health conditions (10). The global prevalence of rheumatoid arthritis was 460 per 100,000 population (11). The global age-standardized years lived with disability rate for osteoarthritis in 2017 was 118.8, an increase of 9.6% from 1990 (12).

Chronic inflammation may play a significant role in the development of arthritis-related disorders such as osteoarthritis and rheumatoid arthritis (13, 14). Inflammation and oxidative stress participate in the development of GDM and exert potentially harmful effects on the short and long-term maternal health (15). In addition, the long-term complications of GDM including obesity, type 2 diabetes, and metabolic syndrome are also positively associated with arthritis (16–20). However, the association between GDM and the risk of arthritis has not been reported in epidemiological studies. Based on the above-mentioned findings, we hypothesize that GDM is associated with increased odds of arthritis. In this study, we first explored the association between a history of GDM and the odds of arthritis in women, and then conducted stratified analyses to determine whether the association could still be observed in the absence of type 2 diabetes and metabolic syndrome. In addition, stratified analyses were also conducted by the modifiable risk factors for arthritis development, including smoking (21–23), alcohol drinking (24, 25), and low levels of physical activity (26, 27).

MATERIALS AND METHODS

Study Populations

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of US adults and children. The survey examines a nationally representative sample of about 5,000 persons each year. We used data from six cycles of the NHANES

TABLE 1 | Characteristics of the 2007–2018 NHANES adults according to the presence or absence of a history of gestational diabetes mellitus (GDM).

Variables	Women with GDM (928)	Women without GDM (11,069)	P^a
Age [years, mean (SD)]	45.45 (12.31)	53.47 (16.76)	<0.01
Race/ethnicity (%)			<0.01
Mexican American	21.77	15.78	
Other Hispanic	11.42	11.66	
Non-Hispanic White	35.78	40.77	
Non-Hispanic Black	17.78	22.12	
Other Race	13.25	9.66	
Annual family income (%)			<0.01
<$20,000	20.74	26.64	
$20,000–$34,999	33.37	33.71	
$35,000–$74,999	18.83	17.58	
≥$75,000	27.06	22.07	
Education (%)			<0.01
≤high school	43.64	50.14	
Some college or AA degree	35.99	30.63	
≥College graduate	20.37	19.23	
Vigorous/moderate recreational activities for at least 10 min continuously in a typical week (%)	44.29	40.85	0.04
Smoking (%)			0.34
Current smoker	18.86	17.45	
Former smoker	18.00	19.64	
Never smoker	63.15	62.91	
Alcohol (g/day)	4.21	4.04	0.70
Obesity (%)	56.06	43.05	<0.01
Current diabetes (%)	35.56	18.21	<0.01
Metabolic syndrome (%)	49.78	40.18	<0.01

M, Mean values; SD, standard deviation.

[a] *t-test was performed for continuous variables, and Chi-square test was performed for categorical variables.*

TABLE 2 | Characteristics of the 2007–2018 NHANES adults according to the presence or absence of arthritis.

Variables	Women with arthritis (4,293)	Women without arthritis (7,704)	P^a
Age [years, mean (SD)]	62.53 (12.22)	47.46 (15.82)	<0.01
Race/ethnicity (%)			<0.01
Mexican American	11.95	18.64	
Other Hispanic	10.65	12.20	
Non-Hispanic White	48.26	35.99	
Non-Hispanic Black	22.36	21.47	
Other Race	6.78	11.70	
Annual family income (%)			<0.01
<$20,000	33.10	22.32	
$20,000–$34,999	33.47	33.80	
$35,000–$74,999	15.97	18.63	
≥$75,000	17.45	25.25	
Education (%)			<0.01
≤High school	54.27	47.06	
Some college or AA degree	31.06	31.03	
≥College graduate	14.67	21.92	
Vigorous/ moderate recreational activities for at least 10 min continuously in a typical week (%)	31.10	40.49	<0.01
Smoking (%)			<0.01
Current smoker	18.57	17.00	
Former smoker	26.42	15.67	
Never smoker	55.02	67.33	
Alcohol (g/day)	3.67 (12.83)	4.27 (13.26)	0.02
Obesity (%)	53.02	39.10	<0.01
Current diabetes (%)	29.54	13.99	<0.01
Metabolic syndrome (%)	51.46	35.05	<0.01

M, Mean values; SD, standard deviation.

[a]*t-test was performed for continuous variables, and Chi-square test was performed for categorical variables.*

cohort (2007/2008 to 2017/2018), as these cycles specifically provided information for a history of GDM.

The inclusion criteria are as follows: (1) women aged 20 years or older; (2) women with at least one live birth; (3) women responding to the questions regarding a history of GDM; and (4) women responding to the questions regarding arthritis. In addition, women who were diagnosed with diabetes or arthritis prior to a diagnosis of GDM were excluded. Finally, we included 11,997 women in this study.

A History of GDM and Arthritis

The exposure for the analysis was the response to the question, "During your pregnancy, were you ever told by a doctor or other health professional that you had diabetes, sugar diabetes, or gestational diabetes?" and we considered women who answered yes to the above question as having a history of GDM (28, 29). The outcome for the analysis was arthritis, and patients with arthritis were identified with the questions of "doctor ever said you had arthritis?" and "which type of arthritis was it?".

Other Variables

According to the previous studies (23, 30, 31), the following covariates were included: age, race/ethnicity (Mexican–American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Races), body mass index (BMI, under/normal weight: <25 kg/m^2, overweight: 25 to <30 kg/m^2, obesity: ≥30 kg/m^2), education (≤high school, some college or AA degree, ≥college graduate), annual family income (<$20,000, $20,000–$44,999, $45,000–$74,999, ≥$75,000), smoking (current smoker, former smoker, never smoker), alcohol drinking (g/day), and physical activity (vigorous/moderate recreational activities for at least 10 min continuously in a typical week). In addition, current diabetes and metabolic syndrome were also considered in stratified analyses. Current diabetes was defined using a self-reported diagnosis of diabetes outside pregnancy or, if diabetes was not previously diagnosed, by a hemoglobin A1c level ≥ 6.5%, a fasting plasma glucose level ≥ 126 mg/dL, or 2-h plasma glucose ≥ 200 mg/dL (32). Type 1 diabetes was defined as an onset age of self-reported diagnosis of diabetes < 30 years and currently taking insulin (29). Any 3 of the 5 following metabolic-related disorders constitute diagnosis of metabolic syndrome (33): elevated blood pressure (≥130 mm Hg

TABLE 3 | Association between population characteristics and arthritis.

Characteristics	Odds ratio (95% confidence interval) of arthritis	P^a
Age	1.07 (1.06–1.08)	<0.01
Race/ethnicity		
Mexican American	1.00	
Other Hispanic	1.41 (1.20–1.65)	<0.01
Non-Hispanic White	2.54 (2.21–2.91)	<0.01
Non-Hispanic Black	1.91 (1.67–2.19)	<0.01
Other Race	1.45 (1.14–1.84)	<0.01
Annual family income		
<$20,000	1.00	
$20,000–$34,999	0.76 (0.67–0.85)	<0.01
$35,000–$74,999	0.65 (0.55–0.75)	<0.01
≥$75,000	0.52 (0.44–0.61)	<0.01
Education		
≤High school	1.00	
Some college or AA degree	0.90 (0.79–1.02)	0.11
≥College graduate	0.58 (0.50–0.67)	<0.01
Vigorous/ moderate recreational activities for at least 10 min continuously in a typical week	1.41 (1.27–1.58)	<0.01
Smoking		
Never smoker	1.00	
Former smoker	1.95 (1.68–2.27)	<0.01
Current smoker	1.37 (1.22–1.54)	<0.01
Alcohol (g/day)	0.99 (0.98–1.00)	<0.01
Obesity	2.09 (1.84–2.36)	<0.01
Current diabetes	2.91 (2.61–3.25)	<0.01
Metabolic syndrome	2.08 (1.88–2.31)	<0.01

[a] *The P values for significance tests.*

systolic blood pressure, ≥85 mm Hg diastolic blood pressure), elevated waist circumference (≥102 cm in men, ≥88 cm in women), reduced HDL-C (<40 mg/dL in men, <50 mg/dL in women), elevated triglycerides (≥150 mg/dL), and elevated fasting glucose (≥100 mg/dL).

Statistical Analysis

The logistic regression was used to calculate the odds ratios (95% confidence interval) [OR (95% CI)] of arthritis for women with a GDM history compared with those without a history of GDM. We calculated three different logistic regression models. Model 1 was adjusted for demographic variables (age and race/ethnicity). Model 2 included the covariates of model 1 with additional adjustment for BMI and socioeconomic status (education and family income). Model 3 included the covariates of model 2 with additional adjustment for health behaviors (alcohol drinking, smoking, and physical activity). Stratified analyses were conducted by arthritis types (osteoarthritis, rheumatoid arthritis, and other types), current status of metabolic syndrome (yes, no), obesity (yes, no), and current diabetes (yes, no), smoking (never, current/former), alcohol drinking (yes, no), and physical activity (vigorous/ moderate recreational activities for at least 10 min continuously in a typical week: yes, no). Tests for interactions were performed by using cross-product terms of GDM with these stratified factors. In addition, because GDM was associated with lower HDL-C, and increased BMI, blood pressure, total cholesterol, triglycerides, and glucose (34), we also conducted a sensitivity analysis in which we further adjusted for metabolic syndrome to determine whether these metabolic-related disorders could account for the association between GDM and the risk of arthritis. New multi-year sample weight was computed by dividing the 2-year sample weights by 6 (six cycles of NHANES were included in this study). All analyses used sample weights, strata, and primary sampling units to account for the complex, multistage, stratified, and cluster-sampling design of NHANES. All analyses were conducted with Stata 12.0, and $P \leq 0.05$ was considered statistically significant.

RESULTS

Among the 11,997 women included in this study, the weighted prevalence of GDM and arthritis was 8.00 and 34.72%, respectively. Women with a GDM history were more likely to be younger, engage in physical activity, and show higher prevalence of obesity, current diabetes (type 1 diabetes accounts for 2%), and metabolic syndrome. Annual family income and education levels differed significantly between women with a history of GDM and women without a history of GDM, while smoking status and alcohol drinking did not differ significantly between the two groups. Detailed characteristics of the participants are shown in **Tables 1**, **2**. The associations between the characteristics of the participants and arthritis are shown in **Table 3**, and all these characteristics were associated with arthritis.

Overall, the findings on the association between a history of GDM and the odds of arthritis were similar across the three statistical models, while the observed association was attenuated slightly in model 2 and model 3. In model 3, a history of GDM was associated with increased odds of arthritis [OR (95% CI): 1.31 (1.06–1.62), $P < 0.05$], and the result was similar in sensitivity analysis with further adjustment for metabolic syndrome [1.30 (1.05–1.60)]. In subgroup analyses by arthritis types, a history of GDM was associated with increased odds of osteoarthritis [1.47 (1.05–2.06)], while no association was observed with rheumatoid arthritis [1.04 (0.69–1.57)] and other types [1.26 (0.94–1.68)] (**Table 4**, **Figure 1**).

In stratified analyses by current status of metabolic syndrome, diabetes, obesity and physical activity, a history of GDM was associated with increased odds of arthritis in obese women [1.64 (1.24–2.16)] and in women without metabolic syndrome [1.34 (1.00–1.78)] and current diabetes [1.35 (1.03–1.76)]. In stratified analyses by status of smoking, alcohol drinking and physical activity, a history of GDM was associated with increased odds of arthritis in current/former smokers [1.43 (1.05–1.95)], current drinkers [1.76 (1.00–3.14)], and individuals engaging in higher levels of physical activity [1.53 (1.06–2.20)]. The interactions between a history of GDM and obesity ($P = 0.05$) and current diabetes ($P < 0.01$) were significant. However, the interactions with metabolic syndrome ($P = 0.12$), smoking ($P = 0.59$), alcohol

TABLE 4 | Odds ratios of arthritis for women with a history of gestational diabetes mellitus compared with those without a history of gestational diabetes mellitus.

Groups	Odds ratios (95% confidence intervals)				
	Cases of arthritis/N	Model 1	Model 2	Model 3	$P_{for\ interaction}$
Overall	4,293/11,997	1.46 (1.18–1.80)**	1.32 (1.06–1.64)*	1.31 (1.06–1.62)*	
Arthritis types					
Osteoarthritis	1,798/11,997	1.66 (1.22–2.29)**	1.46 (1.05–2.03)*	1.47 (1.05–2.06)*	
Rheumatoid arthritis	834/11,997	1.17 (0.77–1.77)	1.11 (0.75–1.63)	1.04 (0.69–1.57)	
Others	1,661/11,997	1.32 (0.99–1.76)	1.25 (0.93–1.67)	1.26 (0.94–1.68)	
Metabolic syndrome					0.12
Yes	2,209/4,909	1.29 (0.99–1.69)	1.18 (0.89–1.57)	1.24 (0.94–1.63)	
No	2,084/7,088	1.42 (1.07–1.88)*	1.39 (1.05–1.85)*	1.34 (1.00–1.78)*	
Obesity					0.05
Yes	2,244/5,233	1.61 (1.24–2.10)**	1.65 (1.24–2.19)**	1.64 (1.24–2.16)**	
No	1,988/6,643	0.95 (0.63–1.43)	0.93 (0.61–1.41)	0.95 (0.62–1.45)	
Current diabetes					<0.01
Yes	1,268/2,346	0.86 (0.62–1.20)	0.83 (0.60–1.15)	0.82 (0.58–1.16)	
No	3,025/9,651	1.39 (1.06–1.83)*	1.34 (1.01–1.76)*	1.35 (1.03–1.76)*	
Smoking					0.59
Never	2,362/7,549	1.40 (1.04–1.89)*	1.25 (0.91–1.73)	1.23 (0.89–1.71)	
Current/former	1,931/4,448	1.59 (1.18–2.14)**	1.42 (1.05–1.94)*	1.43 (1.05–1.95)*	
Current drinker					0.42
Yes	3,355/9,152	1.81 (1.05–3.13)*	1.68 (0.98–2.87)	1.76 (1.00–3.14)*	
No	938/2,845	1.35 (1.09–1.67)**	1.22 (0.97–1.53)	1.20 (0.95–1.52)	
Physical activity[a]					0.63
Yes	2,862/7,064	1.63 (1.15–2.32)**	1.51 (1.07–2.13)*	1.53 (1.06–2.20)*	
No	1,431/4,933	1.32 (1.00–1.74)*	1.16 (0.87–1.53)	1.13 (0.86–1.49)	

*$P < 0.05$, **$P < 0.01$.

Model 1: adjusted for age and race/ethnicity.

Model 2: adjusted for covariates in model 1 and body mass index, education, and annual family income.

Model 3: adjusted for covariates in model 2 and alcohol drinking, smoking, and recreational physical activity.

[a]*Vigorous/moderate recreational activities for at least 10 min continuously in a typical week.*

drinking ($P = 0.42$), and physical activity ($P = 0.63$) were not significant (**Table 4**), respectively, which may arise from the relatively wide range of 95% CIs or the possibility that these variables are independent of the history of GDM.

DISCUSSION

To our knowledge, this is the first epidemiological study to explore the association between GDM and the risk of arthritis. In this national survey cohort of 11,997 women, women with a history of GDM tended to have increased odds of arthritis, and the finding was robust even after accounting for metabolic syndrome that is potentially related to subsequent arthritis. Importantly, women with a history of GDM in whom metabolic syndrome and diabetes does not develop still have increased odds of arthritis. In stratified analyses, the association between a history of GDM and arthritis was observed in smokers, alcohol drinkers, and women engaging in higher levels of physical activity. In addition, GDM was significantly associated with increased odds of osteoarthritis, while no significant association was found with rheumatoid arthritis and other types.

Several potential reasons may explain the association between GDM and the risk of arthritis. First, women with a history of GDM were found to have a nearly 10-fold higher risk of developing type 2 diabetes than healthy controls [relative risk (95% CI): 9.51 (7.14–12.67)] (4), and a previous meta-analysis showed that type 2 diabetes was associated with increased odds of arthritis [OR (95%): 1.45 (1.18–1.78)] (20). Furthermore, patients with diabetes mellitus had 2.18 [95% (1.12–4.24)] times the odds of having osteoarthritis (35), which is the most common type of arthritis (13). Second, a recent meta-analysis found that the OR (95% CI) for metabolic syndrome was 3.45 (2.80–4.25) in women with a history of GDM compared to women without a history of GDM (5), and metabolic syndrome [OR (95% CI): 1.42 (1.16–1.73)], hypertension [1.70 (1.41–2.05), and hyperglycemia [1.23 (1.05–1.42)] were all positively associated with odds of osteoarthritis (19). Third, women with a history of GDM have significantly higher BMI (1.54 kg/m^2, 95% CI: 1.32 to 2.46) (34). Compared to normal weight subjects, overweight and obese subjects had 15% (95%CI: 1.03–1.29) and 31% (1.12–1.53) higher odds of rheumatoid arthritis (36), respectively, and the associations were stronger with osteoarthritis [overweight: 2.45 (1.88–3.20), obesity: 4.55

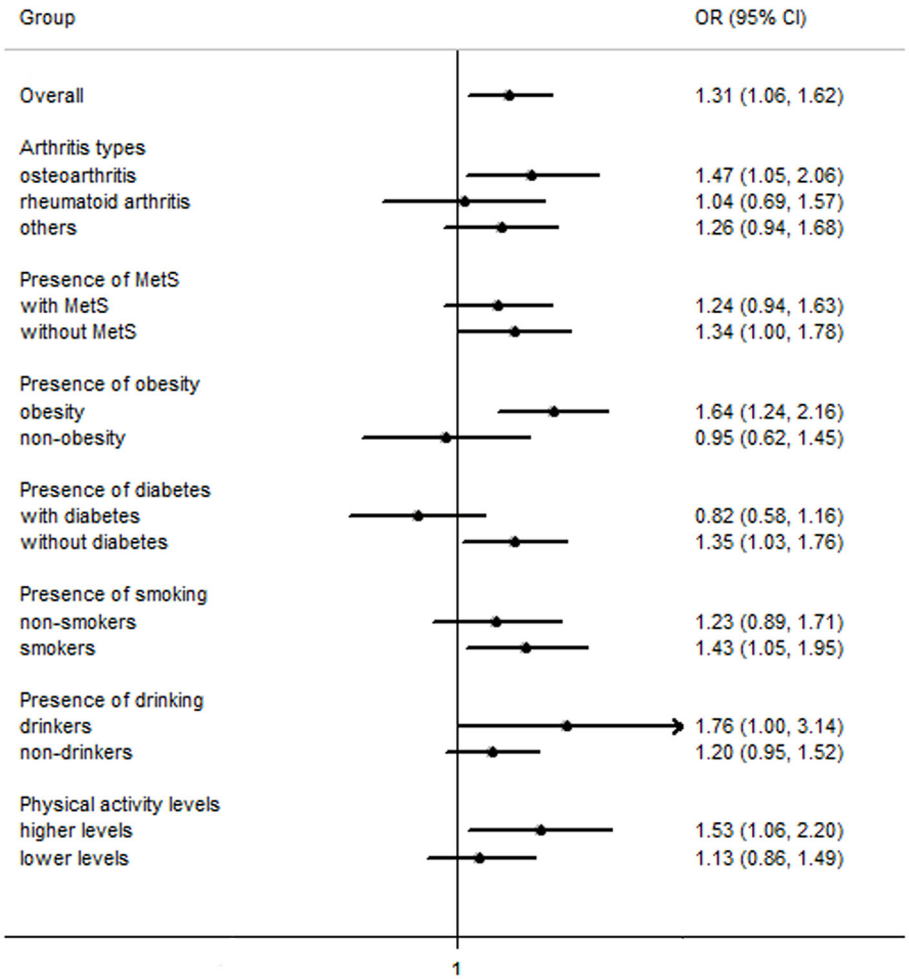

FIGURE 1 | Odds ratios of arthritis for women with a history of gestational diabetes mellitus compared with those without a history of gestational diabetes mellitus. MetS, metabolic syndrome; OR (95% CI), Odds ratio (95% confidence interval).

(2.90–7.13)] (18). These findings are consistent with those from our study in which a history of GDM was associated with odds of osteoarthritis but not rheumatoid arthritis. In addition, the association between a history of GDM and odds of arthritis was only observed in subjects with obesity [1.64 (1.24–2.16)], and the association was attenuated in model 2 also adjusting for BMI [1.32 (1.06–1.64)]. These findings suggested that BMI may partially account for the observed association between GDM and the odds of arthritis. However, the association between a history of GDM and the odds of arthritis remained significant in women without metabolic syndrome [1.34 (1.00–1.78)] and current diabetes [1.35 (1.03–1.76)], and a similar result was found in sensitivity analysis with further adjustment for metabolic syndrome [1.30 (1.05–1.60)]. These findings suggested the observed association between a history of GDM and the odds of arthritis was independent of type 2 diabetes and metabolic syndrome. These findings are comparable with those from previous studies in which the long-term risk for cardiovascular disease associated with GDM was not dependent upon intercurrent type 2 diabetes (7), but maybe explained partly by BMI (28).

Results from this study showed that a history of GDM was significantly associated with increased odds of arthritis among smokers, alcohol drinkers, and women engaging in higher levels of physical activity. While smoking was inversely associated with the risk of osteoarthritis in both observational studies (22) and Mendelian randomization studies (21, 37), a positive association was found between smoking and the risk of rheumatoid arthritis in both observational studies (38) and a Mendelian randomization study (39). These results indicate that the effects of smoking on arthritis may differ by different clinical subtypes of arthritis. Low to moderate alcohol consumption was found inversely associated with the development of both osteoarthritis (24) and rheumatoid arthritis (25), while a positive association was also found between alcohol consumption and osteoarthritis prevalence in

the Korean NHANES assessed by the alcohol use disorders identification test (40). Findings on the association between physical activity and arthritis are conflicting. While physical activity was found to be inversely associated with arthritis in observational studies (26, 27), physical activity may constitute an important risk factor for arthritis progression prediction with a machine learning approach (41). In this study, physical activity was also found positively associated with prevalence of arthritis [1.41 (1.27–1.58)] (**Table 3**). These findings indicate that the association between physical activity and arthritis may differ by clinical subtypes of arthritis, and intensity and measurement methods of physical activity (26, 27, 41), which need to be confirmed further. In summary, the findings available on the associations between smoking, alcohol drinking, and physical activity and arthritis remain contradictory, and the potential interactions between a history of GDM and these life-style factors on the risk of arthritis deserve to the confirmed further.

There are several limitations in this study. First, the causality cannot be determined because this is a cross-sectional study, and the causality should be confirmed further in prospective cohort studies. Second, a GDM history and arthritis diagnosis were based on self-report and misclassification could be of concern. However, data from the NHANES are considered to be valid to assess the prevalence of GDM and arthritis in the general population (10, 28, 29), and misclassification of patients with undiagnosed arthritis and GDM as healthy controls could have weakened the association.

In summary, a history of GDM was associated with increased odds of arthritis in this nationally representative cohort, and the association was independent of metabolic syndrome and type 2 diabetes. The association between a history of GDM and arthritis was observed in smokers, alcohol drinkers, and women engaging in higher levels of physical activity. The causality should be confirmed further in prospective cohort studies.

CODE AVAILABILITY

Analytic code will be made available from the corresponding author.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Center for Health Statistics Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YM and QL designed the study. WH conducted the statistical analysis. YM, BX, LL, and QL drafted the manuscript. QL made critical revisions. All authors contributed to the article and approved the submitted version.

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Impact of Risk Factors on Short and Long-Term Maternal and Neonatal Outcomes in Women With Gestational Diabetes Mellitus: A Prospective Longitudinal Cohort Study

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Aims: Universal screening of gestational diabetes mellitus (GDM) in women with no risk factors (RF) for GDM remains controversial. This study identified the impact of the presence of RF on perinatal and postpartum outcomes.

Methods: This prospective cohort study included 780 women with GDM. GDM RF included previous GDM, first grade family history of type 2 diabetes, high-risk ethnicity and pre-pregnancy overweight/obesity (OW/OB). Outcomes included obstetrical, neonatal and maternal metabolic parameters during pregnancy and up to 1 year postpartum.

Results: Out of 780 patients, 24% had no RF for GDM. Despite this, 40% of them needed medical treatment and they had a high prevalence of glucose intolerance of 21 and 27% at 6-8 weeks and 1-year postpartum, respectively. Despite similar treatment, women with RF had more neonatal and obstetrical complications, but they had especially more frequent adverse metabolic outcomes in the short- and long-term. The most important RF for poor perinatal outcome were previous GDM and pre-pregnancy OW/OB, whereas high-risk ethnicity and pre-pregnancy OW/OB were RF for adverse postpartum metabolic outcomes. Increasing number of RF were associated with worsened perinatal and long-term postpartum outcomes except for pregnancy-induced hypertension, C-section delivery and neonatal hypoglycaemia.

Conclusion: Women with no RF had a high prevalence of adverse perinatal and postpartum outcomes, while the presence of RF particularly increased the risk for postpartum adverse metabolic outcomes. This calls for a RF-based long-term follow-up of women with GDM.

Keywords: risk factors, gestational diabetes mellitus, maternal outcomes, neonatal outcomes, gestational diabetes, GDM

INTRODUCTION

Prevalence of gestational diabetes mellitus (GDM) is estimated to be between 3-30% (1, 2) worldwide and is associated with significant morbidity for the mother and her offspring. In Switzerland, its prevalence is around 11% (3, 4). Women with RF have a 2 to 7-fold prevalence of GDM than those without RF (RF) (2, 4). Although, there are discrepancies in European guidelines regarding the choice of RF that could serve as a base for selective GDM screening (4, 5), classical RF that are found in most guidelines are GDM in previous pregnancy, first grade family history of type 2 diabetes (FH T2DM), high-risk ethnicity and pre-pregnancy overweight or obesity (OW/OB) (5–8).

Even though universal screening is advocated by most international recommendations (9, 10), it remains controversial whether women without RF should also be screened. Many studies have compared various testing recommendations and timing of screening (11–13). Although these studies reported higher prevalence of GDM based on universal screening, its benefits on severe maternal outcomes and cost-effectiveness still remain unclear especially in limited resource settings (11–13). Benhalima et al. showed that the prevalence of GDM in women without established RF varied substantially between 50-70% when different European selective screening guidelines were applied to their cohort (5).

Several studies have shown the associations between RF for GDM and adverse perinatal and post-partum maternal and neonatal outcomes (14–18). The RF included higher oral glucose tolerance test (oGTT) values during pregnancy and in the postpartum period, HbA1c during pregnancy, paternal type 2 diabetes, multigravida, higher parity and longer interval between delivery and follow-up (14–18). However, there is a lack of long-term postpartum follow-up and no studies have investigated the impact of specific factors and of increasing number of GDM RF on perinatal and postpartum outcomes in order to stratify women according to their risk.

The aim of this study was to assess among women with GDM the prevalence of women without any classical RF and evaluate their adverse short- and long-term outcomes in a clinical context. We also sought to identify the impact of each individual RF independently on neonatal and maternal outcomes and to investigate if adverse outcomes increase with increasing number of RF. This could help to identify women who need an intensive long-term follow-up.

METHODS

Study Design and Patient Population

This was a prospective observational cohort of women with GDM followed in the Diabetes and Pregnancy Unit at the Lausanne University Hospital in Switzerland between April 2012 and December 2017. This cohort data has been previously described elsewhere (19–25). Women were followed during pregnancy and at the early (6-8 weeks) postpartum and included a nested subcohort at late (1-year) postpartum. Of all women included, 91% had complete laboratory data at the 6-8 weeks follow-up whereas 22% had complete laboratory data at the 1-year postpartum visit. The main reason for the low numbers of patients at 1-year postpartum visit was that the implementation of the 1-year postpartum follow-up visit started only in August 2015.

GDM Diagnosis, Treatment and Follow-Up

GDM was diagnosed according to the 'International Association of Diabetes and Pregnancy Study Groups' (IADPSG) and American Diabetes Association (ADA) Criteria (10). Thus, GDM was diagnosed if fasting glucose was ≥5.1 mmol/l and/or 1h glucose was ≥10.0 mmol/l and/or 2h glucose was ≥8.5 mmol/l, following a 75 g oGTT at 24-28 weeks of gestational age. The treatment of GDM was based on the current guidelines of the ADA (9) and of the Endocrine Society (7). After GDM diagnosis, women had a weekly appointment with a medical doctor, a specialized diabetes nurse and/or a dietician during which they received information about GDM, were taught how to perform a capillary blood glucose test and received more specific recommendations on lifestyle and gestational weight gain. Physical activity was encouraged and counselling by a physiotherapist and/or participation in GDM physical activity groups were proposed.

Patients were asked to perform 4 times per day self-monitoring of blood glucose according to international and local guidelines including fasting capillary glucose (FBG) in the morning and 2h (or 1h) postprandial glucose after each meal (26). Metformin and/or insulin were introduced when glucose values remained above targets between two or more times during a 1 to 2-week period (FBG > 5.3 mmol/l, 1h postprandial glucose > 8 mmol/l and 2h postprandial glucose > 7 mmol/l) despite lifestyle changes. Treatment was recommended based on glucose values (i.e. insulin in case of relatively high values), patient characteristics (i.e. BMI) and patient medical history and preference. Thus, metformin was especially used in case of patients who would refused insulin or if insulin doses were very high. Short acting insulin analogues were introduced and adapted to achieve 1h postprandial glucose ≤8 mmol/l or 2h post-prandial glucose ≤7 mmol/l and long acting insulin analogues to achieve FBG ≤5.3 mmol/l.

Measures

Measures of Glycaemic Control

HbA1c during pregnancy was measured using a chemical photometric method (conjugation with boronate; Afinion®). The Afinion® analyser has shown to have similar accuracy and precision compared to the high-performance liquid chromatography (HPLC), which is IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) standardized and DCCT (Diabetes Control and Complications Trial) aligned (26). In both postpartum periods, HbA1c was measured using HPLC. HbA1c at the end of pregnancy was only performed after March 2015. Whereas FPG, 2h glucose after a 75g oGTT and HbA1c were measured in the early postpartum visit, only FPG and HbA1c were measured in the late postpartum visit. Glucose intolerance was defined as fasting glucose

≥5.6mmol/l or 2h glucose ≥7.8mmol/l or HbA1c ≥5.7% (39 mmol/mol).

Maternal Predictors and Outcomes Measures

The following predictors were included in this study: previous GDM history, FH T2DM, high-risk ethnicity and OW/OB before pregnancy. Maternal ethnicity was classified as low risk (Europe, North America) and high risk (Asia, Central and South America, Africa, Oceania) groups (9).

Although these predictors are not the only factors recommended by the scientific communities, they are consistent with the ADA and the National Institute for Health and Care Excellence (NICE) RF for prediabetes, type 2 diabetes and GDM (5–8). We selected them because they are measures that are reliable and easy to record in daily practice on a larger scale and are frequent enough in this age group and population to have an impact. We therefore did not include other RF such as macrosomia in a previous pregnancy [also removed in the newest ADA recommendations (9)], polycystic ovary syndrome (PCOS), history of cardiovascular disease, hypertension, hypercholesterolemia and hypertriglyceridemia. We also did not include physical inactivity in the analysis because the accuracy of these data in our cohort was not optimal. Pre-pregnancy weight was taken from participants medical charts or, if missing, was self-reported (for the 1–2 months before pregnancy) and weight was measured during pregnancy and in the postpartum period. Height was measured at the first visit at the GDM clinic, body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in meters (kg/m2) and OW/OB was defined as BMI ≥ 25 kg/m2. Excessive gestational weight gain (GWG) up to presentation at GDM clinic was defined according to the Institute of Medicine recommendations (IOM) (27). We had valid complete data (n=780) for previous GDM history, FH T2DM, and OW/OB before pregnancy but unfortunately we had 27 out of 780 women missing data for ethnicity. Where ethnicity was not a predictor either as a single predictor or in the combined predictor scores, we included all 780 women in the analysis.

Adverse maternal outcomes including HbA1c at presentation and at the end of the pregnancy (20, 28), need for pharmacological treatment during pregnancy, C-section delivery, pre-eclampsia, pregnancy induced hypertension (PIH) and measures of glycaemic control at 6-8 weeks (defined as early postpartum) and 1 year (defined as late postpartum) were assessed. We also assessed composite outcome of maternal complications (including placenta previa and other various pregnancy related, rarer complications such as thrombopenia, chorioamnionitis). The decision for C-section delivery was taken by the patients' obstetrician.

Adverse neonatal outcomes were preterm delivery (defined as <37 weeks of gestation), large-for- gestational age baby [LGA; as defined by Intergrowth (29)], neonatal hypoglycaemia (defined as ≤2.5 mmol/l) and a composite of adverse neonatal outcomes (including Apgar score at 5 minutes < 7 and admission to the intensive care unit).

Statistical Analysis

All data were analysed using Stata/SE 15.0 (StataCorp LLC, TX, USA). Normally distributed continuous variables were expressed as means and standard deviation (SD). Binary outcomes were described in frequency and percentages (n, %). The results did not significantly vary with or without exclusion of nulliparous women and so nulliparous women were included in all descriptive and outcome analyses to increase external validity, except if the predictor was "GDM in previous pregnancy" (**Tables 1**–**4**). Excessive GWG up to presentation at GDM clinic was defined according to the IOM guidelines (27) and was transformed as a binary outcome. In **Table 2**, we presented raw data and differences, but we performed an additional analysis and adjusted for parity, gestational age at presentation, which were different between RF + and RF- women, and for gestational age at delivery for obstetric, neonatal and postpartum outcomes, as some of the outcomes might be influenced by this. In **Table 3**, we performed a univariate analysis with potential predictors of adverse outcomes and predictors with a p-value <0.05 were included in the multivariable logistic regression analysis model with stepwise procedure, adjusting for parity and gestational age at presentation.

In the logistic regression analyses, adjusted odds ratios (OR) were reported along with their respective 95% confidence intervals (CI). **Table 4** shows the results of regression analysis of the cumulative impact of the number of risk factors (0-4) on short and long-term maternal outcomes, adjusted for parity and gestational age at presentation. All statistical significances were two-sided and accepted at p<0.05 except for the multiple regression models where statistical significance was accepted at p<0.1 (in **Table 3**).

RESULTS

Out of the clinical population of 984 women who consented, we excluded 85 women who did not meet eligibility criteria of a clear definition of GDM, including also 16 women who did not attend their first scheduled appointment (**Figure 1**). We also excluded women who did not attend neither the early postpartum visit nor the postpartum laboratory analyses (n=109) and those with missing pre-pregnancy weight information (n=10). In the end, 780 pregnant women with GDM were included in the final analyses (**Figure 1**). Out of 780 women with GDM, 753 (97%) had available data for all four RF (27 missing data for ethnicity). Twenty-four percent (24%) (n=182) of women had no RF for GDM (**Table 1**). When nulliparous women were excluded (n=341), 18.3% of women in our cohort had no RF (RF-), 39.3% had one RF, 27.3% had two RF, 12.8% had three RF and 2.4% had more than three RF. The proportion of RF- women increased to 32% (n=254/780) when BMI ≥ 25 kg/m (2) counted only in combination with other adverse parameters (such as ethnicity, family history or GDM history) as a valid risk factor (6). When comparing RF- women and women with at least one RF (RF+), all descriptive characteristics except for maternal age and excessive GWG up to presentation at GDM clinic were

TABLE 1 | Descriptive characteristics of patients before pregnancy or at presentation.

	No risk factor (24%, n = 182)	At least one risk factor (76%, n = 571)	p-value
Age, years	33.4 (±5.6)	33.0 (±5.4)	0.430
Educational level			0.002
Compulsory school achieved	10 (12%)	44 (20%)	
CFC [a]	20 (23%)	48 (22%)	
High school	6 (7%)	29 (13%)	
University	50 (58%)	84 (38%)	
Not achieved	0	16 (7%)	
Gravidity	2.0 (±1.3)	2.6 (±1.6)	< 0.001
Parity	0.5 (±0.7)	1.0 (±1.1)	< 0.001
Weight before pregnancy, kg	59.5 (±6.4)	72.5 (±16.3)	< 0.001
BMI before pregnancy, kg/m^2	21.8 (±1.9)	27.2 (±5.6)	< 0.001
Gestational age at presentation, weeks	29.3 (±2.7)	28.4 (±3.5)	0.005
Weight at presentation, kg	82.7 (±16.3)	70.6 (±7.8)	< 0.001
Weight gain, kg	11.1 (±4.5)	10.1 (±5.8)	0.009
Excessive weight gain up to presentation at GDM clinic	129 (75%)	444 (79%)	0.175
Excess of weight gain up to presentation at GDM clinic, kg	2.9 (±4.5)	4.3 (5.6)	0.005
GDM in previous pregnancy[+]	0	61 (11%)	*n/a*
FH T2DM	0	248 (43%)	*n/a*
Ethnicity[++] (n=753)			< 0.001
Low risk (Europe, North America, Switzerland)	182 (100%)	301 (53%)	
High risk (Africa, Central and South America, Asia, Oceania)	0	270 (47%)	
OW/OB before pregnancy	0	371 (65%)	*n/a*

Data presented as n (%) or mean (± SD). BMI, Body mass index, FH T2DM, family history with 1st degree relative with type 2 diabetes mellitus, OW/OB, overweight/obesity defined as BMI ≥ 25 kg/m2. n/a, not applicable.

For educational level, data were available for n==307.

[a]CFC means general and vocational education.

[+]Only patients with parity ≥1 (n= 439).

[++]Low risk ethnicity defined as Europe (n=95, 53% and n=156, 27%), North America (n=3, 1% and n=1, 1%) and Switzerland (n=84, 46% and n=144, 25%) ethnic groups for no risk factor and at least one risk factor group respectively. High risk ethnicity defined as Africa (n=125, 22%), Central and South America (n=39, 6%), Asia (n=104, 18%) and Oceania (n=2, 1%) ethnic groups.

found to be significantly different between the two groups (all p ≤ 0.01). Gestational age at delivery was similar between the two groups [38.2 (±2.5) weeks in RF- women vs 38.6 (±1.6) weeks in RF+ women, p=0.826]. There were no significant differences in the number of RF in women attending or not attending the postpartum visits (n=709 at 6-8 weeks and n=171 at 1 year post-partum, p 0.69 and 0.46 respectively).

Table 2 shows the prevalence of maternal and neonatal outcomes according to the presence or absence of RF. The prevalence of severe maternal and neonatal outcomes was high in RF- women with 40% of them needing pharmacological treatment, 37% C-section delivery and 21% and 27% with glucose intolerance in early and late post-partum period respectively. RF+ women had higher glycaemic values at presentation, the end of pregnancy and in the early and late postpartum compared to RF- women and needed more frequently glucose-lowering medical treatment (all p ≤ 0.037 except for impaired glucose tolerance (IGT) in the early postpartum, p=0.05). Overall, 12% (n=46) were treated with metformin only, 5% (n=19) with a combination of metformin and insulin and 83% (n=317) with insulin alone. Although overall glucose intolerance was already 21% and 27% in the early and late postpartum in RF- women, this was increased by 2.1-2.9-fold in RF+ women (all p≤ 0.037, see above). In terms of obstetrical outcomes, RF- had higher rates of pre-eclampsia (4% vs 1% in RF+ women, p=0.031) but there were no differences in C-section delivery, PIH or in the composite outcome of maternal complications. When we adjusted for parity, gestational age at presentation and gestational age at delivery, all results remained unchanged except for pre-eclampsia, which lost its significance [OR 0.51 (95% CI 0.25-1.04), p=0.07)].

In terms of neonatal outcomes, RF+ women had almost twice the proportion of LGA (p=0.019), but less frequent preterm delivery (p=0.015). This difference was mostly driven by high-risk ethnicities (**Table 3**) without any differences in neonatal hypoglycaemia or the composite neonatal complications.

Regarding the impact of each of the four RF [GDM in previous pregnancy, FH T2DM, high-risk ethnicity and OW/OB before pregnancy (**Table 3**)] on short and long-term maternal and neonatal outcomes, OW/OB before pregnancy showed a significant impact on the majority of outcomes. This included the need for pharmacological treatment, PIH, HbA1c during pregnancy, C-section delivery, LGA, and overall glucose intolerance in the early and late postpartum. High-risk ethnicity was associated with reduced risk for preterm delivery, especially with but increased risk for overall glucose intolerance in the early and late postpartum. GDM in previous pregnancy showed an impact on HbA1c during pregnancy, on composite maternal complications, and on overall glucose intolerance in the early postpartum and FH T2DM on increased need for pharmacological treatment.

Table 4 shows the cumulative impact of increasing the number of RF on each maternal outcome. The addition of each risk factor was associated with an increased risk for worsened adverse, particularly maternal metabolic outcomes

TABLE 2 | Impact of the absence or presence of any risk factors on short and long-term maternal and neonatal outcomes.

	No risk factor (n = 182)	At least one risk factor (n = 571)	OR#/β-coefficient (95% confidence interval)	p-value
Maternal outcomes				
HbA1c at presentation, %	5.3 (±0.4)	5.5 (±0.4)	0.17 (0.09 – 0.24)	< 0.001
HbA1c at presentation, mmol/mol	34.7 (±3.9)	36.5 (±4.7)	1.85 (1.06 – 2.63)	< 0.001
HbA1c at the end of pregnancy, %	5.4 (±0.4)	5.6 (±0.4)	0.13 (0.02 – 0.23)	0.018
HbA1c at the end of pregnancy, mmol/mol	36 (±3.9)	37 (±4.4)	0.36 (0.24 – 2.49)	0.018
Need for pharmacological treatment	72 (40%)	310 (54%)	1.82# (1.29 – 2.55)	< 0.001
C-section delivery	59 (37%)	222 (41%)	1.22# (0.85 – 1.75)	0.285
Pregnancy induced hypertension	5 (3%)	19 (3%)	1.22# (0.45 – 3.31)	0.693
Pre-eclampsia	7 (4%)	7 (1%)	0.31# (0.11 – 0.89)	0.031
Composite maternal complications [a]	2 (1%)	21 (4%)	3.44# (0.79 – 14.79)	0.098
Overall glucose intolerance in the early postpartum+	33 (21%)	182 (36%)	2.07# (1.35 – 3.16)	0.001
Abnormal fasting glucose at 6-8 weeks postpartum	11 (7%)	84 (17%)	2.68# (1.39 – 5.16)	0.001
Pre-diabetes (IFG)	11 (7%)	76 (15%)		
Diabetes	0	8 (2%)		
Abnormal 2h glucose at 6-8 weeks postpartum	7 (5%)	46 (9%)	2.11# (0.94 – 4.78)	0.051
Pre-diabetes (IGT)	6 (4%)	39 (8%)		
Diabetes	1 (1%)	7 (1%)		
Abnormal HbA1c at 6-8 weeks postpartum	22 (16%)	126 (25%)	2.04# (1.25 – 3.33)	0.003
Pre-diabetes	22 (16%)	122 (24%)		
Diabetes	0	4 (1%)		
Overall glucose intolerance in the late postpartum+	10 (27%)	68 (52%)	2.91# (1.31 – 6.50)	0.006
Abnormal fasting glucose at 1 year postpartum	10 (27%)	60 (46%)	2.28# (1.02 – 5.09)	0.037
Pre-diabetes (IFG)	10 (27%)	57 (44%)		
Diabetes	0	3 (2%)		
Abnormal HbA1c at 1 year postpartum	1 (3%)	26 (19%)	8.75# (1.15 – 66.78)	0.004
Pre-diabetes	1 (3%)	23 (17%)		
Diabetes	0	3 (2%)		
Neonatal outcomes				
Preterm delivery	24 (14%)	43 (8%)	0.51# (0.30 – 0.88)	0.015
LGA	16 (10%)	95 (17%)	1.95# (1.11 – 3.42)	0.019
Neonatal hypoglycaemia	13 (7%)	49 (9%)	1.22# (0.65 – 2.30)	0.532
Composite neonatal complications[b]	22 (16%)	60 (12%)	0.72# (0.42 – 1.22)	0.236

Data presented as n (%) or mean (±SD). Odds ratio (OR) are marked with #.

Nulliparous patient were included in the analysis, as results were similar when they were excluded.

For HbA1c at presentation and at the end of pregnancy, data were available for n==298 and n=168, respectively. Early post-partum was defined as 6-8 weeks post-partum and late post-partum as 1 year post-partum. Glucose intolerance defined as fasting glucose ≥5.6mmol/l or glucose T120 ≥7.8mmol/l (only for early post-partum) or HbA1c ≥5.7% (39 mmol/mol). Preterm delivery was defined as < 37 weeks. LGA = large for gestational age. Neonatal hypoglycaemia was defined as ≤ 2.5 mmol/l.

+Overall glucose intolerance includes women with prediabetes and in addition 14 cases of diabetes in the early postpartum and 5 cases in the late post-partum.

[a]Maternal complications include various pregnancy related complications such as placenta praevia, thrombopenia,…

[b]Composite neonatal complications include Apgar score at 5 minutes < 7 and admission to intensive care unit (data available for n = 615).

except C-section delivery, PIH and composite maternal complications. The risk for overall glucose intolerance in the late postpartum increased by 1.7 with an additional risk factor resulting in a cumulative increased risk of 6.8 in the presence of all 4 RF compared to those with no RF(p=0.001). In contrast, the presence of more RF was associated with a reduced risk for pre-eclampsia (p=0.04). For neonatal outcomes, the cumulative impact of RF increased the risk for LGA, reduced the risk for preterm delivery (both $p \leq 0.025$), and had no impact on the other outcomes.

When nulliparous women were excluded from the stepwise regression analysis, the cumulative impact of the number of RF on short and long-term maternal outcomes was similar except that HbA1c at the end of pregnancy and LGA did not remain significant (p=0.2 and p=0.6 respectively) (**Supplementary Table 1**).

When excessive GWG up to presentation at GDM clinic was added as an independent risk factor (**Supplementary Table 2**), the prevalence of RF- women decreased from 24% to 6% (n=43, $p < 0.001$). Maternal and neonatal outcomes were similar when excessive GWG up to presentation at GDM clinic was included except for loss in significance for the differences in pre-eclampsia and abnormal IGT in early post-partum (**Supplementary Table 2**). However, when we included GWG, the composite neonatal outcome became significantly different and was higher in RF- compared to RF+ women ($p = 0.01$).

DISCUSSION

This prospective cohort study explored the impact of RF on perinatal and postpartum outcomes in women with GDM in a clinical setting. We demonstrated that RF- women had a high prevalence of adverse maternal and neonatal outcomes despite a clinical follow-up. The presence of RF had a particular impact on overall glucose intolerance in the early and late postpartum. Pre-pregnancy OW/OB was a main predictor for both perinatal and

TABLE 3 | Independent impact of individual risk factors on maternal and neonatal outcomes.

	Significant risk factors	OR #/β-coefficient (95%CI)	p-value
Maternal outcomes			
HbA1c at presentation	Previous GDM	0.23 (0.12 – 0.35)	< 0.001
	OW/OB	0.17 (0.10 – 0.22)	< 0.001
HbA1c end pregnancy, %	Previous GDM	0.17 (-0.02 – 0.36)	0.078
	OW/OB	0.10 (0.01 – 0.19)	0.023
Need for pharmacological treatment	FH T2DM	1.52# (1.1 – 2.1)	0.009
	OW/OB	1.70# (1.26 – 2.29)	< 0.001
C-section delivery	OW/OB	1.36# (1.01 –1.83)	0.046
Pregnancy induced hypertension	OW/OB	2.48# (1.00 – 6.17)	0.050
Composite maternal complications [a]	Previous GDM	4.01# (1.32 – 12.20)	0.014
Overall glucose intolerance in early postpartum[+]	Previous GDM	2.17# (1.16 – 4.04)	0.015
	High risk ethnicity	1.67# (1.19 – 2.34)	0.003
	OW/OB	1.67# (1.19 – 2.33)	0.003
Overall glucose intolerance in late postpartum[+]	High risk ethnicity	2.20# (1.11 – 4.38)	0.025
	OW/OB	2.45# (1.29 – 4.69)	0.007
Neonatal outcomes			
Preterm delivery	High risk ethnicity	0.39# (0.21 – 0.73)	0.004
LGA	OW/OB	1.97# (1.28 – 3.03)	0.002

Stepwise multiple regression including all variables at 0.05 of significance was performed. All 4 risk factors and all outcomes were tested, but for readability only significant ones reported (p < 0.1, i.e. statistical significance was defined as a p-value < 0.1). All analyses were adjusted for parity and gestational age at presentation. Nulliparous patients were included in the analysis, as results were similar when excluded. Odds ratio (OR) are marked with #.

OW/OB= pre-pregnancy overweight or obesity. FH T2DM = family history of 1st degree with type 2 diabetes mellitus. Early post-partum was defined as 6-8 weeks post-partum (n=670) and late post-partum as 1 year post-partum (n=168). Glucose intolerance was defined as fasting glucose ≥5.6mmol/l or glucose T120 ≥7.8mmol/l (only for early post-partum) or HbA1c ≥5.7% (39 mmol/mol). Preterm delivery defined as < 37 weeks. LGA = large for gestational age.

[+]Overall glucose intolerance includes women with prediabetes and in addition 14 cases of diabetes in the early post-partum and 5 cases in the late post-partum.

[a]Maternal complications include various pregnancy related complications such as placenta praevia, thrombopenia,…

TABLE 4 | Cumulative impact of the number of risk factors (0-4) on short and long-term maternal outcomes.

	OR#/β-coefficient (95%CI)	p-value
Maternal outcomes		
HbA1c at presentation	0.12 (0.09 – 0.15)	< 0.001
HbA1c at the end of pregnancy, %	0.08 (0.04 – 0.13)	< 0.001
Need for pharmacological treatment	1.50# (1.2 – 1.7)	< 0.001
C-section delivery	1.18# (1.00 – 1.40)	0.225
Pregnancy induced hypertension	1.00# (0.64 – 1.55)	0.996
Pre-eclampsia	0.47# (0.23 – 0.96)	0.040
Composite maternal complications [a]	1.42# (0.92 – 2.19)	0.116
Glucose intolerance in early post-partum[+]	1.39# (1.16 – 1.66)	< 0.001
Glucose intolerance in late post-partum[+]	1.66# (1.15 – 2.38)	0.001
Neonatal outcomes		
Preterm delivery	0.71# (0.53 – 0.96)	0.025
LGA	1.31# (1.05 – 1.64)	0.016
Neonatal hypoglycaemia	0.98# (0.74 – 1.31)	0.926
Composite neonatal complications [b]	0.94# (0.73 – 1.21)	0.808

All analysis were adjusted for parity and gestational age at presentation. Nulliparous patients were included in the analysis. Odds ratio (OR) are marked with #.

For HbA1c at presentation and at the end of pregnancy, data were available for n==298 and n=168, respectively. Early post-partum was defined as 6-8 weeks post-partum and late post-partum as 1 year post-partum. Glucose intolerance defined as fasting glucose ≥5.6mmol/l or glucose T120 ≥7.8mmol/l (only for early post-partum) or HbA1c ≥5.7% (39 mmol/mol). Preterm delivery defined as < 37 weeks. LGA = large for gestational age. Neonatal hypoglycaemia defined as ≤ 2.5 mmol/l.

[+]Overall glucose intolerance includes women with prediabetes and in addition 14 cases of diabetes in the early postpartum and 5 cases in the late post-partum.

[a]Maternal complications include various pregnancy related complications such as placenta praevia, thrombopenia,…

[b]Composite neonatal complications include Apgar score at 5 minutes < 7 and admission to intensive care unit (data available for n=615).

postpartum outcomes. Finally, an accumulation of RF was associated with a gradual increase in adverse outcomes, particularly the need for pharmacological treatment, LGA and overall postpartum glucose intolerance, while pre-eclampsia and preterm delivery were reduced.

The prevalence of RF- women in our cohort is similar to those found in a recent multi-ethnic Belgian study (24% in our cohort vs 25.6% in Benhalima et al) (5). Even though all women in our cohort regardless of the number of RF received a regular follow-up and lifestyle advice, the prevalence of adverse maternal outcomes in RF- women was still high. The need for a pharmacological treatment was higher in our study than in other studies (40-54% in our study vs 23% in Benhalima et al. (30) and 27-30% in Alves et al. (14) studies respectively) which

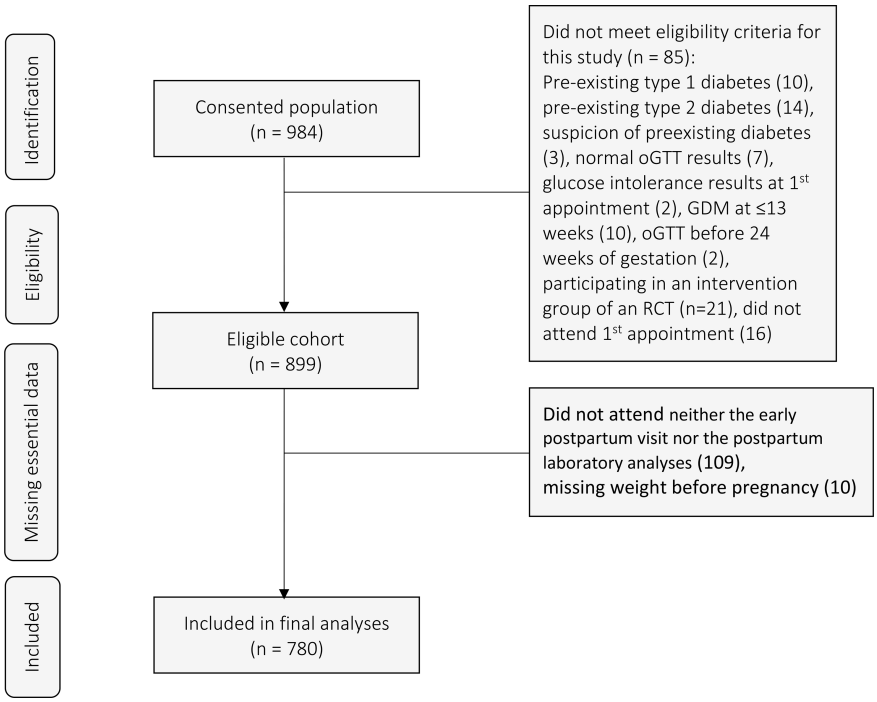

FIGURE 1 | Flow chart of participating patients. oGTT, oral Glucose Tolerance Test; GDM, gestational diabetes mellitus; RCT, randomized controlled trial.

may be related to the elevated prevalence of high-risk ethnicities and family history of diabetes in the current cohort. Moreover, pregravid obesity has an impact on excessive fetal growth that can be attenuated by appropriate and early initiation of medical therapy (31–33).

Moreover, the prevalence of glucose intolerance in RF- women was 2-4 fold increased compared to the prevalence described in healthy cohorts of similar age (34, 35). Nevertheless, the incidence of most adverse maternal outcomes was higher in RF+ women compared to those RF-. This was not the case for C-section delivery, which might be dependent on the obstetrician and the diagnosis of GDM, and not just a protocol decision, nor for pre-eclampsia and preterm delivery. When adjusted for parity and gestational age at delivery and gestational age at presentation, preeclampsia was no longer significantly reduced in RF+ women. The reduced risk for preterm delivery in RF+ women might be explained by the lower risk found in non-Caucasian ethnicities. Indeed, preterm delivery was no longer reduced in RF+ women when adjusted for ethnicity (p=0.16, data not shown).

In a study conducted by Benhalima et al., the authors showed that as high as 33% of cases of GDM were missed when selective screening guidelines were applied (5). Recently, the ADA recommendations were modified and OW/OB was added as a risk factor in combination with other RF (36). In our cohort, we chose to analyse OW/OB as an independent risk factor. Most importantly, OW/OB is a modifiable GDM risk factor that had a considerable impact on most maternal outcomes and on LGA. When adapted to the new ADA definition (6), the prevalence of adverse maternal outcomes in the absence of RF would be even higher than what we have reported (**Table 2**). RF+ women had higher prevalence of overall glucose intolerance in early and late postpartum compared to their RF- counterparts. Our results are consistent with other studies that reported the general prevalence of glucose intolerance after GDM (14, 30) but higher than what was reported in an Irish study with a mean follow-up of 2.6 years (46% vs 18%) (37).

We found that previous GDM and particularly OW/OB were major RF associated with adverse outcomes. In our study, the odds of overall glucose intolerance in the early or late postpartum period were 1.7 and 2.4 times higher in OW/OB women. Although previous studies did not compare the respective importance of different RF, our data regarding the role of OW/OB as an independent risk factor for adverse maternal outcomes in women with GDM is in line with previous data (1, 14, 38). These previous studies reported that higher pre-pregnancy BMI was associated with higher risk of developing type 2 diabetes after pregnancy (1, 14, 38). Other RF such a previous GDM and high risk ethnicity have also been significantly linked to a higher risk of developing glucose intolerance and diabetes after GDM (14, 39–41). In our cohort, previous GDM and high-risk ethnicity were particularly associated with adverse outcomes in the postpartum period whereas FH T2DM was not as important in women already diagnosed with GDM. As OW/OB and excessive GWG up to presentation at GDM clinic represent the only modifiable established RF, they constitute an important target

to change outcomes. As previous GDM is one of the most important RF for development of GDM, all women with previous GDM regardless of the presence of other RF should receive follow-up to detect and treat diabetes and also glucose intolerance (9). On the other side, our data also suggest that the cumulative presence of several RF is associated with a higher prevalence of adverse, mostly metabolic outcomes and thus the number of RF should inform the intensity of long-term follow-up in women with GDM.

The strengths of our study include our prospective design and the follow-up within usual clinical care. The multi-ethnic background of our population and the high rate of adherence to early postpartum testing (91%) increase the generalizability of our findings. Limitations of our study include the relatively low proportion of women (22%) followed until 1-year postpartum (as the 1-year follow-up started in 2015) and the absence of a control population. However, the glucose intolerance results at 6-8 weeks postpartum and 1 year postpartum are very similar even if outcomes were evaluated at the end of the follow-up. Other known RF for postpartum glucose intolerance that are not included in the recommendation of international societies were pre-pregnancy RF (maternal age, age of menarche, multiparity), glycaemic values of the oGTT, gestational weight gain and need for insulin treatment during pregnancy (5, 16–18) could be considered, but for reasons of simplicity they were not added in our analyses. We did not include maternal age (≥ 35 years) as a risk factor, because it is not part of the ADA recommendations but this could be a helpful tool for selective screening. However, the inclusion of women aged ≥ 35 years, (74 women) did not significantly change the results. Finally, our population was had a high prevalence of high-risk ethnicities and family history of diabetes. This, however, also reflects the multiethnicity of the population in Switzerland.

CONCLUSION

We found that, among women with GDM, even those without diabetes-related RF had a high prevalence of adverse perinatal and postpartum outcomes. Most of these outcomes were more prevalent (%) in RF+ women and increased with increasing numbers of RF. Based on our results, postpartum follow-up should be proposed to all women with GDM regardless of the presence or absence of RF. OW/OB status was strongly associated with adverse perinatal and maternal complications, especially with adverse long-term metabolic outcomes. These women should be considered as a priority target during and after pregnancy as OW/OB, but also excessive GWG up to presentation at GDM clinic could be altered by lifestyle changes. High priority should be given to women with several RF to promote more intense and personalized patient-centred care.

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 Human Research Ethics Committee of the Canton de Vaud (No. 326/15) approved the study protocol. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AC and JP wrote the first draft of the manuscript. AC, CK, DQ and JP had full access to the study data. All authors contributed to the interpretation of data, critically revised the manuscript and approved the final version for submission. JP is the guarantor of this work, and, as such, takes full responsibility for the integrity of the data used in the analysis.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.866446/full#supplementary-material

Supplementary Table 1 | Multivariate regression analysis of cumulative impact of the number of risk factors on short and long-term maternal outcomes with exclusion of nulliparous women. All analysis were adjusted for parity and gestational age at presentation. For HbA1c at presentation and at the end of pregnancy, data were available for n==298 and n=168, respectively. Early post-partum was defined as 6-8 weeks post-partum and late post-partum as 1 year post-partum. Glucose intolerance defined as fasting glucose ≥5.6mmol/l or glucose T120 ≥7.8mmol/l (only for early post-partum) or HbA1c ≥5.7% (39 mmol/mol). Preterm delivery defined as < 37 weeks. LGA = large for gestational age. Neonatal hypoglycaemia defined as ≤ 2.5 mmol/l. [+] Overall glucose intolerance includes women with prediabetes and in addition 14 cases of diabetes in the early postpartum and 5 cases in the late post-partum. [a] Maternal complications include various pregnancy related complications such as placenta praevia, thrombopenia,… [b] Composite neonatal complications include Apgar score at 5 minutes < 7 and admission to intensive care unit (data available for n=615).

Supplementary Table 2 | Impact of the absence or presence of any risk factors on short and long-term maternal outcomes including excessive GWG up to presentation at GDM visit as a risk factor. Data presented as n (%) or mean (±SD). Nulliparous patient were included in the analysis, as results were similar when excluded. For HbA1c at presentation and at the end of pregnancy, data were available for n==298 and n=168, respectively. Early post-partum was defined as 6-8 weeks post-partum and late post-partum as 1 year post-partum. Glucose intolerance defined as fasting glucose ≥5.6mmol/l or glucose T120 ≥7.8mmol/l (only

for early post-partum) or HbA1c ≥5.7% (39 mmol/mol). Preterm delivery defined as < 37 weeks. LGA = large for gestational age. Neonatal hypoglycaemia defined as ≤ 2.5 mmol/l. [+] Overall glucose intolerance includes women with prediabetes and in addition 14 cases of diabetes in the early postpartum and 5 cases in the late post-partum. [a] Maternal complications include various pregnancy related complications such as placenta praevia, thrombopenia,… [b] Composite neonatal complications include Apgar score at 5 minutes < 7 and admission to intensive care unit (data available for n=615).

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Is the Development of Gestational Diabetes Associated With the ABO Blood Group/Rhesus Phenotype?

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Aims: There are few published data on the putative association between the ABO blood group/rhesus (Rh) factor and the risk of developing gestational diabetes mellitus (GDM). Our aim was to explore the link between each one factor and GDM development.

Methods: All women having given birth at Lille University Medical Center (Lille, France) between August 1st, 2017, and February 28th, 2018, were tested for GDM, using the method recommended in the French national guidelines. The risk of GDM was assessed for each ABO blood group, each Rh phenotype and combinations thereof, using logistic regression models.

Results: 1194 women had at least one GDM risk factor. The percentage of GDM varied with the ABO group (p=0.013). Relative to group O women, group AB women were more likely to develop GDM (OR = 2.50, 95% CI [1.43 to 4.36], p=0.001). Compared with the Rh-positive O group, only the Rh-positive AB group had an elevated risk of developing GDM (OR = 3.02, 95% CI [1.69 to 5.39], p < 0.001).

Conclusions: Our results showed that Rh-positive group AB women have a greater risk of GDM. With a view to preventing GDM, at-risk individuals could be identified by considering the ABO blood group phenotype either as a single risk factor or in combination with other risk factors.

Keywords: gestational diabetes mellitus, pregnancy, ABO blood group, rhesus factor, risk factor

INTRODUCTION

The ABO blood group classification is based on the presence or absence of A and B antigens controlled by the gene coding for ABO glycosyltransferase (located on chromosome 9) (1). Increased susceptibility to many diseases have been linked to modulation of the expression of ABO blood group antigens, including infections (2), vascular diseases (3), and cancer (4). A few

epidemiologic and genetic studies have examined possible associations between ABO blood and the risk of type 2 diabetes mellitus (T2DM); however, the results have been inconsistent. Group A was found to be associated with T2DM in some studies (5, 6), whereas group B protected against DM in others (7, 8). The rhesus(Rh)-negative group O and Rh-positive group A phenotype were significantly more frequent in a cohort of 224 diabetic patients in Nigeria than in controls (9). A prospective study of a cohort of 82,104 people in France found that group A and group B had a greater risk of T2DM, relative to group O (10).

Gestational diabetes mellitus (GDM) is defined as a glucose tolerance disorder with onset during pregnancy. In 2010, the Societé Francophone de Diabétologie/Collège National des Gynécologues et Obstétriciens français (SFD/CNGOF) have proposed a selective screening, based the preence of risk factors. The expert panel for the Franch guidelines has recommended GDM screening if at least on of the following convential criteria is present: maternel age ≥ 35 years, preconception BMI≥ 25 kg/m2, a personal history of GDM, or the presence of diabetes in a first degree relative, or birth of a child with macrosomia. It's not excluded that other risk factor could be integrated in this screening's strategy. Other risk factors such as polycystic ovary syndrome, metabolic syndrome have not however been retained in France. It is associated with elevated fetal-maternal morbidity and long-term complications in the mother and child. The incidence of GDM and pregestational diabetes is rising worldwide (11). It is generally accepted that women with GDM are at a greater risk of subsequently developing T2DM (12). Although glucose values usually normalize soon after delivery, underlying beta-cell dysfunction may persist.

In contrast to the data on T2DM, there are reports on the possible association between the ABO blood type and the risk of developing GDM. A study of 792 healthy Iranian women reported that AB individuals had significantly higher fasting glucose levels in the second trimester (13). Other larger studies have come to the opposite conclusion (14, 15). Even though the discrepancies between these studies might be due (at least in part) to genetic differences between ethnic groups, there is a need to investigate the possible relationship between the ABO/Rh phenotypes and GDM in other populations. Given the lack of robust literature data, the objective of the present study was to investigate this association in a large cohort of pregnant women in France.

RESEARCH DESIGN AND METHODS:

Study Population

This single-center, retrospective observational study was conducted at Lille University Medical Center (Lille, France) and was based on electronic medical records that are routinely completed at delivery for every woman who gives birth. According to French law, patients are informed that care-related data may be used for research purposes unless he/she opposes this use. The present study data had been anonymized prior to analysis, and we registered the study database with the French National Data Protection Commission (*Commission nationale de l'informatique et des libertés* (Paris, France); reference: 21/846.

All patients who received antenatal care and gave birth at the Obstetrics and Gynecology Department at Jeanne de Flandres Hospital between August 1st, 2017, and February 28th, 2018, were tested for GDM, using the protocol recommended by the French-speaking Society of Diabetes and the French National College of Obstetricians and Gynecologists (16). The protocol involves the measurement of the fasting plasma glucose (FPG) level at the initial prenatal visit for women with one or more of the following risk factors: preconception body mass index (BMI), ≥25 kg/m^2, age ≥35, a personal history of gestational diabetes, a child with macrosomia, or a familial history of diabetes. The expert consensus considers patients with fasting glucose ≥7 mmol/L at the initial visit to have type 2 diabetes, so the diagnostic criterion for GDM is FPG 5.1 to 6.9 mmol/L. Women with an initial FPG below 5.1 mmol/L were retested at between 24 and 28 weeks, using a 75 g 2-hour oral glucose tolerance test (OGTT); GDM was defined according to the criteria issued by the International Association of Diabetes and Pregnancy Study Group (17). The exclusion criterion were missing data, loss to follow-up, a lack of GDM screening, and other type of diabetes (i.e. women without GDM risk factors).

Intervention

Once the diagnosis had been confirmed, the patients attended an initial consultation at which preventive hygiene and dietary measures were explained. The women were instructed to self-monitor their blood glucose six times a day (before and after each of their three meals). The results were collected using dedicated telemonitoring software (MyDiabby, Healthcare SAS, Bordeaux, France) and/or by phone with a specialist nurse twice a week. The women were given specific glycemic targets. Insulin therapy (either with short-acting insulin analogues before meals and/or long-acting insulin analogues at bedtime) was initiated when the glucose targets were not met after 7 to 10 days of good adherence to hygiene and dietary rules. The follow-up with an obstetrician complied with the French guidelines (16).

Collected Data and Definitions

Data on the women's demographic characteristics, the ABO blood group, the Rh phenotype and the presence of risk factors were extracted from medical charts. Data on age, preconception body mass index (BMI, in kg/m^2), any previous pregnancies, and risk factors were collected from electronic and paper-based hospital records. GDM risk factors (including preconception BMI ≥25 kg/m^2, age ≥35, a personal history of gestational diabetes, a child with macrosomia, and a family history of diabetes) were recorded. For patients with GDM, we also recorded the date of the GDM diagnosis, the type of GDM screening, the plasma glucose values (fasting or during an OGTT), the treatment start date, and the type of treatment (diet or insulin therapy). The management of gestational

diabetes was to determine the proportion of women on dietary measures alone and the proportion on insulin.

Laboratory Analysis

The ABO-RH blood group and the Rh-positive KEL 1 phenotype were determined at the French Blood Agency's laboratory (Lille, France). The determination was based on automated hemagglutination in microplate assays (Qwalys, Diagast) or in column microfiltration assays (AutoVue Innova, Ortho or IH 500, Biorad).

Statistical Analysis

Continuous variables are reported as mean (standard deviation, SD) when normally distributed or median (interquartile range, IQR) otherwise. Categorical variables are reported as frequency (percentage). The normality of distributions was assessed using histograms and using the Shapiro-Wilk test. Associations between maternal characteristics during pregnancy according to their ABO blood groups and rhesus were measured using analysis of variance for Gaussian continuous variables, Kruskal-Wallis test for non-Gaussian continuous variables and Chi-Square test for binary variables. The risk of having gestational diabetes was assessed for each ABO blood group, each rhesus system and combination thereof, using logistic regression models. Odds ratios (OR) and their 95% confidence intervals were reported as effect size. All statistical tests were done at the two-tailed α-level of 0.05 using the SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

The Study Population

Between August 1st, 2017, and February 28th, 2018, 1660 women were screened for GDM and considered for enrollment in the study (**Figure 1**). We excluded 466 pregnancies: two women had T2DM before pregnancy, data on GDM status was missing for 4 patients, and 460 women had no GDM risk factors. Ultimately, we assessed 1194 women (351with GDM and at least one risk factor and 843 without GDM).

Baseline Maternal Characteristics

The women's clinical characteristics are summarized in **Table 1**. Overall, the mean age was 31.2 ± 5.8 years, and the median [IQR] preconception BMI was 26.2 kg/m^2 [22.7 – 30.1]. Of the 1194 women, 429 (36.0%) had a first-degree family history of diabetes, 122 (10.3%) had a child with macrosomia, and 159 (13.4%) had a history of GDM. 34.2% of women with GDM and 33.1% without GDM had an age ≥35 years and respectively 70.1% and 57.8% have a BMI ≥ 25 kg/m^2.With regard to the ABO blood group, there were 510 group O women (42.7%), 481 group A women (40.3%), 146 group B women (12.2%) and 57 group AB women (4.8%). 148 of the women (12.4%) were Rh-negative. After GDM screening, 351 (29.4%) women GDM, and 93 (26.8%) were being treated by insulin therapy and diet. The GDM group and non-GDM groups differed significantly with regard to the ABO blood group distribution but not with regard to the Rh phenotype.

Maternal Characteristics During Pregnancy, as a Function of the ABO and Rh Blood Groups

No differences were found in age or BMI as a function of the ABO blood group (**Table 2**). The first-trimester fasting plasma glucose differed significantly by ABO blood group (p=0.017) but not by Rh group (p=0.38).

The blood glucose levels after 0, 60 and 120 minutes of the OGTT differed as a function of the ABO phenotype (p=0.022, p=0.009, p=0.007, respectively). The percentage of women with GDM differed significantly when comparing the ABO groups (p=0.013). No differences were found between Rh phenotype.

Associations Between the ABO Blood Group and the Rh Phenotype With the Presence of GDM

Compared with group O, group AB women were more likely to develop GDM (OR=2.50 95%CI [1.43 to 4.36], p=0.001) (**Figure 2**). The differences were not statistically significant for blood groups A and B compared with group O (p=0.20, p=0.38, respectively).

One ABO/Rh combination were associated with the presence of GDM (p=0.023). Compared with Rh-positive group O women, Rh-positive group AB women had a significantly higher risk of developing GDM (OR =3.02,95%CI [1.69 to 5.39], p < 0.001). The analysis could not be performed for Rh-negative group AB women because the sample size (n=4) was too small.

DISCUSSION

Few researchers have examined the potential link between the ABO blood type or the Rh system and the development of GDM. The objective of the present single-center study was to determine whether a link was present among a relatively large cohort of women having given birth at a large French tertiary hospital. We found that the first-trimester fasting plasma glucose level varied significantly according to the ABO blood group (p=0.017) but not according to the Rh group. Interestingly, we also found that group AB women had a greater risk of developing GDM, relative to group O women (OR [95%CI] = 2.50, [1.43 to 4.36], p=0.001). Compared with Rh-positive group O women, only Rh-positive group AB had a significantly higher risk of developing GDM (OR [95%CI] = 3.02, [1.69 to 5.39], p < 0.001).

In the general population in France, the blood type distribution is 45% for group A, 9% for group B, 3% for group AB, and 43% for group O, 15% for the Rh-negative phenotype, and 85% for the Rh-positive phenotype (18). The blood type distribution in our study population (40.3%, 12.2%, 4.8% and 42.7% for groups A, B, AB and O, respectively) was therefore in line with the general population data. One can usually observe minor differences within countries and major

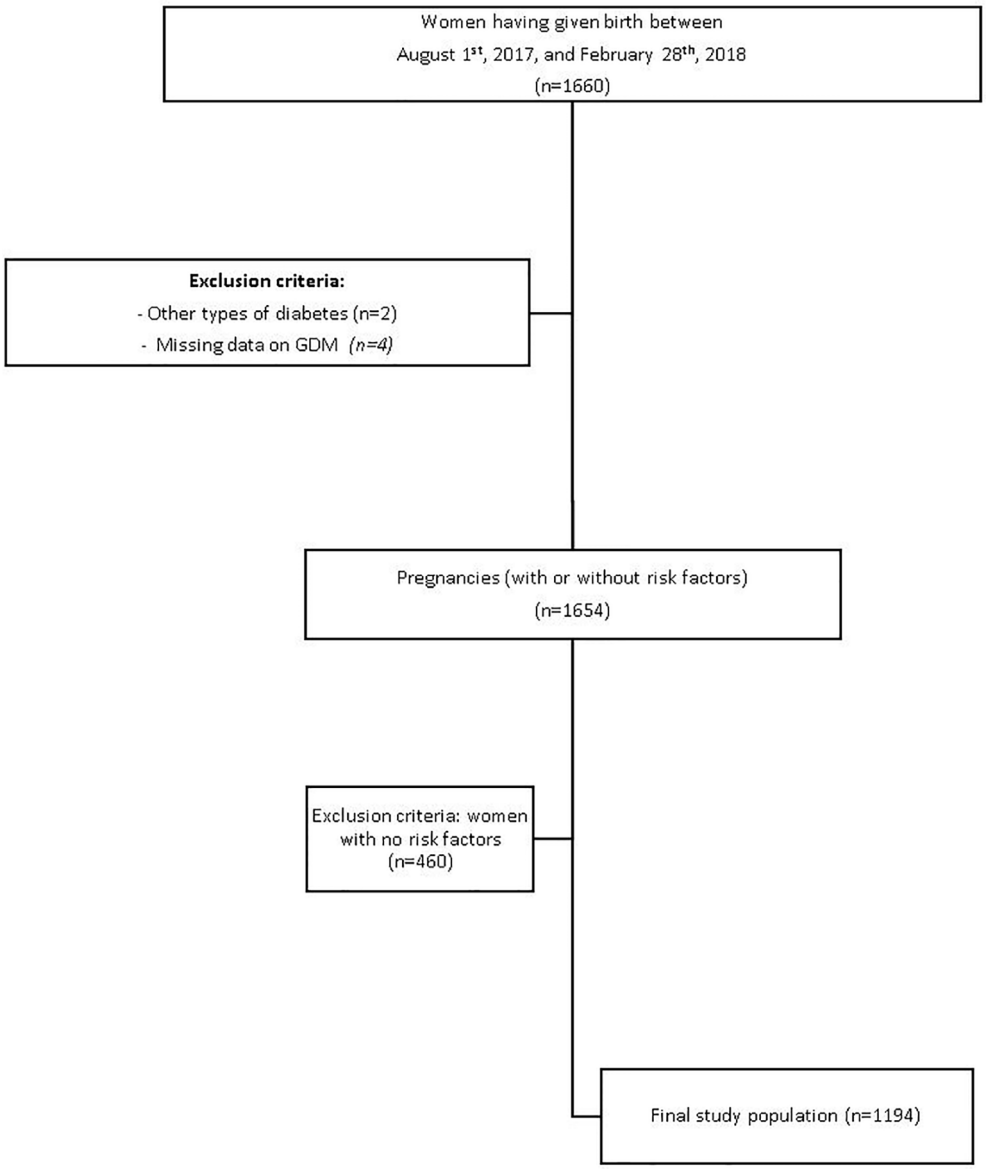

FIGURE 1 | Study flow chart.

differences between countries and continents; for example, the Rh-negative phenotype is extremely rare in Asia (19). Hence, caution must be taken when comparing our present results with data from non-French or non-European cohorts. Our GDM population cohort had much the same characteristics (in terms of age and BMI, etc.) as other French cohorts (20). The prevalence GDM (29.4%) is line with other studies performed in the Lille area, where the local population has a high prevalence of risk factors (overweight and/or obesity, a family history of diabetes, etc.).

A study of the French E3N cohort of 82104 patients found that the O blood group was associated with a lower risk of developing type 2 diabetes, relative to the A, B, and AB groups (10). However, the study publication did not report the percentage of women with a personal history of GDM (10). The latter results are consistent with a Nigerian study in which the proportion of people with an O+ group was significantly lower in patients with DM than in non-diabetics. In contrast to our present results, Nigerian people with O- or A+ blood groups appeared to be at a greater risk of developing DM in the (9). A study of a population in northwest Ethiopia suggested that antigen B was associated with a greater increased risk of T2DM, whereas a O blood group was associated with a lower risk (21).

The literature data on women with GDM are heterogeneous. A study of 792 pregnant women in Iran found that the second-

TABLE 1 | Baseline characteristics of the study population.

	Total (n = 1194)	With GDM (n=351)	Without GDM (n=843)
Age *years*	31.2 ± 5.8	31.3 ± 6.0	31.1 ± 5.7
Preconception BMI *kg/m²*	26.2 [22.7 ; 30.1]	27.5 [23.7 ; 32.1]	25.6 [22.3 ; 29.3]
1rst degree history of diabetes	429/1193 [36.0]	149/351 [42.5]	280/842 [33.3]
Personal history of macrosomia	122/1185 [10.3]	42/347 [12.1]	80/838 [9.5]
Personal history of GDM	159/1190 [13.4]	101/350 [28.9]	58/840 [6.9]
Nulliparity	418/1194 [35.0]	111/351 [31.6]	307/843 [36.4]
ABO blood groups			
Group O	510/1194 [42.7]	135/351 [38.5]	375/843 [44.5]
Group A	481/1194 [40.3]	145/351 [41.3]	336/843 [39.9]
Group B	146/1194 [12.2]	44/351 [12.5]	102/843 [12.1]
Group AB	57/1194 [4.8]	27/351 [7.7]	30/843 [3.6]
Rhesus system			
Rhesus -	148/1194 [12.4]	44/351 [12.5]	104/843 [12.3]
Rhesus +	1046/1194 [87.6]	307/351 [87.5]	739/843 [87.7]
GDM	351/1194 [29.4]	–	–
GDM with insulin therapy	93/347 [26.8]	93/347 [26.8]	–

Values are expressed as the number/total number (%), mean ± standard-deviation or median [interquartile range].
BMI, body mass index; GDM, gestational diabetes mellitus.

trimester fasting blood glucose levels was higher in blood group AB women than in blood group A women (14). In a study of 233 women with GDM, Karagoz et al. found that the AB blood group was more frequent in patients with GDM than in the control group (p=0.029) (22). The disparities between these literature findings and our present results might be due to a difference in ABO blood group distribution in the population: the proportion of AB patients was greater in Karagoz et al.'s study (12% in the GDM group and 8% in controls) than in our study (7% and 3.8%, respectively). Furthermore, Karagoz et al.'s study did not report data on traditional risk factors for GDM. In contrast, risk factors were prevalent in our study population. Shimodaira et al. confirmed that the AB blood group was a risk factor for GDM in Japanese population having undergone universal, two-step screening for this disease (23). Here, we found that only the Rh-positive AB group had a significantly greater risk of developing GDM (OR = 3.02, 95% CI = 1.69 to 5.39, p < 0.001 vs. the Rh-positive O group). Shimodaira et al. could not adequately study the Rh phenotype because (as was mentioned above) Rh-negative status is extremely rare in Japan (0.5%) (23).

Our results differ from other published data. In a large, prospective, population-based study of pregnant women in China, the AB blood group was associated with a lower risk of GDM (relative to A, B, and O blood groups), and the largest group of non-GDM women had a B blood group (33.4%) (24). In

TABLE 2 | Characteristics of the study population during pregnancy, according to the ABO blood group and the Rh phenotype.

	O (n=510)	A (n=481)	B (n=146)	AB (n=57)	p	Rhesus - (n=148)	Rhesus + (n=1046)	p
Age *years*	31.2 ± 5.8 510/510	31.0 ± 5.9 481/481	31.1 ± 5.0 146/146	32.2 ± 6.0 57/57	0.56	30.4 ± 5.7 148/148	31.3 ± 5.8 1046/1046	0.087
BMI *kg/m²*	26.3 [22.6 ; 29.7] 504/510	26.0 [22.7 ; 30.1] 479/481	26.5 [22.9 ; 30.3] 145/146	27.3 [23.1 ; 31.6] 57/57	0.53	26.3 [22.0 ; 30.4] 148/148	26.2 [22.8 ; 29.9] 1037/1046	0.83
FPG 1^{rst} trimester *g/L*	4.73 ± 0.44 452/510	4.78 ± 0.45 425/481	4.71 ± 0.40 124/146	4.90 ± 0.51 50/57	**0.017**	4.79 ± 0.52 130/148	4.75 ± 0.43 921/1046	0.38
75 OGTT t.=0 min. *g/L*	4.46 [4.24 ; 4.73] 363/510	4.51 [4.24 ; 4.79] 339/481	4.46 [4.24 ; 4.79] 108/146	4.62 [4.46 ; 4.90] 39/57	**0.022**	4.51 [4.24 ; 4.79] 111/148	4.46 [4.24 ; 4.73] 738/1046	0.59
75 OGTT t.= 60 min. *g/L*	6.82 [5.67 ; 8.09] 353/510	7.10 [6.00 ; 8.31] 330/481	6.88 [5.67 ; 8.14] 102/146	8.11 [6.44 ; 9.24] 38/57	**0.009**	7.07 [5.72 ; 8.31] 106/148	6.93 [5.89 ; 8.20] 717/1046	0.74
75 OGTT t.= 120 min. *g/L*	6.05 [5.12 ; 7.15] 355/510	6.16 [5.28 ; 7.21] 333/481	6.35 [5.17 ; 7.21] 102/146	6.71 [6.00 ; 8.64] 39/57	**0.007**	6.44 [5.01 ; 7.54] 107/148	6.11 [5.23 ; 7.21] 722/1046	0.49
GDM	135/510 [26.5]	145/481 [30.1]	44/146 [30.1]	27/57 [47.4]	**0.013**	44/148 [29.7]	307/1046 [29.3]	0.92
GDM with insulin therapy	34/134 [25.4]	40/142 [28.2]	12/44 [27.3]	7/27 [25.9]	0.96	12/44 [27.3]	81/303 [26.7]	0.94

Values are expressed as the number/total number (%), mean ± standard-deviation, or median [interquartile range].
BMI, body mass index.
FPG, fasting plasma glucose.
OGTT, oral glucose tolerance test.
GDM, gestational diabetes mellitus.
Significant values are in bold.

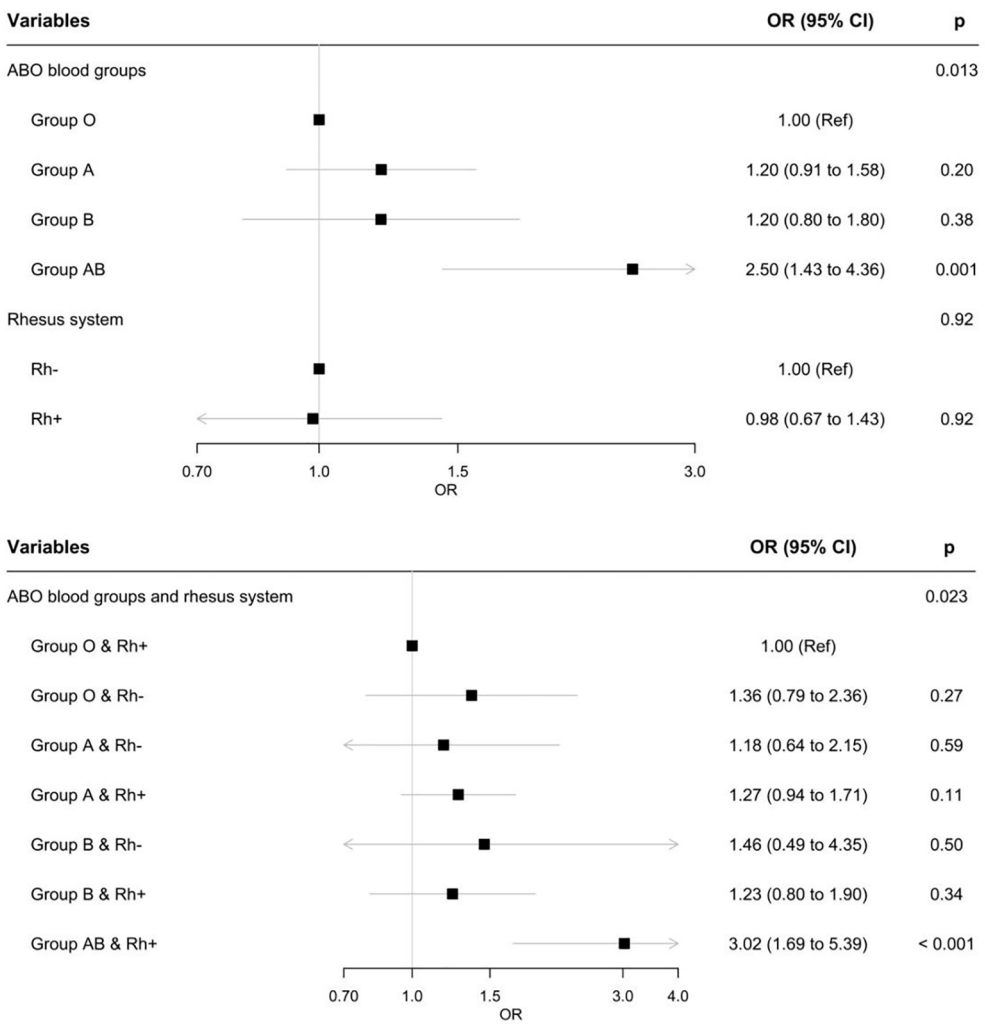

FIGURE 2 | Associations between ABO blood groups and GDM, between the Rh phenotype and GDM, and combinations of ABO and Rh phenotypes and GDM.

contrast, the A blood group accounted for the largest group (45%) of non-GDM women in our study.

A retrospective cohort study in Israel found that the AB blood group was associated with a lower risk of developing GDM (defined according to Carpenter and Coustan's criteria) than other blood groups, after adjustment for maternal age, parity, and the number of fetuses. The frequency of the Rh phenotype was similar in the GDM and control groups (25). Lastly, our findings are not in line with Sapanont et al.'s observations 600 pregnant women in Thailand who were screened for GDM screening according to Carpenter and Coustan's criteria; in a regression analysis designed to adjust for traditional risk factors, the O blood group was independently associated with an elevated risk of GDM (26).

The Rh factor's major roles are related to the membrane organization of phospholipids and the expression of various membrane glycoproteins. It has been suggested that the Rh factor can influence glucose transport and thus the development of diabetes. The few studies of Rh factor and GDM did not observe an association. In a Turkish study, the Rh-negative phenotype was significantly more frequent in diabetic patients than in control non-diabetic patients (27). Our study showed that only the Rh-positive AB women had a significantly greater risk of developing GDM. Our results therefore showed that in combination with other factors (i.e. blood groups), Rh-positive status increases the risk of GDM.

It is known that the ABO blood group distribution varies significantly from one ethnic group to another. Therefore, our results indicate that the strength of the association between the ABO blood group/Rh system and the risk of GDM will depend on the population in question. These results need certainly to be replicated in other popualtions. Even if this is a single center study, the implication is all women are French nationals. These findings might be quite a bit more generalizable to other western European population.

GDM is probably a multifactorial disease of pregnancy that can be induced by genetic factors, insulin resistance, and/or inflammatory processes. In view of the pathogenic similarity

between T2DM and GDM, these biomarkers might be also involved in the pathogenesis of GDM. Identifying risk factors early in pregnancy might help to predict a subsequent clinical diagnosis of GDM. Our present results suggest that the incidence of GDM is higher for the AB blood group than for the other blood groups. Blood typing is an inexpensive test that could be readily performed during the antepartum period. Hence, the blood type might constitute another factor for predicting the occurrence of GDM. Accordingly, we suggest that the AB blood type could be added to the list of risk factors for GDM.

Our study had several strengths. Firstly, the present study was the first to address this topic in a population of women screened for GDM in accordance with the French national guidelines. Secondly, this was a large, population-based study in which all the traditional GDM risk factors were documented in detail. The study also had some limitations. Firstly, the single-center cohort design means that the data might not be readily generalizable - even though we checked that the ABO blood group distribution was similar to that of the general population in France. For France, the suggestion that AB blood type be considered as an additional risk factor would only apply for those who do not already have a risk factor, because those with other risk factor would be screened under existing guidelines. Unfortunately, patients without risk factor were excluded from the present study. Lastly, we did not access a number of variables though to influence with the development of GDM (e.g. the women's levels of physical activity, socioeconomic factors, and weight gain during pregnancy).

CONCLUSION

Our results showed that the AB/Rh-positive women have a higher risk of GDM. Given the clinical implications of GDM and the fact that ABO/Rh blood group phenotypes are stable over the lifespan, it is important to determine the nature of the association between the ABO blood groups and the risk of GDM. With a view to prevention and if our present findings can be replicated by studies of larger populations in other countries, it might be possible to use the ABO blood group phenotype (as a single risk factor or combined with other risk factors) to identify individuals at risk of GDM in early pregnancy. However, further epidemiological and genetic studies are needed to define the relationship between ABO blood groups and GDM. So, to date, the evidence for the relationship between ABO blood group and GDM is still limites and inconsistent. Even if Chen et al. will conducted a metaanalysis to further confirm the relationship between ABO blood group and GDM, it would be interesting to carried out others prospectives studies considering this risk factor alone or in combinaison with the others usuals risk factors in a Caucasian population (28).

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CNIL 21/846. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MP collected data. ML and AV wrote the manuscript. CM, ED supervised and conducted the statistical analyses. LG, DS, CM, ED and AV reviewed the manuscript. AV initiated and supervised the study and reviewed the manuscript. AV is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

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Gestational Diabetes Mellitus and Energy-Dense Diet: What Is the Role of the Insulin/IGF Axis?

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Gestational diabetes mellitus (GDM), is one of the most important pregnancy complications affecting approximately 15% of pregnant women. It is related to several gestational adverse outcomes in the fetus, *e.g.*, macrosomia, shoulder dystocia, stillbirth, neonatal hypoglycemia, and respiratory distress. Women with GDM have a high risk of developing type 2 diabetes in the future. The pathogenesis of GDM is not completely understood; nevertheless, two factors could contribute to its development: β-cell dysfunction and failure in insulin secretion in response to insulin resistance induced by gestation. Both processes, together with the physiological activities of the insulin-like growth factors (IGFs), play a crucial role in glucose transport to the fetus and hence, fetal growth and development. IGFs (both IGF-1 and IGF-2) and their binding proteins (IGFBPs) regulate glucose metabolism and insulin sensitivity. Maternal nutritional status determines the health of the newborn, as it has substantial effects on fetal growth and development. Maternal obesity and an energy-dense diet can cause an increase in insulin and IGF-1 serum levels, producing metabolic disorders, such as insulin resistance, GDM, and high birth weight (> 4,000 g) due to a higher level of body fat. In this way, in GDM pregnancies there is an increase in IGF-1 and IGF-2 serum levels, and a decrease in IGFBP-1 and 4 serum levels, suggesting the crucial role of the insulin/IGF system in this gestational outcome. Here, the present review tries to elucidate the role that energy-dense diets and the insulin/IGF-1 signaling pathway perform in GDM pregnancies.

Keywords: IGF-1 (insulin-like growth factor-1), energy-dense diet, obesity, gestational diabetes mellitus (GDM), placenta

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Abbreviations: AKT, protein kinase B; ALS, acid-labile subunit; FAK, focal adhesion kinase; FGR, fetal growth restriction; GDM, gestational diabetes mellitus; GH, growth hormone; GHRH, growth hormone-releasing hormone; HUVECs, human umbilical vein endothelial cells; IGFs, insulin-like growth factors; IGF-1, insulin-like growth factor 1; IGF1R, IGF-1 receptor; IGF-2, insulin-like growth factor 2; IGF2R, IGF-2 receptor; IGFBPs, IGF binding proteins; IGFBP-rPs, IGFBP-related protein 1; INSR, insulin receptor; IRS-1, insulin receptor substrate 1; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; MAPK, mitogen-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; NO, nitric oxide; PAPP-A, enzyme pregnancy-associated plasma protein-A; PI3K, phosphatidylinositol-3-kinase; PL, placental lactogen; RTK, tyrosine kinase receptor; sFlt-1, fms-like tyrosine kinase receptor-1; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor A; sVEGFR-1, soluble form of the vascular endothelial growth factor receptor 1; VEGFR-2, vascular endothelial growth factor receptor 2; WHO, World Health Organization.

INTRODUCTION

According to the World Health Organization (WHO), malnutrition refers to deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients, leading to undernutrition or overnutrition (1). The increasing prevalence of obesity has implications for the health of human population as this condition augments the risk of developing several serious diseases (2). Overweight and obesity rates increased by two-fifths between 1990 and 2010, especially in women of reproductive age (3, 4), being a highly prevalent pathology in Latin American countries (> 30%) (5, 6). Therefore, obesity represents an enormous threat to public health (7, 8).

Maternal obesity before and after conception increases the risk of a wide range of pregnancy-related complications (9). Experimental animal studies have shown that obesity during gestation impairs glucose tolerance, promotes insulin resistance, endothelial cell dysfunction, hypertension, hyperphagia and increases adiposity in offspring (10, 11). Moreover, obesity during pregnancy can lead to gestational diabetes mellitus (GDM), an adverse condition that increases the risk of fetal overgrowth (macrosomia), fetal adiposity and several alterations throughout infant's life, including predisposition to obesity, type 2 diabetes mellitus (T2DM) and metabolic disorders (7, 12). As it is shown in several clinical studies, GDM has been associated with high concentrations of numerous hormones, such as insulin-like growth factor 1 (IGF-1, an essential hormone for intrauterine and postnatal growth and development), insulin; and other molecules with endogenous functions, *e.g.*, glucose, C-reactive protein, fibrinogen, lipids, etc. (13). Particularly, a recent systematic review summarizes the clinical studies of GDM where some molecular biomarkers of IGF-1 signaling pathway have been analyzed; but the existing evidence is inconclusive, so it is necessary to elucidate this mechanism (14).

The main reason for this rise in obesity, and thus diabetes and GDM problems, is due to the consumption of foods and/or diets rich in fats and sugars, which may be attributable to alterations in the insulin/IGF-1 signaling pathway (15). However, the relationship between this cascade and pregnancy adverse outcomes is not entirely known.

ENERGY-DENSE (HIGH INTAKE OF SUGARS AND SATURATED FATTY ACIDS) DIET IN PREGNANCY

Nowadays, energy-dense diets are a constant trend in society, due to the accessibility of their products, both in large and small commerces. In the Western world these diets are regularly consumed during pregnancy (16). These diets are characterized by an elevated intake of sugars and fatty acids, foods that have a high energy density (4 kcal/g and 9 kcal/g, respectively), defined as the amount of energy in a particular weight of food (17, 18).

Due to its main functions in growth, IGF-1, as well as growth hormone (GH), nutrients are an important part of its signaling transduction regulation. In this sense, clinical and experimental studies have shown that intake of protein (especially from milk and yogurt), fibre, starch from wholegrains, redmeats, fats and oils are positively associated with IGF-1 serum levels (19–21). The disparity of one or more nutrients could affect growth, anabolism and nutrient sensing.

In addition to the increased availability of high density foods, the decreased needs for physical exertion have promoted the raise in obesity before, during and after pregnancy. Clinical studies have shown that overweight women during pregnancy have higher insulin and IGF-1 levels, which can have substantial impact on women and fetal health (15). For example, maternal malnutrition during pregnancy can lead to fetal growth restriction (FGR), an IGF-1 deficiency condition characterized by a low neonatal birth weight (< 2,500 g) (22). Conversely, maternal obesity before gestation, excessive weight gain during pregnancy or an energy-dense diet (high intake of sugars and saturated fatty acids) can promote high birth weight (> 4,000 g), the development of insulin resistance and GDM during pregnancy, and the incidence of metabolic disorders and high deposition of body fat in children born from obese mothers (15, 23–25).

Experimental models of high fat diets have shown hyperphagia in the offspring from mothers fed with sugar high diets, but not high in fat or low in carbohydrates (10), preferring high-fat, sugary and salty foods rather than normal chow diet (26, 27). Moreover, these high-sugar diets and a combination of being overweight/obese before pregnancy and/or junk food diet during this period may increase the risk of macrosomia and overweight in newborns and in later life (28–30).

Likewise, energy-dense diets reduce glucose tolerance, alter insulin sensitivity in late pregnancy and feto-placental glucose metabolism, as insulin/IGF signaling is impaired, leading to maternal metabolic dysfunction that can have several consequences for fetal growth (16, 30). For example, experimental studies have disclosed that energy-dense diets promote fetal hepatic steatosis, due to an increase in circulating triglycerides, and hypoxemia, increasing amino acid metabolism for energy production in fetal liver (31, 32). Furthermore, clinical studies disclosed that low adherence to the Mediterranean diet (characterized by the consumption of a high intake of extra virgin oil, fruits, cereals, legumes, vegetables; and a moderate/low intake of fish, seafood, eggs, meat and dairy products) is associated with an altered GH/IGF-1 response, resulting in a poor body composition and cardiometabolic profile (21, 33).

Furthermore, regardless of maternal obesity, high-fat diets and excess of energy-dense diet intake throughout pregnancy can result in placental alterations in morphology and/or function. This increases inflammation and fatty acid transport, that could permanently alter offspring physiology (27), promoting adiposity, adult hyperinsulinemia, hyperleptinemia, and the development of T2DM and cardiovascular diseases (11, 34–36).

GESTATIONAL DIABETES MELLITUS (GDM)

GMD is the most prevalent metabolic disorder during pregnancy, diagnosed in the second or third trimesters with

high blood glucose levels, frequently disappearing after delivery, where glucose tolerance is restored to normal levels. An excessive gestational weight gain in the first trimester of pregnancy might denote a serious period for GDM development (12).

Predominantly, the second trimester of gestation is a period where insulin sensitivity is impaired, in order to limit maternal glucose uptake to maintain a suitable nutrient supply for the growing fetus (37, 38). This could be due to the effects of placental hormones, *e.g.*, placental lactogen (PL) and GH, which stimulate the liver increasing growth factor levels, including IGF-1 (39). It could also be a result of a normal augment in maternal adiposity, as lipolysis and free fatty acids metabolism are promoted, causing compensatory hyperinsulinemia that increases adipogenesis, inflammatory adipokines and insulin resistance (40).

GDM increases the development of maternal, fetal and neonatal complications. It is related to numerous gestational difficulties, such as placental vasculature alterations, macrosomia, shoulder dystocia, stillbirth, neonatal hypoglycemia and respiratory distress (41). This disorder could be a risk factor for T2DM, metabolic and cardiovascular disorders development in the mother and her offspring in later life (13, 42–44).

Although the pathogenesis of GDM is still unknown, two contributing factors have been involved in its progression: β-cell dysfunction and alterations in insulin secretion to compensate for insulin resistance induced by pregnancy (45, 46). Also, it has been observed in animal experimental models and clinical studies that obesity during pregnancy, besides promoting insulin resistance, can impair glucose tolerance, increase IGF-1 serum levels, reduce insulin-like growth factor binding proteins (IGFBPs), and endorse endothelial cell dysfunction, hypertension, hyperphagia and increased adiposity in offspring (10, 11, 47–49).

GDM is associated with fetal hyperglycemia and hyperinsulinemia, which in turn lead to feto-placental endothelial dysfunction, at both macro and microvasculature levels, similar to that found in adult T2DM patients (50). Also, GDM pregnancies exhibit alterations in nitric oxide (NO) bioavailability (51) and other vasoactive molecules (*e.g.*, adenosine) and/or differential responses to hormones (*e.g.*, insulin, vascular endothelial growth factor -VEGF-) (51–54), that can result in distorted angiogenesis and hence, the aforementioned endothelial dysfunction (51, 55). This endothelial dysfunction, known as the diminished ability of the placenta to stimulate vasodilation, can involve signaling mechanisms from the disease itself or adaptative responses to the abnormal intrauterine environment (56).

Glucose is the primary metabolic fuel for the fetus (50-80%), the amniotic fluid is the second largest source for this metabolite *via* fetal swallowing (10-15%) (57–59). In this sense, metabolites and hormones in amniotic fluid play an important role in fetal development. For example, in GDM pregnancies there is a decrease in IGFBP-1 levels and an increase in glucose and insulin levels in amniotic fluid, leading to an intrauterine exposure to glucose that accelerate the exhaustion of β-cells, a characteristic effect of GDM (59, 60).

ROLE OF THE INSULIN/IGF AXIS IN GDM

The insulin-like growth factor (IGF) system is conformed of two growth factors, IGF-1 and IGF-2; three receptors, IGF-1 receptor (IGF1R), IGF-2 receptor (IGF2R) and hybrid receptor; and IGFBPs (61). This system is involved in growth, particularly during fetal development, metabolism and crucial cellular processes such as proliferation, survival, cell migration and differentiation (62).

As aforementioned, the production of IGF-1 is dependent on a suitable supply of nutrients, such as glucose, amino acids and lipids. It is secreted in practically every tissue for autocrine and/or paracrine purposes (63). GH is responsible for stimulating IGF-1 secretion, forming the GH/IGF-1 axis, where GH secretion is promoted by growth hormone-releasing hormone (GHRH) and inhibited by somatostatin. Herein, IGF-1 can inhibit GH expression by stimulating somatostatin secretion, thus hindering GH secretion (64).

Most IGF-1 actions are mediated through the union of this molecule to its putative receptor, IGF1R, an $\alpha_2\beta_2$ heterotetrameric tyrosine kinase receptor (RTK), that activates the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) (**Figure 1**) and mitogen-activated protein kinase (MAPK) signaling pathways, both related with cell survival, growth and proliferation (65). Due to its homology to proinsulin and IGF-2 structures (22), and the homology between receptors, IGF-1 can also bind to the insulin receptor (INSR) and IGF2R (a scavenger receptor homologous to manose-6-phosphate receptor), with lower affinity (65). Furthermore, IGF-1, IGF-2 and insulin can bind with lower affinity to hybrid receptors, conformed by one αβ-chain from INSR and another αβ-chain from IGF1R (65).

Both IGF-1 and IGF-2 are involved in cell survival and proliferation. Particularly, IGF-1 plays an essential role in modulating fetal growth due to its actions on mother and/or the placenta, *e.g.*, regulating nutrient supply and bioavailability (66). Moreover, IGF-1, *via* IGF1R and INSR downstream signaling pathways, participates in glucose transport to insulin sensitive tissues, such as skeletal muscle, adipose tissue and liver, decreasing glucose levels and improving insulin sensitivity, as IGF-1 levels does not oscillate over time as insulin does (67), thus reducing the hyperglycemic effect of GH (39). In normal pregnancies, placental hormones, *e.g.*, PL, progesterone, cortisol, GH and prolactin, can decrease the phosphorylation of insulin receptor substrate 1 (IRS-1), a key regulator of this signaling pathway, decreasing insulin sensitivity and β-cell function, leading to insulin resistance (68).

Clinical studies of GDM pregnancies have revealed an increase in maternal IGF-1 levels and a decrease in cord blood, and a positive correlation between insulin and IGF-1 fetal concentrations and birth weight of a newborn (69), suggesting the implication of this hormone in fetal intrauterine growth, that could lead to the development of macrosomia (70–72). Also, in GDM pregnancies, IGF-1 plays a crucial role in glucose homeostasis. Experimental and clinical studies have shown that placental insulin/IGF-1 pathway is promoted in GDM, as with

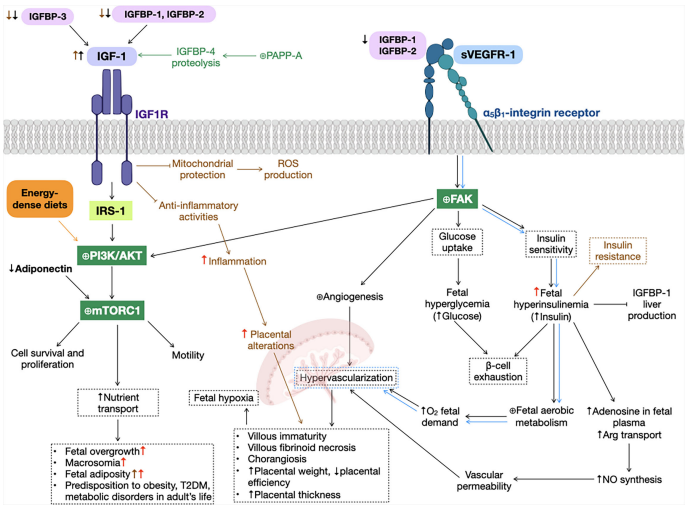

FIGURE 1 | Gestational diabetes mellitus (GDM) alterations in insulin-like growth factor 1 (IGF-1) signaling pathway. GDM (black arrows) and preeclampsia (green text and arrows) reduce insulin-like growth factor binding protein 1 (IGFBP-1) levels, increasing IGF-1 bioavailability, that promotes phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) cascade (as well as energy-dense diets, orange text and arrows), activating mammalian target of rapamycin complex 1 (mTORC1), that results in cell survival and proliferation, motility and an augment nutrient transport, leading to fetal overgrowth, macrosomia, fetal adiposity, type 2 diabetes mellitus (T2DM), metabolic disorders and predisposition to obesity in adult life. Additionally, soluble form of the vascular endothelial growth factor receptor 1 (sVEGFR-1) can bind to $\alpha_5\beta_1$-integrin receptor (blue arrows), expressed predominantly in extravillous trophoblasts, activating the focal adhesion kinase (FAK), promoting fetal hyperglycemia and hyperinsulinemia, that lead to β-cell exhaustion, a principal characteristic of GDM. This increase in insulin levels cause promote nitric oxide (NO) synthesis and fetal aerobic metabolism, both producing hypervascularization in the placenta, that could result in several physiological alterations in this organ, such as villous immaturity, villous fibroid necrosis, chorangiosis, increased placental weight and thickness, and decreased placental efficiency. Also, FAK activation is involved in angiogenesis in several organs, *e.g.*, the placenta. Obesity before and/or during pregnancy (brown text and arrows) inhibit IGF-1 anti-inflammatory and mitochondrial protection activities, resulting in an increase in inflammation, ROS production and, hence, placental alterations. High-dense diets (red arrows) exacerbate GDM alterations, such as fetal overgrowth, macrosomia, fetal adiposity, inflammation, placental alterations and predisposition to disorders in adult's life. ⊕ means enhancing protein activity.

energy-dense diets, increasing the activation of several downstream molecules, particularly mammalian target of rapamycin complex 1 (mTORC1), that augments nutrient transport across the placenta (73, 74) and regulates mitochondrial biogenesis and function (75, 76). In this way, mTORC1 activation could lead to fetal overgrowth, as it is positively correlated to birth weight (77–80). This mTORC1 activation could be a result of low circulating levels of adiponectin observed in the mother, a hormone that regulates glucose levels by inhibiting insulin/IGF-1 signaling pathway (76, 81) (**Figure 1**). In this sense, an inverse correlation between free IGF-1 and the risk of developing GDM has been found (13, 72).

IGF-1 activities must be rigorously controlled by its association with binding proteins (IGFBPs 1-6), found in several biological tissues and fluids, such as follicular liquid, amniotic liquid, vitreous humor, lymph, plasma, seminal fluid, cerebrospinal fluid and gastrointestinal secretions. However, the main source of IGFBPs is the liver (22). These binding proteins prolong the half-life in the circulation and modulate IGFs activities, due to their high affinity for both IGFs, rather than their own receptors (22). These binding proteins are capable of both inhibiting (*e.g.*, IGFBP-1) and enhancing (*e.g.*, IGFBP-3) IGFs biological activities, predominantly IGF-1. Recently, nine IGF-related binding proteins (IGFBP-rPs) have arose that can bind IGFs, but with lower affinity than IGFBPs (22).

IGFBP-3 is one of the principal proteins for IGF-1, as it regulates the bioavailability of this hormone. In the circulation, IGF-1 is found forming a ternary complex together with IGFBP-3 and ALS (acid-labile subunit) (22). It has been observed that increased concentrations of IGF-1 and IGF-1/IGFBP-3 molar ratio are related to an increased risk of GDM in early pregnancy (10-14 weeks of gestation) (82). Also, low cord serum levels of IGFBP-3 in GDM and obese women have been reported (83).

Another binding protein characterized by a high affinity for IGF-1, more than its own receptor, is IGFBP-1. This binding protein inhibits IGF-1´s biological action, thus reducing IGF-1 levels and preventing its downstream signaling pathway. IGFBP-1 is the principal binding protein in fetal circulation, whose production in the liver is inhibited by insulin (84) and food intake (85). In clinical studies, maternal obesity and GDM have been associated with an increase in IGF-1 levels, and low maternal and cord plasma levels of IGFBP-1, 3, 6 and IGFBP related protein 1 (IGFBPrP-1) (83, 86). These results hint that low serum and blood cord IGFBP-1 levels lead to an increase in IGF-1 bioavailability in GDM, probably due to the reduced phosphorylation of this binding protein observed in diabetes (84). This increase in IGF-1 accessibility produces the enlargement of the placenta and thus, an extra nutrient supply to the fetus, promoting fetal growth (84) and macrosomia, a characteristic detected in GDM pregnancies (70, 87). In this

sense, IGFBP-1 levels are inversely correlated to fetal birthweight. Moreover, this decrease in IGBP-1 levels can be an outcome of increased fetal insulin secretion that inhibits the production of this binding protein (87).

Contrary to IGFBP-1, IGFBP-2, a binding protein that lacks postprandial fluctuation, has pleiotropic functions and is associated with glucose homeostasis (88). During early pregnancy (10-14 weeks of gestation), its levels are reduced and could function as an early marker of GDM risk (82). Clinical studies have shown decreased IGFBP-2 levels in both maternal and cord blood in GDM pregnancies (82, 87), leading to an augment of biologically active IGF-1 and IGF-2 that accelerates fetal growth.

Although most binging proteins have either inhibitory or enhancing functions, there are some that can have both roles. An example of this is IGFBP-4, the major substrate for the enzyme pregnancy-associated plasma protein-A (PAPP-A), a metalloproteinase that controls the bioavailability of IGFs. Particularly, PAPP-A modulates IGFs action through proteolysis of IGFBP-2, 4 and 5 (89), being expressed in several tissues. In the case of IGFBP-4, IGF-2 is a stronger facilitator of degradation then IGF-1 (90, 91), increasing in this way IGF-1 bioavailability and promoting cell growth (89). PAPP-A levels increase with the progress of gestation, as it is critical for trophoblast differentiation and invasion. Consequently, this enzyme has been employed as a diagnostic biomarker, especially during the first trimester, for several pregnancy disorders, such as Down syndrome (92). Experimental studies in macrophages and human preeclamptic placentas have shown that PAPP-A overactivation activates PI3K/AKT signaling pathway, producing an inflammatory response (93–96), that could lead to endothelial dysfunction, a common feature of both preeclampsia and GDM (**Figure 1**).

IGFBPs not only serve to control the bioavailability and activities of IGFs. IGFBP-1 and 2 have IGF-independent effects, as they can bind to $\alpha_5\beta_1$-integrin receptors and activate the PI3K/AKT signaling pathway, triggering several molecular targets, *e.g.*, focal adhesion kinase (FAK), involved in glucose uptake and insulin sensitivity (67, 97–99). This molecular cascade activated *via* FAK, as shown in cell cultures of extravillous trophoblasts (100), it is also involved in focal adhesions and cell motility *via* both PI3K/AKT and MAPK signaling pathways (67, 101, 102), embroiled in developing an adequate placentation. Another ligand that bind to integrins is the soluble form of the vascular endothelial growth factor receptor 1 (sVEGFR-1 or fms-like tyrosine kinase receptor-1, sFlt-1), a decoy receptor for vascular endothelial growth factor A (VEGF-A). It decreases angiogenesis at the embryogenesis stage *via* vascular endothelial growth factor receptor 2 (VEGFR-2) signaling (103–105). sVEGFR-1 is a key regulator of the formation of new blood vessels during embryogenesis. Mutant mice for this receptor die at this stage due to an abnormal growth and dysfunction of blood vasculature (106). Also, the overexpression of sVEGFR-1 in human placentas alters angiogenesis and results in endothelial dysfunction (37, 107–109), due to the impairment of signal transduction through VEGF-A (110–113). This adverse circumstance, could result in hypervascularization of the placenta, that lead to numerous physiological alterations in this organ, such as villous immaturity, villous fibrinoid necrosis and chorangiosis, as it is observed in GDM pregnancies (114). This reveals the increasing oxygen demand of the fetus, due to the insulin-stimulated enhanced fetal aerobic metabolism (115, 116) (**Figure 1**). Moreover, studies in human placentas showed decreased VEGFR-1 (mRNA and protein) and VEGFR-2 levels (mRNA) (115, 117), while reports in human umbilical vein endothelial cells (HUVECs) disclosed that GDM enhanced cell migration (115), suggesting that GDM promotes an angiogenic state that could affect the pathophysiological function of the placenta.

CONCLUSION

IGF-1 bioavailability is one of the main discordant factors for the development of GDM during pregnancy, this is where IGFBPs, especially IGFBP-1 and IGFBP-2, play a significant role. Obesity, both before and/or during pregnancy, a condition related to consumption of energy-dense diets, can alter IGF-1 secretion and actions, leading to GDM. Obesity also decreases the levels of these IGFBPs, thus increasing the bioavailability of IGF-1, promoting an increase of nutrient availability to the fetus, which can lead to overgrowth and other metabolic complications, characteristics of GDM. Similarly, there are other molecules capable of exacerbating the adverse effects of GDM, such as sVEGFR-1, which activates FAK, a protein also indirectly involved in the IGF-1 signaling pathway, β-cell exhaustion and placental hypervascularization. Therefore, knowledge of the molecular targets of IGF-1 and their interaction with other molecules involved in several important cellular processes during pregnancy, *e.g.*, placental angiogenesis, are a good starting point to develop new therapeutic targets. This could lead to a better quality of life in patients and, in this case, newborns, reversing or even preventing the development of metabolic diseases in adulthood, which would have serious consequences for their health.

AUTHOR CONTRIBUTIONS

All authors participated directly in the manuscript. IM-E: investigation, writing-review and digital art; FC-T: conceptualization, investigation and writing-review. All authors have read and agreed to the published version of the manuscript.

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The Role of Slit-2 in Gestational Diabetes Mellitus and Its Effect on Pregnancy Outcome

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Background: Slit guidance ligand 2 (Slit-2), as a member of the Slit family, can regulate the inflammatory response and glucose metabolism. The purpose of this study was to explore the expression of Slit-2 in maternal peripheral blood and neonatal cord blood of gestational diabetes mellitus (GDM) patients and its potential importance in disease progression.

Methods: This study included 57 healthy pregnant women and 61 GDM patients. The levels of Slit-2, C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP-1), C-peptide (C-P), galectin-3(Gal-3), HbA1c, fasting blood glucose (FBG) and fasting insulin (FINS) in maternal peripheral blood and neonatal cord blood were detected by ELISA. Spearman's rank correlation test was used to assess the association between peripheral Slit-2 and inflammatory indicators, insulin resistance, and pregnancy outcomes. Logistic regression analysis was used to analyze the risk factors of GDM.

Results: Slit-2 levels in maternal peripheral blood and neonatal cord blood of the GDM patients were higher than those of the HC. Slit-2 levels in maternal peripheral blood and neonatal cord blood of the GDM patients were positively correlated with inflammatory factors CRP and MCP-1 levels. The level of Slit-2 in the maternal peripheral blood of the GDM patients was positively correlated with the level of homeostasis model assessment insulin resistance (HOMA-IR) and HbA1c in maternal peripheral blood, but was negatively correlated with the level of homeostasis model assessment –β (HOMA-β). We also found that the Slit-2 level in the maternal peripheral blood of the GDM patients was negatively correlated with neonatal blood glucose, positively correlated with neonatal weight and independent of neonatal total bilirubin.

Conclusion: Our study suggests that the abnormal increase in Slit-2 in GDM may be related to its pathogenesis, and it was correlated with neonatal blood glucose and weight in patients with GDM, suggesting that Slit-2 may be a potential biomarker of GDM.

Keywords: Slit guidance ligand 2, gestational diabetes mellitus (GDM), cord blood, pregnancy outcome, peripheral blood

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a common complication of pregnancy and occurs the first time that blood glucose levels are elevated during pregnancy. The incidence rate of this condition is 9%-25% worldwide (1, 2). GDM is associated with insulin resistance (3, 4), the inflammatory response (5, 6), islet β cell dysfunction and obesity (7). GDM not only increases the risk of metabolic diseases but also leads to adverse pregnancy outcomes such as neonatal hypoglycemia, macrosomia, jaundice and fetal distress (8–11). Therefore, it is important to explore the pathogenesis of GDM and to prevent, monitor and treat GDM in a timely and effective manner.

Slit guidance ligand 2 (Slit-2) is a new type of adipoprotein, and the full-length Slit-2 protein is a secretory ligand. This protein splits into two fragments, a 140 kDa N-terminal product (Slit-2-N) and a 50–60 kDa C-terminal product (Slit-2-C) (12), and interacts with Robo receptors. Robo receptors are divided into Robo1, Robo2, Robo3 and Robo4, and the binding of Slit-2 to specific Robo receptors regulates specific cell functions (13–15). Slit-2 has been reported to play an important role in neuronal and vascular development (16–18). Slit-2 is also involved in the development of many organs and is related to cancer apoptosis, migration, invasion, occurrence and development (19, 20). In addition, Slit-2 can regulate different inflammatory diseases and inflammatory phenotypes and then determine the activity and severity of the disease (21, 22). Recently, the role of Slit-2 in glucose metabolism has become a new research hotspot. Zhou et al. confirmed that Slit-2 concentration in the vitreous fluid of patients with diabetes was significantly higher than that of nondiabetic patients through a diabetic rat model and proposed the role of Slit-Robo signaling in different stages of diabetic retinopathy (23). Svensson et al. proposed that Slit-2, as a beige fat secretion factor (24), has certain influence on adipose tissue homeostasis and glucose metabolism under the control of PRDM16 and cold exposure. Studies have further confirmed that peripheral Slit-2 is related to human serum glucose level and insulin secretion function (25). In addition, it has been proved that Slit-2 overexpression increases the diameter of maternal blood sinuses and fetal capillaries, promoting vascular remodeling in the Slit-2 overexpression mouse model (26). Li et al. found that Slit-2/Robo1 signal could regulate trophoblast differentiation and invasion, thereby limiting β-subunit of human chorionic gonadotropin (β-HCG) production and inhibiting placental angiogenesis, leading to abortion and threatened abortion in early pregnancy (27). Tiensuu H et al. proposed that the risk of spontaneous preterm birth and fetal growth is associated with the level of Slit-2 (28). In short, Slit-2 has certain effects on glucose metabolism and pregnancy outcomes, but the role of Slit-2 in GDM and its pregnancy outcomes remain unclear.

Galectin-3(Gal-3) is a member of galectin family (29), which has the effects of promoting fibrosis and inflammation (30). Many studies have shown that the imbalance of serum Gal-3 level in patients with GDM may be an important predictor of GDM (31–33). Patients with GDM have systemic inflammatory response (34, 35), and the inflammatory factors C-reactive protein (CRP) and monocyte chemoattractant protein-1 (MCP-1) are significantly increased in patients with GDM, which are involved in the occurrence and development of GDM (36, 37). HbA1c represents the level of glycosylated hemoglobin, which can reflect the average blood glucose level in the past 2-3 months, so it is necessary to detect the HbA1c in GDM patients1-2 (38, 39). GDM is also closely related to the increase of homeostasis model assessment insulin resistance (HOMA-IR) and the decrease of homeostasis model assessment-β (HOMA-β) (40, 41), which is also one of the important characteristics of GDM.

Therefore, in this study, we explored the level of Slit-2 in maternal peripheral blood and neonatal cord blood of GDM patients, its relationship with inflammatory factors, insulin resistance, islet β cell function and the correlation with Gal-3. In addition, we explored the relationship between Slit-2 levels in maternal peripheral blood and neonatal cord blood of GDM patients and adverse pregnancy outcomes to further understand the role of peripheral blood Slit-2 in glucose metabolism.

METHODS

Study Populations

From September 2018 to March 2019, we selected 67 pregnant women with GDM and 66 healthy pregnant women who came to the Affiliated Hospital of Qingdao University for regular routine obstetric examination as the research subjects. GDM was defined according to the Chinese guidelines for the prevention and treatment of diabetes (42). The inclusion criteria were as follows: previous physical health, no history of drug and alcohol abuse, age-appropriate pregnancy (aged 20–40 years), and no other pregnancy complications except gestational diabetes mellitus. Fifteen participants were excluded because of gestational hypertension (six cases), preeclampsia (three cases), acute fatty liver in pregnancy (one case) and premature delivery (five cases). Finally, 61 GDM patients and 57 healthy control (HC) were selected as the research subjects, all subjects were not disturbed by exogenous insulin. All participants were informed and signed a consent form. The experimental protocol was formulated according to the Declaration of Helsinki in 1964 and was consistent with the guidelines of the Human Ethics Committee of the Affiliated Hospital of Qingdao University (QYFYWZLL26496) (43).

Clinical Data

The height (cm), weight (kg), waist circumference (cm) and blood pressure (mmHg) of all subjects on the day of delivery were measured, and the BMI [weight (kg)/height (m^2)] was calculated. Sex, birth height (cm), birth weight (kg), blood glucose (mmol/l) and Apgar score of newborns were recorded. The knee joint, hip joint and head of the newborn were fixed, and the height of the newborn was measured from the highest point of the top of the head to the highest point of the foot with tape. The weight of the newborn was measured with a baby scale, the newborn was placed in the center of the scale, and the weight of

the newborn was read (kg). After the fingertips of the newborns were disinfected with 75% alcohol, the blood glucose of the newborns was detected by a fingertip blood glucose detector. The Apgar score was calculated according to skin color, heart rate, respiration, muscle tension and reflex.

Detection of Maternal Peripheral Blood and Neonatal Cord Blood by ELISAs

Fasting blood of pregnant women before delivery and cord blood of newborns were collected on the day of delivery. Neonatal cord blood samples were collected in the umbilical artery within 5 minutes after delivery. The samples were centrifuged twice (3000 rpm/min) in a centrifuge for 10 minutes each time, and the collected serum was stored at -80°C until use. The levels of Slit-2, C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP-1), C-peptide (C-P), HbA1c, fasting insulin (FINS), fasting blood glucose (FBG) and galectin-3(Gal-3) in maternal peripheral blood and neonatal cord blood were detected by ELISA kits (Yilairuite Biotech Co., Wuhan, China). Three wells were set for all samples, and the average value was taken as the final value.

$$\text{HOMA} - \text{IR} = \text{FBG}\,(\text{mmol/L}) \times \text{FINS}(\mu\text{mU/mL}) / 22.5.$$

$$\text{HOMA} - \beta = 20 \times \text{FINS}(\mu\text{mU/mL})/(\text{FBG}(\text{mmol/L}) - 3.5)$$

Statistical Analysis

Standard statistical analysis was conducted using GraphPad Prism 8 and SPSS, version 22.0 (IBM, Armonk, NY). Normality of variables was determined through a Shapiro–Wilk test. Qualitative variables are expressed as percentages, and quantitative variables are expressed as the mean ± standard deviation. A t-test was used for intergroup continuous variable comparisons, and a χ^2 test was used for intergroup categorical variable comparisons. Spearman's rank correlation test was performed to study the correlation between clinical parameters. A P value of <0.05 was considered statistically Multivariable logistic regression analysis was applied to identify the risk factors of GDM, using the factors with $P < 0.05$ in the univariable analysis.

RESULTS

Clinical and Demographic Characteristics of Subjects

A total of 118 subjects participated in the study: 57 HC and 61 patients with GDM. The weight of newborns in the GDM group (3494.38 ± 459.01 g) was higher than that in the HC group (3307.49 ± 397.53 g), and the blood glucose of the newborns in the GDM group (3.76 ± 1.46 mmol/L) was lower than that in the HC group (4.35 ± 1.46 mmol/L). There was no significant difference in maternal height, blood pressure, gestational age, BMI or gestational weeks between the GDM group and the HC group, and there was no significant difference in neonatal height, sex or Apgar score between the GDM group and the HC group, as shown in **Table 1**. The levels of Slit-2, CRP, MCP-1 HbA1c and FINS in maternal peripheral blood and neonatal cord blood in GDM group were higher than those in HC group, and the level of FBG in neonatal cord blood was lower than that in HC group, as shown in **Table 2**.

Increased Levels of Maternal Peripheral Blood and Neonatal Cord Blood Slit-2 in GDM Patients

We investigated the changes in maternal peripheral blood and neonatal cord blood Slit-2 levels between the GDM patients and the HC. The level of maternal peripheral blood Slit-2 in the GDM patients was higher than that in the HC ($P < 0.0001$; **Figure 1A**). The Slit-2 level in the neonatal cord blood of the GDM patients was also higher than that of the HC ($P < 0.0006$; **Figure 1B**).

Association Between Slit-2 Levels in Maternal Peripheral Blood and Neonatal Cord Blood and Inflammatory Factors in GDM Patients

We analyzed the correlation between Slit-2 levels in maternal peripheral blood and neonatal cord blood and inflammatory factor CRP and MCP-1 levels. The level of Slit-2 in maternal peripheral blood was positively correlated with the CRP and MCP-1 levels (P=0.0006, r=0.4246; P= 0.0045, r=0.3589; **Figures 2A, B**). The level of Slit-2 in neonatal cord blood was also positively correlated with the inflammatory factors CRP and

TABLE 1 | Baseline characteristics of study population.

	Control (n=57)	GDM (n=61)	p value
Maternal age (years)	31.25 ± 5.54	32.49 ± 4.35	0.178
Maternal BMI (kg/m2)	20.33 ± 2.72	21.32 ± 3.24	0.078
Maternal BMI (at birth, (kg/m2))	27.44 ± 5.16	28.76 ± 4.27	0.132
Systolic Blood pressure (mmHg)	113.5 ± 11.2	111.2 ± 10.3	0.255
Diastolic Blood pressure (mmHg)	75.5 ± 8.0	75.3 ± 9.4	0.914
Gestational weeks	39.29 ± 0.82	39.58 ± 1.01	0.102
Vaginal delivery	34 (59.65%)	33 (54.10%)	0.543
Fetal sex (male)	28 (49.12%)	32 (52.45%)	0.717
Birth weight (g)	3307.49 ± 397.53	3494.38 ± 459.01	0.021
Birth height (cm)	50.7 ± 1.4	51.2 ± 1.4	0.122
Blood glucose (mmol/L)	4.35 ± 1.46	3.76 ± 1.46	0.030
Birth Apgar (5min)	9.5 ± 0.5	9.4 ± 0.5	0.899

TABLE 2 | Research results of study population.

	Control (n=57)	GDM (n=61)	p value
Maternal Slit-2 (ng/ml)	1.36 ± 0.46	2.66 ± 0.82	0.000
Maternal C-P (mIU/L)	0.91 ± 0.29	1.05 ± 0.39	0.032
Maternal MCP-1 (pg/ml)	187.34 ± 38.77	202.49 ± 41.78	0.044
Maternal CRP (μg/ml)	75.95 ± 21.17	84.65 ± 21.04	0.027
Maternal Galectin-3 (ng/mL)	8.02 ± 0.76	32.08 ± 2.75	0.000
Maternal FINS (mIU/L)	7.88 ± 0.70	15.28 ± 1.28	0.000
Maternal FBG (mmol/L)	4.32 ± 0.39	7.33 ± 1.22	0.000
HbA1c (%)	4.73 ± 0.42	7.50 ± 0.88	0.000
Maternal HOMA-IR	1.51 ± 0.20	4.99 ± 1.00	0.000
Maternal HOMA-β	261.65 ± 182.15	89.78 ± 34.43	0.000
Neonatal Slit-2 (ng/ml)	0.79 ± 0.27	0.97 ± 0.30	0.001
Neonatal MCP-1 (pg/ml)	83.93 ± 14.36	90.97 ± 21.60	0.038
Neonatal CRP (μg/ml)	39.10 ± 12.71	43.82 ± 6.59	0.014
Neonatal Galectin-3 (ng/mL)	1.65 ± 0.42	1.69 ± 0.29	0.560
Neonatal FINS (mIU/L)	8.03 ± 1.39	16.13 ± 2.77	0.000
Neonatal FBG (mmol/L)	3.36 ± 0.87	2.61 ± 0.92	0.000
Neonatal total bilirubin (umol/L)	147.37 ± 23.16	155.34 ± 26.67	0.086
Neonatal HOMA-IR	1.21 ± 0.39	1.86 ± 0.71	0.000

MCP-1 ($P<0.0001$, r=0.7597; $P<0.0001$, r=0.7778; **Figures 2C, D**).

Association Between Slit-2, HbA1c and HOMA in Maternal Peripheral Blood and Neonatal Cord Blood in GDM Patients

We investigated the association between Slit-2 levels in maternal peripheral blood and neonatal cord blood HbA1c and HOMA steady state model to evaluate islet β cell function and Insulin Resistance level. The level of Slit-2 in maternal peripheral blood was positively association with HbA1c and HOMA-IR but negatively association with HOMA-β in maternal peripheral blood. (P<0.0001, r=0.6447 **Figure 3A**; P<0.0001, r=0.5885 **Figure 3B**; P<0.0001, r=-0.6010 **Figure 3C**). The level of Slit-2 in neonatal cord blood was significantly positively correlated with HOMA-IR level in neonatal cord blood (P < 0.0001, r=-0.6462; **Figure 3D**). Due to the immature neonatal islet β cell function, there is no assessment of neonatal cord blood HOMA-β and the correlation with neonatal cord blood Slit-2.

Association Between Slit-2 Level and Gal-3 Level in Maternal Peripheral Blood and Neonatal Cord Blood in GDM Patients

The Slit-2 levels in maternal peripheral blood were negatively correlated with the Gal-3 level in maternal peripheral blood ($P<0.0001$; r=-0.4919; **Figure 4A**). Correlation analysis showed that the levels of neonatal cord blood Slit-2 had no significant correlation with the Gal-3 level in neonatal cord blood ($P=0.49224$, r=0.08957; **Figure 4B**).

Association of Maternal Peripheral Blood and Neonatal Cord Blood Slit-2 Expression With Adverse Pregnancy Outcomes in GDM Patients

In the patients with GDM, we investigated the association of maternal peripheral blood and neonatal cord blood Slit-2 overexpression with neonatal blood glucose, neonatal weight and neonatal total bilirubin. The results showed that there was

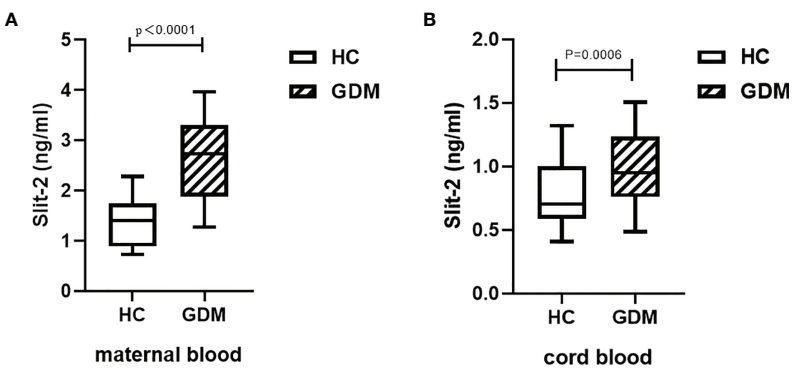

FIGURE 1 | Slit-2 levels in maternal peripheral blood and neonatal cord blood of GDM patients and HC. **(A)** Comparison of Slit-2 levels in maternal peripheral blood between the GDM patients and the HC. **(B)** Comparison of neonatal cord blood Slit-2 levels between the GDM patients and the HC. Slit-2, Slit guidance ligand 2; HC, Healthy Control; GDM, gestational diabetes mellitus.

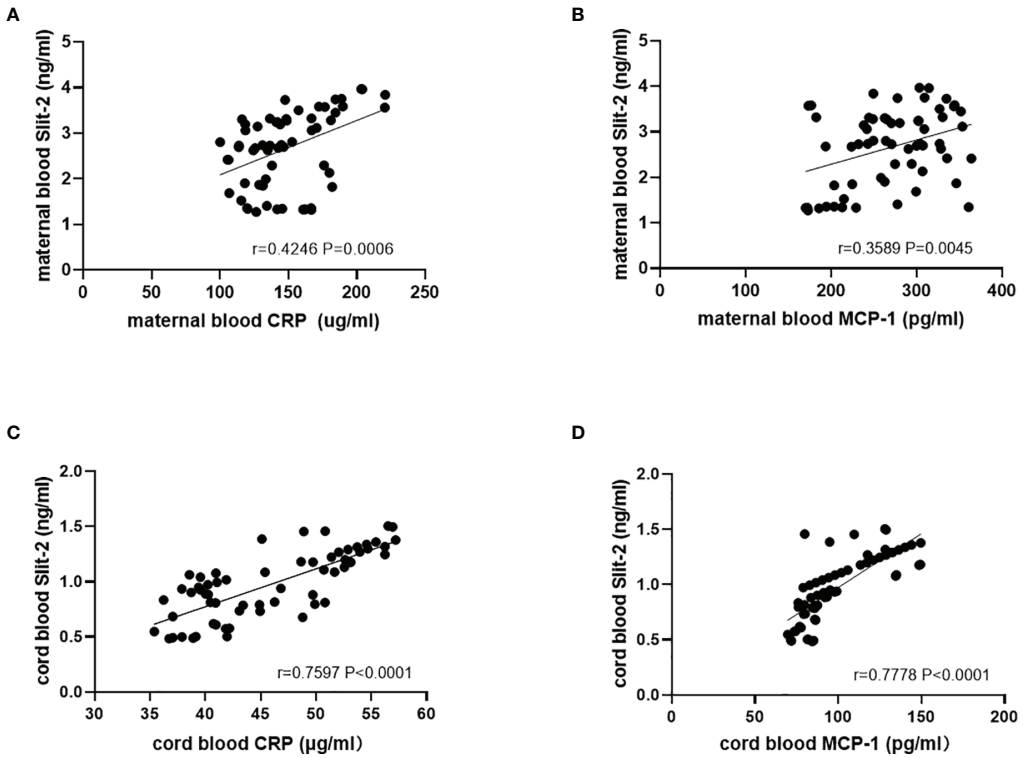

FIGURE 2 | Relationship between the Slit-2 level and CRP and MCP-1 in maternal peripheral blood and neonatal cord blood of patients with GDM. **(A)** Relationship between the Slit-2 level and CRP in maternal peripheral blood of the patients with GDM. **(B)** Relationship between the Slit-2 level and MCP-1 in maternal peripheral blood of the patients with GDM. **(C)** Relationship between the Slit-2 level and CRP in neonatal cord blood of the patients with GDM. **(D)** Relationship between the Slit-2 level and MCP-1 in neonatal cord blood of the patients with GDM. Slit-2, Slit guidance ligand 2; CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1.

a negative correlation between maternal Slit-2 level and neonatal blood glucose (P<0.0001, r=-0.6256; **Figure 5A**). The level of Slit-2 in neonatal cord blood was also negatively correlated with neonatal blood glucose, although not significantly (P = 0.1874, r =-0.1711; **Figure 5B**). The level of Slit-2 in maternal peripheral blood was positively correlated with the weight of newborns (P=0.0056, r=0.3503; **Figure 5C**) and that of neonatal cord blood was not related to the weight of newborns (P=0.2266, r=0.1571; **Figure 5D**). The level of Slit-2 in maternal peripheral blood was not related to neonatal total bilirubin (P=0.5777, r=0.07269).

Risk Factors of GDM Patients Were Detected by Logistic Regression

We evaluated the risk factors of GDM patients. In univariate analysis, Slit-2, C-P, CRP, MCP-1 and Gal-3 in peripheral blood of GDM patients were the risk factors of GDM patients. After adjustment of multivariate logistic regression analysis, it is confirmed that the levels of Slit-2 and Gal-3 in maternal peripheral blood are risk factors for GDM patients (**Table 3**).

DISCUSSION

In this study, we elucidated the correlation between peripheral Slit-2 and GDM patients and newborns for the first time. Maternal and fetal material exchange through the placenta. Maternal blood first contact with the placenta, then the umbilical vein to the fetus. Fetal blood contacts with umbilical artery first and then passes through the placenta to maternal blood (44). Slit-2, CRP, MCP-1, Gal-3, FINS and other indexes in blood complete maternal-fetal blood circulation through placenta transmission (28, 44–51). Therefore, we measured maternal peripheral blood and neonatal umbilical artery blood to reflect the metabolic concentration of maternal and neonatal. Some important findings emerge out of the present study, Slit-2 levels in maternal peripheral blood and neonatal cord blood of the GDM patients were significantly increased and were positively correlated with inflammatory factors, including CRP and MCP-1 levels. In addition, the level of Slit-2 in maternal peripheral blood was positively correlated with HbA1c and HOMA-IR but negatively correlated with HOMA-β in maternal peripheral blood. The Slit-2 level in the neonatal cord blood of the GDM patients was positively correlated with the HOMA-IR level in neonatal cord blood, and the Slit-2 level in the maternal peripheral blood of the GDM patients was negatively correlated with the Gal-3 level in maternal peripheral blood. The study also demonstrated that the Slit-2 level in maternal peripheral blood was negatively correlated with neonatal glycemia, positively correlated with

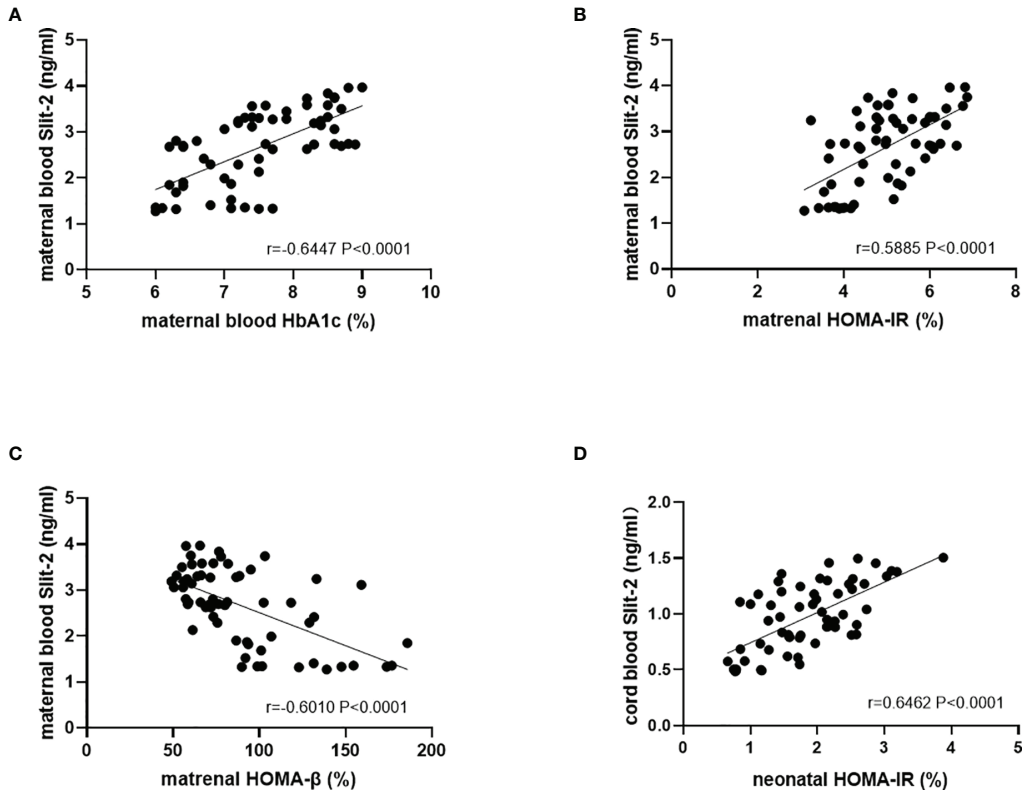

FIGURE 3 | Correlation between the Slit-2, HbA1c and HOMA in maternal peripheral blood and neonatal cord blood of the patients with GDM. **(A)** Correlation between the Slit-2 level and HbA1c in maternal peripheral blood of the patients with GDM. **(B)** Correlation between the Slit-2 level and HOMA-IR in maternal peripheral blood of the patients with GDM. **(C)** Correlation between the Slit-2 level and HOMA-β in maternal peripheral blood of the patients with GDM. **(D)** Correlation between the Slit-2 level and HOMA-IR in neonatal cord blood of the patients with GDM. Slit-2, Slit guidance ligand 2; HOMA-IR, Homeostasis model assessment insulin resistance; HOMA-β, Homeostasis model assessment -β.

neonatal weight. Moreover, we proved that Slit-2 may be a risk factor for patients with GDM by logistic regression analysis.

Slit-2, a secreted extracellular matrix protein, is a homologous protein of Slit (21). In recent years, the role of Slit-2 in glucose metabolism has attracted much attention. Studies have shown that Slit-2 is expressed in the fibrous vascular membrane of diabetic patients, and Slit-2/Robo1 signaling has been proved to contribute to the development of diabetic retinopathy (52). Slit-2/Robo1 signaling is involved in early diabetic nephropathy and may be an effective therapeutic target for abnormal angiogenesis

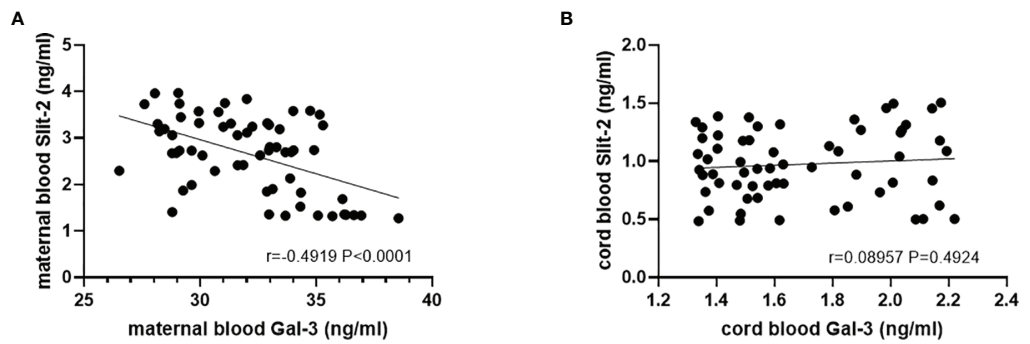

FIGURE 4 | Correlation between the Slit-2 level and Gal-3 level in maternal peripheral blood and neonatal cord blood of the patients with GDM. **(A)** Correlation between the Slit-2 level and Gal-3 level in maternal peripheral blood of the patients with GDM. **(B)** Correlation between the Slit-2 level and Gal-3 level in neonatal cord blood of the patients with GDM. Slit-2 (Slit guidance ligand 2); Gal-3 (Galectin 3).

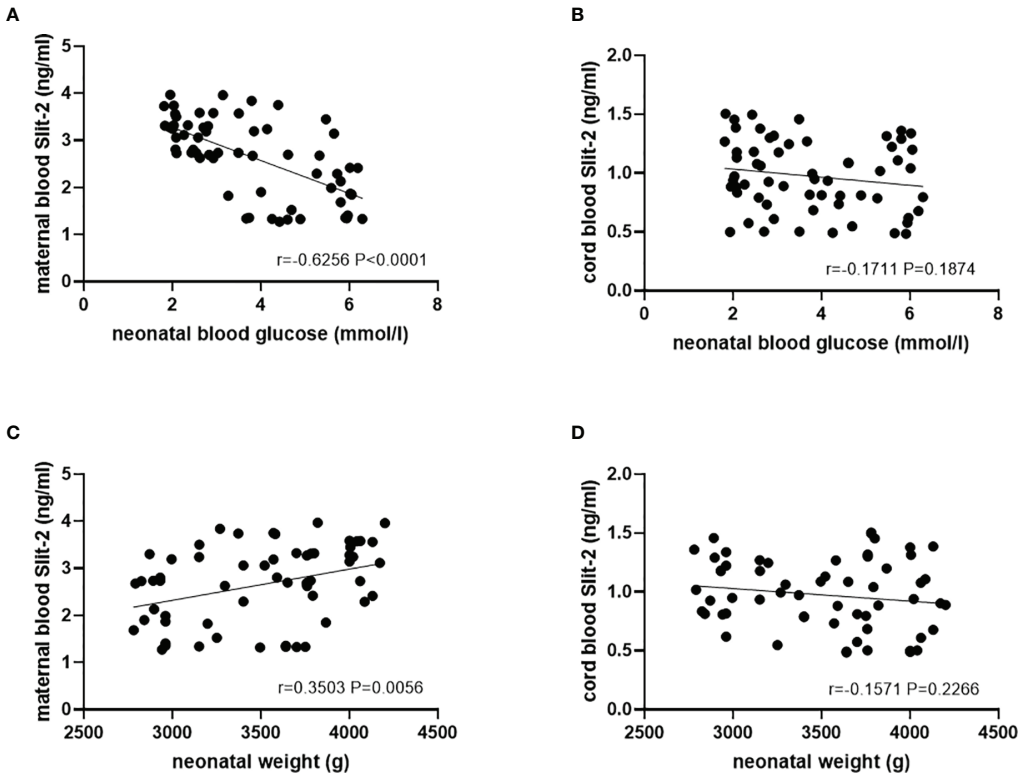

FIGURE 5 | Relationship between the Slit-2 level in maternal peripheral blood and neonatal cord blood and adverse pregnancy outcomes of the patients with GDM. **(A)** Correlation between the Slit-2 level in maternal peripheral blood and neonatal blood glucose of the patients with GDM. **(B)** Correlation between the level of Slit-2 in neonatal cord blood and neonatal blood glucose of the patients with GDM. **(C)** Correlation between the Slit-2 level in maternal peripheral blood and neonatal weight of the patients with GDM. **(D)** Correlation between the level of Slit-2 in neonatal cord blood and neonatal weight of the patients with GDM. Slit-2, Slit guidance ligand 2.

in early diabetic nephropathy (53). Slit-2/Robo4 plays an important role in the occurrence and development of Type 1 Diabetes Mellitus (54). In addition, Kang et al. investigated Slit-2 levels in human serum and determined the role of Slit-2 in diabetes (25). In our study, we assessed the levels of Slit-2 in maternal and cord blood in HC and GDM patients and discovered that Slit-2 was significantly increased in maternal peripheral blood and neonatal cord blood in GDM patients. Moreover, we proved that Slit-2 may be a risk factor for GDM patients through logistic regression analysis. In addition, we also found that the level of Slit-2 in maternal peripheral blood was positively correlated with HOMA-IR and negatively correlated with HOMA-β. The results were consistent with Kang et al.'s study on peripheral Slit-2 and HOMA-β in diabetic patients (25). Yang et al. confirmed that Slit-2 is expressed in islet β cells and Slit/Robo signal regulates the survival of β cells by regulating apoptosis (55). HOMA-IR as an indicator of insulin resistance and HOMA-β as an indicator of islet β cell function are correlated with peripheral Slit-2, which may be related to insulin resistance and islet β cell function in GDM patients.

TABLE 3 | Logistic regression analysis for GDM.

	Univariable			Multivariable		
	Hazard Ratio	**95% CI**	**P value**	**Hazard Ratio**	**95% CI**	**P value**
Maternal age (years)	1.052	0.977-1.132	0.177			
Maternal BMI (kg/m2)	1.115	0.987-1.260	0.079			
Maternal BMI (at birth, (kg/m2))	1.061	0.982-1.146	0.134			
Gestational weeks	1.391	0.936-2.069	0.103			
Maternal Slit-2 (ng/ml)	14.159	5.573-35.976	0.000	18.789	6.227-56.691	0.000
Maternal C-P (mIU/L)	3.139	1.083-9.101	0.035	2.377	0.510-11.087	0.270
Maternal MCP-1 (pg/ml)	1.009	1.000-1.019	0.046	0.990	0.976-1.005	0.186
Maternal CRP (μg/ml)	1.020	1.002-1.038	0.030	1.005	0.963-1.050	0.815
Maternal Galectin-3 (ng/mL)	3.560	2.306-5.479	0.000	5.612	2.417-13.027	0.000

Slit-2 is a double-edged sword in inflammation. Slit-2 has been reported to play an anti-inflammatory role through its specific receptor Robo4, and Slit-2 can also play a proinflammatory role through its other specific receptor Robo1 (15). Chen et al. believed that Slit-2 could indirectly affect the placental microenvironment by regulating the activity and movement of inflammatory macrophages in the placenta (56). In an article on thyroid-associated ophthalmopathy, some scholars proposed that Slit-2 determines the activity and severity of the disease by regulating the inflammatory phenotype of CD34+ orbital fibroblasts (OF) (21). In addition, Slit-2 is overexpressed in periodontitis and aggravates the inflammatory response, lymphocyte/macrophage infiltration and disease progression (22). In brief, Slit-2 is a regulator of inflammatory response. Inflammation plays a central role in GDM, patients with GDM had low-grade inflammatory reaction, and CRP and MCP-1 were increased. In our study on the relationship between Slit-2 and inflammatory factors CRP and MCP-1 in GDM patients, we found that Slit-2 was positively correlated with CRP and MCP-1 in maternal peripheral blood and neonatal cord blood of GDM patients, suggesting that it may play a proinflammatory role in GDM through Slit 2/Robo1 axis (15).

Studies have shown that Gal-3 is involved in the development of prediabetes and diabetes, which may be related to inflammation, insulin resistance and diabetes β cell dysfunction (57). Our study showed that a negative correlation was found between Slit-2 level and Gal-3 level in maternal peripheral blood of GDM patients. Nancy Freitag suggested that the dysregulation of Gal-3 during pregnancy may lead to the effect of the chimera-type lectin to this adverse pregnancy outcome (31). Therefore, we speculated that Slit-2 may affect the progression of GDM and pregnancy outcome by affecting the level of Gal-3.

Slit-2 plays an important role in the placental microenvironment by participating in macrophage migration through the Robo receptor signaling pathway (56). Li et al. speculated that Slit-2/Robo1 signaling may be involved in the pathogenesis of adverse pregnancy outcomes (27). Slit-2/Robo1 signaling regulates cytotrophoblast epithelial-mesenchymal transition (EMT) by affecting the expression of E-cadherin, which eventually leads to superficial trophoblast invasion, missed abortion and threatened abortion (27). In view of the above relationship between Slit-2 and adverse pregnancy outcomes (28), we studied the correlation between Slit-2 and neonatal weight, neonatal blood glucose and neonatal total bilirubin in the GDM patients. Cord artery blood can well reflect the metabolic concentration of infants and can be used to respond to adverse pregnancy outcomes (58, 59). The results showed that Slit-2 in the maternal peripheral blood of the GDM patients was negatively correlated with neonatal blood glucose and positively correlated with neonatal weight, this may increase the incidence of neonatal hypoglycemia and macrosomia, it is consistent with previous research results (56). In this study, we did not evaluate the correlation between Slit-2 and GDM in placental tissues. It has been reported that the expression of Slit-2 was detected in placenta (45, 46), and the effect of maternal obesity on the expression of Slit-2 was also confirmed (51). Tiensuu H et al. proposed that Slit-2/Robo1 signal may be involved in the pathogenesis of adverse pregnancy outcomes through its effect on trophoblast cell function (28). We speculated that Slit-2 in placenta and blood may play a synergistic role in the development of GDM and adverse pregnancy outcomes, which requires further experimental evidence.

Our study has some limitations. First of all, the role of Slit-2 in human peripheral blood was analyzed through a cross-sectional study. Therefore, only relationship of Slit-2 and other clinical parameters could be provided, and no causal relationship could be drawn from the data in this study. Secondly, the sample size of our study population was limited, subgroup analysis and stratified analysis were not performed. In the follow-up study, the sample size should be expanded to verify the specific effects of Slit-2 *in vivo* and *in vitro* in GDM.

In conclusion, we found elevated Slit-2 levels in maternal peripheral blood and neonatal cord blood of GDM patients for the first time. The Slit-2 levels were correlated with HbA1c, inflammatory factors, insulin resistance, islets β Cell function and Gal-3 level. In addition, Slit-2 was also associated with neonatal blood glucose and neonatal weight. Moreover, we proved that Slit-2 may be a risk factor for GDM patients through logistic regression analysis. We speculated that Slit-2 is closely related to the pathogenesis of GDM and may be a key risk factor in the occurrence and development of GDM, which not only provides a theoretical basis for the study of insulin resistance and inflammatory response induced GDM, but also provides a new target for the prevention and treatment of GDM.

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 QYFYWZLL26496. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTION

Our manuscript has 7 authors, all of whom contributed significantly to this study. Conceived and designed the experiments: YW, SZ, and YGW. Collected the specimen: YW and WP. Conduct experiments: YW, JC, and KC. Analyzed the data: YW and YC. Wrote the paper: YW and SZ. Supervised the paper: YC and YGW. All authors contributed to the article and approved the submitted version.

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The Relationship Between Pre-Operative Glycosylated Haemoglobin and Opioid Consumption After Caesarean Section in Women With Gestational Diabetes Mellitus

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Introduction: Women with Gestational diabetes mellitus (GDM) had a higher need and consumption of analgesics than women without GDM. The preoperative level of HbA1c was associated with the postoperative consumption for analgesics in diabetic patients. This prospective observational study go further to investigate the relationship between the pre-operative HbA1c and the post-operative consumption for analgesics in women with GDM.

Methods: Women with GDM and a singleton pregnancy undergoing elective cesarean section under combined spinal-epidural anaesthesia were divided into two groups based on pre-operative HbA1c: group HbA1c < 6% and group HbA1c ≥ 6%. Analgesics consumption, number of patient-controlled analgesia (PCA) compression, and pain scores in 6 hours and 24 hours post-operation were compared between the two groups. Then Pearson's correlation coefficient and a stepwise multivariate linear regression were performed to investigate possible independentpredictors of post-operative 24-hour sufentanil consumption.

Results: Analgesics consumption was significantly lower (18.8 ± 0.4 vs 23.2 ± 4.3; 82.7 ± 2.4 vs 115.8 ± 17.4, P < 0.001), and number of PCA compressions was significantly less frequent (1 [1-2] vs 3 [1-5]; 5 [3-7] vs 7 [3-15], P < 0.001), and in group HbA1c < 6% than in group HbA1c ≥ 6% in 6 hours and 24 hours post-operation.The univariate analysis showed that sufentanil consumption at 24 hours post-operation was significantly related to pre-operative HbA1c (r = 0.338, P < 0.001) and parity (r = 0.184, P = 0.03) and was related to blood glucose management methods (r = 0.172, P = 0.043). Multivariate linear regression analysis showed that HbA1c was the independent factor related to post-operative 24-hour sufentanil consumption (adjusted r2 = 0.246, P < 0.001)

Conclusions: This study demonstrated that in pregnant women with GDM, the pre-operative HbA1c is independently related to the need for and consumption of analgesics in 24 hours after CS.

Keywords: gestational diabetes mellitus, postoperative analgesia, cesarean section, visual analog scale, Glycated hemoglobin

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a common pregnancy complication. According to the International Diabetes Federation (IDF), the incidence of GDM is approximately 14% worldwide (1). In China, the incidence is 11.91% (2). Unlike classic diabetes mellitus (DM), GDM is a transient form of diabetescharacterized by varying degrees of hyperglycaemia caused by impaired glucose tolerance that is discovered or develops during pregnancy. In most cases, GDM is resolved within one to two months after delivery (3).

Glycosylated haemoglobin (HbA1c) is a highly reliable indicator of blood glucose management in the previous 8 to 12 weeks (4). In a prospective observational study, Kim et al. (5) discovered a positive correlation between perioperative HbA1c and post-operative opioid (fentanyl) consumption in diabetic patients undergoing total hysterectomy. This phenomenon may occur because prolonged hyperglycaemia affects opioid receptors and changes the pharmacokinetics/pharmacodynamics of opioids (6) or because it causes metabolic (7) or neurotransmitter disorders (8). Our previous study (9) showed that immediately after caesarean section (CS), women with GDM had a higher need for and consumption of analgesics than women without GDM. However, we were unable to analyse the relationship between pre-operative HbA1c and post-operative analgesic consumption due to the small size of the GDM group. We hypothesised that there is correlation between pre-operative HbA1c and post-operative opioid consumption.

This prospective observational study enrolled a larger number of women with GDM undergoing CS in order to investigate the ability of pre-operative HbA1c to predict the post-operative need for analgesics and to determine the relationship between pre-operative HbA1c and post-operative opioid consumption.

MATERIALS AND METHODS

Experimental Design

This prospective study was conducted at the Obstetrics and Gynaecology Hospital of Fudan University. Written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment. Women with GDM and a singleton pregnancy who elected to undergo CS under combined spinal-epidural anaesthesia were enrolled. Exclusion criteria were a history of opioid allergy, a history of opioid use, contraindications for spinal anaesthesia, and other pregnancy comorbidities, such as gestational hypertension, gestational hypothyroidism, and pre-eclampsia.

After enrolment, each subject's medical history was reviewed. Fasting blood glucose (on the morning of surgery), HbA1c, maternal age, height, weight, gestation, CS history, and blood glucose management methods (diet, oral medication, or insulin injections) were recorded.

No pre-medication was given. After the patient entered the operating room, an 18 G trocar needle was used to establish access to a vein in the right upper arm. An in-dwelling urinary catheter was placed. Blood pressure (non-invasive), electrocardiogram (ECG), heart rate, and pulse oximetry were monitored, and baseline values were recorded. The patient was placed in the right decubitus position, a puncture at the L3-4 or L2-3 interspace was performed using the needle-through-needle technique. After the epidural space was identified using the technique of loss of resistance to normal saline, a spinal needle was used to puncture the dura mater and enter the subarachnoid space. Next, 8~10 mg bupivacaine was diluted with cerebrospinal fluid to 3 ml for intrathecal injection, and an epidural catheter was immediately placed. The patient was placed in the supine position, and the operating table was tilted to the left. The sensory block level was tested with a needle every 2 minutes for 10 minutes. The operation was started once the block reached T6. During the operation, 40 μg of phenylephrine was intravenously injected (and the dose was repeated if necessary), and fluid infusion rate was increased in cases of hypotension (systolic blood pressure < 90 mmHg or > 20% below baseline). In cases of sinus bradycardia (heart rate < 50 bpm), 0.2 mg of atropine was intravenously injected, and the dose was repeated if necessary.

Once the infant was delivered and the umbilical cord was clamped, 50 mg of flurbiprofen axetil and 4 mg of ondansetron were intravenously injected (bolus). Before the end of the operation, 5 μg of sufentanil (diluted to 5 ml with normal saline) was injected epidurally. The epidural catheter was then removed. The operation time and blood loss were recorded.

After the operation, the patient was sent to the post-anaesthesia care unit (PACU). An intravenous analgesia pump (Aipeng, Nantong Aipu Medical Equipment Co., Ltd.) was connected once the patient's blood pressure and heart rate were normal and the block level was below T6. The patient was educated about how to use the pump for patient-controlled intravenous analgesia (PCIA). Analgesics included sufentanil 150 μg and ondansetron 4 mg diluted to 150 ml with normal saline. The background infusion rate was 3 ml/h, the bolus dose was 3 ml, and the locking time was set at 15 minutes. The anaesthesia nurse involved in the study recorded the patients' use of the post-operative analgesia pump (opioid consumption, number of PCA compression) and any adverse reactions, such as nausea, vomiting, or pruritus. A visual analogue scale (VAS) was used to assess pain at rest and during physical activity at 6 and 24 hours after the operation, with "0 cm" indicating no pain and "10 cm" indicating the worst pain imaginable. Additionally, patient satisfaction with post-operative analgesia was assessed using the following rating scale: 1(very dissatisfied), 2(dissatisfied), 3(neutral), 4 (satisfied), and 5 (very satisfied). Nausea and vomiting were managed with ondansetron 4 mg (intravenous injection), which was repeated if necessary. Patients were excluded from the study under the following conditions: 1) a different anaesthesia method was required due to anaesthesia failure or surgical needs; 2) hysterectomy due to

Abbreviations: ASA, American Society of Anesthesiologists; GDM, Gestational diabetes mellitus; HbA1c, Glycated hemoglobin; NGDM, Non-GDM; PCA, Patientcontrolled analgesia; PCIA, Patient-controlled intravenous analgesia; SPSS, Statistical package for social science; VAS, Visual analog scale.

bleeding or other reasons; 3) discontinuation of the use of the analgesia pump for any reason; 4) the patient requested withdrawal from the study.

Statistical Analysis

SPSS (v 22.0, SPSS, Inc., Chicago IL, USA) was used for the statistical analysis, and $P < 0.05$ was considered statistically significant. The patients were divided into two groups based on pre-operative HbA1c: group HbA1c < 6% and group HbA1c ≥ 6%. The primary measure was post-operative 24-hour sufentanil consumption. The secondary measures were post-operative 6-hour sufentanil consumption, post-operative 6-hour and 24-hour number of PCA compressions, VAS score, adverse reactions during post-operative analgesia, and patient satisfaction with post-operative analgesia. The Kolmogorov–Smirnov test was performed to confirm whether the data were normally distributed. Normally distributed measurement data were expressed as the mean ± standard deviation (SD) and were analysed with the independent sample t test. Non-normally distributed variables were expressed as median (interquartile range) and were analysed with the Mann-Whitney U test. Categorical variables were expressed as number and were analysed with Fisher's exact test.

To analyse the relationship between pre-operative HbA1c and post-operative opioid consumption, Pearson's correlation coefficient was used in the univariate analysis to investigate the relationship between post-operative 24-hour sufentanil consumption and each variable, including fasting blood glucose, HbA1c, gestational age, number of CSs, age, weight, and blood glucose management methods. Then, a stepwise multivariate linear regression was performed to analyse variables with $P < 0.2$ in the univariate analysis to identify the independent risk factors for post-operative opioid consumption.

The sample size of this study was based on the original hypothesis, assuming a positive correlation between pre-operative HbA1c and post-operative 24-hour sufentanil consumption is 0.4. The enrolment of at least 61 patients was required to allow 90% power to detect a difference between the null hypothesis and the alternative hypothesis using a two-sided hypothesis test with a significance level of $P = 0.05$. Considering a dropout rate of 10%, it was necessary to enrol at least 69 patients in the study.

RESULTS

A total of 73 women with GDM were enrolled in this study, including 55 in group HbA1c < 6% and 18 in group HbA1c ≥ 6%. All the patients completed the study (**Figure 1**). The maternal demographics, intraoperative observations, laboratory tests, and blood glucose management methods (diet management/oral medication/insulin injection) are listed in **Table 1**.

HbA1c was significantly different between the two groups. Group HbA1c ≥ 6% had a smaller gestational age (37.57 ± 1.11 vs 38.14 ± 1.64 weeks, $P < 0.001$) and a higher rate of insulin use ($P < 0.001$) than group HbA1c < 6%. The remaining indicators showed no significant differences.

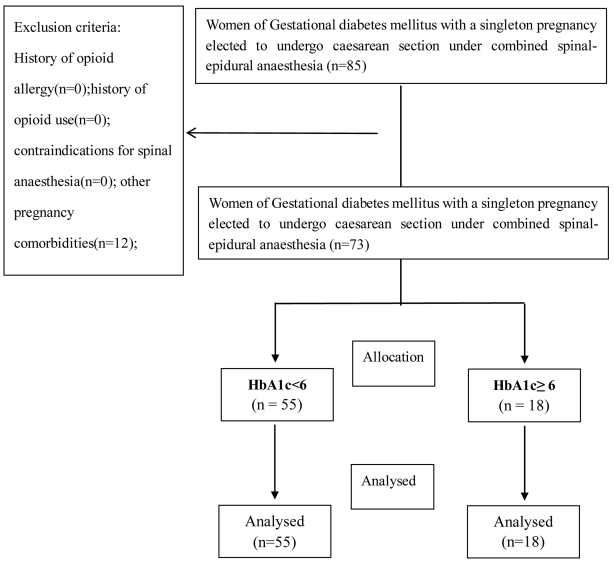

FIGURE 1 | Consort recruitment flow chart.

Post-operative analgesia is shown in **Table 2**. Analgesics consumption in 6hours and 24hours post-operation was significantly lower (18.8 ± 0.4 vs 23.2 ± 4.3; 82.7 ± 2.4 vs 115.8 ± 17.4, $P < 0.001$), and The number of PCA compression in 6 hours and 24 hours post-operation was significantly less frequent (1 [1-2] vs 3 [1-5]; 5 [3-7] vs 7 [3-15], $P < 0.001$), in group HbA1c < 6% than in group HbA1c ≥ 6%. No significant between-group difference was observed in the pain score at any time point (at rest or after physical activity at both 6 and 24 hours after the operation).

The univariate analysis showed that sufentanil consumption at 24 hours post-operation was significantly related to pre-operative HbA1c ($r = 0.338$, $P < 0.001$) and parity ($r = 0.184$, $P = 0.03$) and was related to blood glucose management methods ($r = 0.172$, $P = 0.043$). The variables with $P < 0.2$ included age, gestational age, number of CSs, HbA1c, and blood glucose management methods (**Table 3**). Multivariate linear regression analysis showed that HbA1c was the independent factor related to post-operative 24-hour sufentanil consumption (adjusted $r2 = 0.246$, $P < 0.001$) (**Table 4**).

No significant difference in side effects or satisfaction with post-operative analgesia was observed between the groups (**Table 5**).

DISCUSSION

This prospective study showed that after CS, women with GDM with pre-operative bad-managed blood glucose had a significantly greater need for and consumption of sufentanil during the first 24 hours post-operation than women with well-managed blood glucose. Post-operative 24-hour sufentanil consumption was related to maternal age, pre-operative HbA1c, the number of CSs, and blood glucose management methods.

TABLE 1 | Clinical characteristics of the patients.

	HbA1c<6 (n=55)	HbA1c≥6 (n=18)	P
Age (years)	33.68 ± 1.64	34.04 ± 1.74	0.235
Gestation (weeks)	38.14 ± 1.64	37.57 ± 1.11	0.001
Height (cm)	162.70 ± 3.20	163.00 ± 5.50	0.56
Weight (kg)	72.69 ± 12.15	69.76 ± 10.04	0.08
Number of CSs (first/repeat)	39/16	10/8	0.6
Blood glucose (mmol/l)	5.58 ± 0.62	5.07 ± 0.67	0.42
HbA1c (%)	5.23 ± 0.34	7.29 ± 2.4	0.001
blood glucose management methods (Diet control/oral drugs/insulin injection)	47/8/0	6/7/5	0.001
Amount of bleeding (ml)	315 ± 65	310 ± 70	0.48
Duration of surgery (min)	45. 3 ± 6.7	45.7 ± 5.5	0.56
Newborn weight(g)	3262 ± 149.2	3278 ± 147.8	0.34

Data are presented as the mean ± SD or number.

TABLE 2 | Postoperative analgesia.

		HbA1c<6 (n=55)	HbA1c≥6 (n=18)	P
Number of PCA	6 h	1 [1-2]	3 [1-5]	0.001
compression	24 h	5 [3-7]	7 [3-15]	0.001
Sufentanil	6 h	18.8 ± 0.4	23.2 ± 4.3	0.001
consumption (ug)	24 h	82.7 ± 2.4	115.8 ± 17.4	0.001
VAS scores (cm)	6 h	2 [0-3]	2 [2-2.75]	0.12
Rest	24 h	2 [0-2]	1 [0-2]	0.18
VAS scores (cm)	6 h	5 [4-6]	5 [5-6]	0.56
Movement	24 h	5 [4-5]	5 [3-5]	0.124

Data are presented as the mean ± SD or median [IQR].

TABLE 3 | Correlation analysis to examine factors affecting postoperative sufentanyl requirements variable.

Variable	Simplecoefficient	SE	P value	Partial coefficient	P value
Age (years)	0.162	0.082	0.057	0.169	0.048
Weight (kg)	0.026	0.069	0.758	0.086	0.318
Number of CSs	0.184	0.085	0.030	0.262	0.002
Gestation (weeks)	-0.128	0.105	0.132	0.012	0.888
Blood glucose (mmol/l)	-0.009	0.026	0.916	0.025	0.772
HbA1c (%)	0.338	0.053	<0.001	0.339	<0.001
Blood glucose management methods	0.172	0.074	0.043	0.065	0.454

TABLE 4 | Independent factors affecting postoperative sufentanyl requirements as obtained by multivariate analysis using linear regression with stepwise selection.

Variables	B	SE	95%CI	beta	P	R2	Adjusted R2
constant	50.253	10.449	29.586-70.920		<0.001	0.268	0.246
HbA1c (%)	2.589	0.62	1.363-3.816	0.33	<0.001		
Number of CSs	10.838	2.294		0.391	<0.001		
Age	1.176	0.295	0.593-1.758	0.327	<0.001		
Blood glucose management methods	4.636	2.078	0.525-8.746	0.183	0.027		

B, regression coefficients; CI, confidence interval; SE, standard error.

Our previous study (9) showed that despite their short duration of high blood glucose, women with GDM had a greater need for opioids after CS. This study (which had a larger sample size in women with GDM than the previous study) showed that for women with GDM, pre-operative HbA1c was an independent risk factor for 24-hour opioid use after CS. HbA1c reflects blood sugar control over a certain period. High blood glucose affects the protein expression levels of opioid receptors (10, 11) and reduces the analgesic potential of opioid receptor agonists (12, 13). Moreover, high blood glucose has pro-inflammatory, pro-oxidative, and pro-thrombotic properties, which may play a key role in enhancing hyperalgesia (14). Ion channels of nociception are upregulated, gamma-aminobutyric acid (GABA)ergic neurons are downregulated, and inhibitory pain signal transmission is weakened, resulting in double hyperalgesia (15). Animal studies have shown that rats with acutely elevated blood glucose for 8 weeks are slow to respond to morphine (16); the

TABLE 5 | Comparison of adverse reactions and patient satisfaction between two groups.

	HbA1c<6 (n = 55)	HbA1c≥6 (n = 18)	P
Nausea	9	3	0.12
Vomiting	2	1	0.65
Pruritus	0	0	0.34
Satisfaction (1/2/3/4/5)	0/0/6/47/2	0/1/3/13/1	0.56

Data are presented as number.

short course of GDM may exert similar effects on the body, which may explain why the results of this study are similar to those of DM studies (5, 17).

A retrospective study (18) showed that the need for analgesia was higher in women undergoing a repeated CS than in women undergoing an initial CS. Surgical history is a risk factor for inadequate post-operative analgesia (19). Past surgery often causes severe adhesions, which may contribute to increased post-operative pain (20, 21). Moreover, past surgery may enhance pain sensitivity (18). These data are consistent with our findings that the number of CSs in patients is positively correlated with post-operative 24-hour sufentanil consumption.

A risk factor analysis of GDM based on the International Association of Diabetes Pregnancy Study Groups criteria found that age, history of GDM, family history of diabetes, and large arm circumference are all independent risk factors for GDM (22). Age > 35 years is a risk factor for a high need for analgesia in women with GDM (23). In this study, more women with GDM in group HbA1c ≥ 6% received insulin treatment because treatment for GDM is based on HbA1c. Therefore, age and blood glucose management methods, which are related to HbA1c, are also independent risk factors for post-operative 24-hour sufentanil consumption.

This study has some limitations. First, it followed the internationally accepted diagnostic criteria for GDM (24); that is, for glucose tolerance, the threshold is 5.6 mmol/L for fasting blood glucose, 10.3 mmol/L at 1 hour, 8.6 mmol/L at 2 hours, and 6.7 mmol/L at 3 hours. GDM is confirmed if two or more values meet or exceed the thresholds. No additional tests were performed throughout pregnancy. The patients were instructed to fast for 8-12 hours before the test; however, some (few) patients may not have followed the instructions, resulting in a false positive finding of impaired glucose tolerance. Second, postoperative analgesia did not fully follow the consensus of statement (no use of neutaxial morphine, and NSAIDs was not used enough) (25), we just want to find whether the need for analgesics in patients with GDM is related to HbA1c through intravenous analgesia. We wonder if the effect of different HbA1c levels on the need for analgesics still exists after the application of neuraxial morphine and regular administration of sufficient NSAIDs. Finally, this study enrolled only patients with simple GDM. Patients with other pregnancy comorbidities, such as thyroid dysfunction during pregnancy (26), which may be related to the development of GDM, were excluded from this study to minimize interference. Therefore, the results of this study apply only to women with simple GDM post-operation, and further studies are needed to investigate the need for long-term post-operative analgesia and the analgesic needs of patients with multiple pregnancy comorbidities.

CONCLUSION

For women with GDM, pre-operative HbA1c is independently related to the need for and consumption of analgesics during the 24 hours after CS. HbA1c should be closely monitored in women with GDM and advanced maternal age or a history of CS to provide personalized treatment and improve the quality of and satisfaction with post-operative analgesia.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Obstetrics and Gynaecology Hospital of Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CY and SH conceived the study. JW conducted the statistical analyses. CY, YL, and JH collected and interpreted the clinical data. CY and SH drafted the manuscript. All authors contributed to the interpretation of the results and approved the final manuscript.

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Association Between Gestational Diabetes Mellitus and the Risks of Type-Specific Cardiovascular Diseases

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Objective: Gestational diabetes mellitus (GDM) has been linked to subsequent overall cardiovascular diseases. However, evidence on the associations of GDM with type-specific cardiovascular diseases is lacking, and findings on the potential impact of type 2 diabetes on the associations are not consistent. This study aimed to explore the associations between GDM and the risks of type-specific cardiovascular diseases.

Methods: Data were from 12,025 women (≥20 years) who had delivered at least one live birth in the National Health and Nutrition Examination Survey, 2007–2018. GDM history and type-specific cardiovascular diseases including coronary heart disease (CHD), heart failure and stroke were defined by self-report. We also combined our results with those from previously related publications on the associations between GDM and risks of type-specific cardiovascular diseases with a random-effect model.

Results: Compared with women without GDM, the multivariable-adjusted odds ratios (95% confidence intervals) were 1.82 (1.21–2.72) for CHD, 1.43 (0.80–2.53) for heart failure, and 1.19 (0.76–1.86) for stroke among women with a history of GDM. Type 2 diabetes was associated with 43.90, 67.44, and 63.16% of the excess odds of CHD, heart failure and stroke associated with GDM, respectively. Combining results from this study with those from previously related studies yielded odds ratios (95% confidence intervals) of 1.81 (1.60–2.05) for CHD (12 studies, 7,615,322 participants, I^2 = 72.6%), 1.66 (1.25–2.21) for heart failure (5 studies, 4,491,665 participants, I^2 = 88.6%), and 1.25 (1.07–1.46) for cerebrovascular disease (9 studies, 6,090,848 participants, I^2 = 77.8%).

Conclusions: GDM showed stronger associations with coronary heart diseases and heart failure than cerebrovascular disease, and the excess risks are attributable, in part, to type 2 diabetes.

Keywords: gestational diabetes mellitus, type 2 diabetes, coronary heart disease, heart failure, cerebrovascular disease

INTRODUCTION

Globally, the prevalence of gestational diabetes mellitus (GDM) was estimated at 14.0%, and the standardized prevalence of GDM in low-, middle- and high-income countries was 12.7, 9.2, and 14.2% (1), respectively. GDM could increase the risk of long-term complications including type 2 diabetes, metabolic syndrome and hypertension (2–6), which are detrimental to cardiovascular health. In particular, women with a history of GDM have a nearly 10-fold higher risk of developing type 2 diabetes than women without a history of GDM (2). A recent meta-analysis of 9 studies found a 2-fold higher risk of subsequent overall cardiovascular diseases in women with a history of GDM than women without GDM (7). Therefore, the diagnosis of GDM provides unique opportunities for early intervention and risk modification of cardiovascular diseases (8, 9), although screening for cardiovascular disease has not been included in current guidelines for the care of women with a history of GDM (10, 11).

However, evidence on the associations between GDM and type-specific cardiovascular diseases is lacking (7, 12), and findings from a few recent studies on the associations between GDM and type-specific cardiovascular diseases are not consistent (12–14). In addition, whether the excess risk of cardiovascular diseases linked with GDM is attributable to subsequent type 2 diabetes has not been fully clarified (10, 12). While several studies found that the association between GDM and cardiovascular disease is independent of intercurrent type 2 diabetes (7, 14), subsequent type 2 diabetes partly explained the increased risk of cardiovascular disease linked with GDM in a recent large population-based cohort study (12). Therefore, in this study, we aimed to explore the associations between a history of GDM and type-specific cardiovascular diseases, and assess the potential impact of type 2 diabetes on the associations, using data from the National Health and Nutrition Examination Survey (NHANES), 2007–2018. In addition, we also combined our results with those from previously related publications with a random-effect model.

MATERIALS AND METHODS

Study Populations

The NHANES examines a nationally representative sample of about 5,000 persons each year, and the sample represents the non-institutionalized civilian population residing in counties across the United States. The sample design consists of multi-year, stratified, clustered four-stage samples, and data are released in 2-year cycles. Combination of 2 or more 2-year cycles is also a nationally representative sample (15). Data from NHANES have been widely used to determine the prevalence of major diseases and risk factors for diseases (15). The recent six NHANES 2-year cycles (2007/2008 to 2017/2018) specifically provided information for a history of GDM, and thus were included in this analysis.

Women fulfilling the criteria are included: (1) responding to the questions regarding a history of GDM; (2) with at least one live birth; (3) aged 20 years or older; and (4) responding to the questions regarding the presence of type-specific cardiovascular diseases. Women were excluded from the analysis if they were diagnosed with diabetes or type-specific cardiovascular diseases prior to a diagnosis of GDM. Finally, a total of 12,025 women were included in this analysis.

Previously observational studies with the exposure of interest as GDM and the outcomes of interest as type-specific cardiovascular diseases were included. However, studies only providing the results on GDM and overall cardiovascular diseases were excluded from this analysis, because the association between GDM and overall cardiovascular diseases has been addressed in a previous meta-analysis (7).

History of GDM and Type-Specific Cardiovascular Diseases

A history of GDM was identified based on the question, "During your pregnancy, were you ever told by a doctor or other health professional that you had diabetes, sugar diabetes or gestational diabetes?", and "How old were you when you were first told you had diabetes during a pregnancy?". Women who answered yes to the question were considered to have a history of GDM (16, 17).

Coronary heart disease (CHD), heart failure and stroke were the outcomes of interest, and were self-reported through the following questions: "Has a doctor or other health professional ever told you that you had (1) coronary heart disease? (2) heart attack? (3) angina/angina pectoris? (4) congestive heart failure? (5) stroke?" and "How old were you when you were first told you had (1) coronary heart disease? 2) heart attack? (3) angina/angina pectoris? (4) congestive heart failure? (5) stroke?" In this analysis, women were identified to develop CHD if they answered reported having a diagnosis of coronary heart disease, heart attack, angina/angina pectoris, or congestive heart failure.

Covariates

The following variables were included as covariates: age (continuous), race/ethnicity (Mexican–American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Races), body mass index (<25 kg/m^2, 25 to <30 kg/m^2, ≥ 30 kg/m^2), education ($\leq$high school, some college or AA degree, $\geq$college graduate), annual family income ($<$\$20,000, \$20,000-\$44,999, \$45,000-\$74,999, $\geq$\$75,000), smoking (never smoker, former smoker, current smoker), alcohol drinking, recreational physical activity (vigorous/moderate recreational activities for at least 10 min continuously in a typical week), and daily intakes of energy, fat, fiber, vitamin C, vitamin B6 and vitamin D. The body measures data were collected by trained health technicians in the Mobile Examination Center. Demographics, smoking, alcohol and physical activity questionnaires were asked, in the home, by trained interviewers using the Computer-Assisted Personal Interview system.

Diabetes, Hypertension, and Metabolic Syndrome

Women were identified to develop diabetes if they reported having a diagnosis of diabetes (other than during pregnancy) or, the hemoglobin A1c level was $\geq$6.5%, fasting plasma glucose level $\geq$126 mg/dL, or 2-h plasma glucose $\geq$200 mg/dL if diabetes was not diagnosed previously (18). Women were identified to develop type 1 diabetes if their age at diagnosis was $<$30 years

and they are currently taking insulin (16). Metabolic syndrome was defined if there are any 3 of the 5 following metabolic-related disorders (19): elevated fasting glucose (≥100 mg/dL), elevated triglycerides (≥150 mg/dL), reduced HDL-C (<40 mg/dL in men, <50 mg/dL in women), elevated waist circumference (≥102 cm in men, ≥88 cm in women), and elevated blood pressure (≥130 mm Hg systolic blood pressure, ≥85 mm Hg diastolic blood pressure, mean values of three measurements). Women were identified to develop hypertension if they are currently taking antihypertensive medication, if systolic blood pressure was ≥130 mmHg, or if diastolic blood pressure was ≥80 mmHg (mean values of three measurements) (20).

Statistical Analysis

Odds ratios (95% confidence interval) [OR (95% CI)] for type-specific cardiovascular diseases were calculated for women with a history of GDM compared to those without GDM. Sample weights, strata, and primary sampling units were used in logistic regression to account for the complex sample design of NHANES. Four different logistic regression models were calculated. Demographic variables including age and race/ethnicity were considered in model 1. Model 2 was further adjusted for body mass index and socioeconomic status (annual family income and education). Model 3 included the variables of model 2 with additional adjustment for health behaviors including alcohol drinking, smoking, and recreational physical activity. Model 4 included the variables of model 3 with additional adjustment for dietary factors (energy, fat, fiber, vitamin C, vitaminB6, and vitamin D). In order to determine the potential impact of individual chronic conditions (type 2 diabetes, hypertension and metabolic syndrome) on the risks of type-specific cardiovascular diseases conferred by GDM, we calculated the excess odds of type-specific cardiovascular diseases conferred by individual chronic conditions as [(OR_base – OR_adjusted)/(OR_base-1)] × 100 (12, 21). OR_base was derived from model 4, and OR_adjusted was further adjusted for individual chronic conditions of diabetes, metabolic syndrome, and hypertension, respectively. The 2-year sample weights were divided by 6 to compute the new multi-year sample weight, because 6 NHANES 2-year cycles were included in this analysis. Study-specific logarithms of risk estimates of type-specific cardiovascular diseases were combined with a random-effects model, which considers both between-study and within-study variation. I^2 statistic was used to assess the between-study heterogeneity (22). Study quality was assessed using the 9-star Newcastle-Ottawa Scale, and a sensitivity analysis was conducted restricting to studies with higher quality scores (≥7 stars). Stata 12.0 was used in this study, and the analysis was considered significant if the corresponding P-value was ≤0.05.

RESULTS

Population Characteristics

The weighted prevalence was 8.00% for GDM, 6.74% for CHD, 3.76% for stroke, and 2.73% for heart failure, respectively. Compared with women without GDM, women with a history of GDM tended to be younger ($P < 0.01$), more obese ($P < 0.01$), engage in more recreational physical activity ($P = 0.05$), and show higher prevalence of type 2 diabetes mellitus ($P < 0.01$) and metabolic syndrome ($P < 0.01$). Distributions of race/ethnicity ($P < 0.01$) and annual family income ($P < 0.01$) also differed significantly between the two groups, while there were no significant differences in smoking ($P = 0.29$) and alcohol drinking ($P = 0.76$). **Table 1** presents the population characteristics of the participants according to the presence or absence of a history of GDM.

TABLE 1 | Characteristics of the 2007–2018 NHANES adults according to the presence or absence of a history of gestational diabetes mellitus (GDM).

Variables	Women with GDM (926)	Women without GDM (11,099)	P^a
Age [years, mean (SD)]	45.45 (12.31)	53.49 (16.76)	<0.01
Race/ethnicity (%)			<0.01
Mexican American	21.92	15.77	
Other Hispanic	11.34	11.69	
Non-Hispanic White	35.75	40.76	
Non-Hispanic Black	17.71	22.12	
Other race	13.28	9.67	
Annual family income (%)			<0.01
<$20 000	20.79	26.66	
$20 000–$34 999	33.45	33.70	
$35 000–$74 999	18.87	17.57	
≥$75,000	26.89	22.07	
Education (%)			<0.01
≤High school	43.74	50.15	
Some college or AA degree	36.07	30.64	
≥College graduate	20.19	19.20	
Vigorous/moderate recreational activities for at least 10 min continuously in a typical week (%)	44.04	40.84	0.05
Smoking			0.29
Current smoker	18.90	17.46	
Former smoker	17.82	19.65	
Never smoker	63.28	62.89	
Body mass index (%)			<0.01
<25 kg/m^2	18.33	27.26	
25–29 kg/m^2	25.70	29.66	
≥30 kg/m^2	55.97	43.08	
Alcohol [g/day, mean (SD)]	4.18 (16.56)	4.04 (12.77)	0.76
Type 2 diabetes (%)	34.99	17.83	<0.01
Hypertension (%)	47.95	56.25	<0.01
Metabolic syndrome (%)	49.68	40.19	<0.01

M, Mean values, SD, standard deviation.
[a]t-test was performed for continuous variables, and Chi-square test was performed for categorical variables.

We identified 11 studies (5 prospective cohort studies, 5 retrospective cohort studies, 1 cross-sectional study) on GDM and the risks of type-specific cardiovascular diseases (**Table 2**). Therefore, there are a total of 12 studies (including our study) in the combined analysis on GDM and CHD (12 studies, 7,615,322 participants), heart failure (5 studies, 4,491,665 participants),

TABLE 2 | Included studies on the associations between gestational diabetes mellitus and type-specific cardiovascular diseases.

Reference	Study design, age	Follow-up years	No. of participants	No. of cases	Outcomes	Risk estimates (95% CIs)	Impact of T2DM on the findings
Yu et al. (12), Denmark	Prospective cohort study, Parous women (≥18 years at baseline)	16.2	1,002,486	24,045 17,347 3,888	CHD Cerebrovascular disease Heart failure	2.02 (1.85–2.21) 1.47 (1.30–1.67) 2.20 (1.76–2.74)	T2DM accounts for 25.0–38.3% (CHD), 2.1% (cerebrovascular disease) and 64.2% (heart failure) of the elevated risks associated with GDM.
Sun et al. (13), Korea]	Retrospective cohort study, 20–49 years	12.8	1,500,168	12,698 8,890 2,367	CHD Cerebrovascular disease Heart failure	1.26 (1.05–1.51) 1.04 (0.98–1.11) 1.20 (1.07–1.35)	The associations with type- specific cardiovascular diseases were much stronger in women with both GDM and T2DM.
Gunderson et al. (14), USA	Prospective cohort study, 18–30 at baseline	25	1,133	183	CHD	1.66 (1.13–2.42)	Levels of subsequent glucose tolerance did not influence the results materially. However, the association was only significant in women without diabetes.
Echouffo-Tcheugui et al. (23), Canada	Prospective cohort study, Mean age: 30 years at baseline	7	906,319	763	Heart failure	1.62 (1.28–2.05)	The association was attenuated after further adjustment for other chronic diseases including diabetes.
Perera et al. (24), USA	Cross-sectional study, 20–73 years	–	8,262	93	CHD	1.6 (0.8–2.8)	–
McKenzie-Sampson et al. (25), Canada	Retrospective cohort study, mean age: ∼28 years at baseline	A maximum of 25.2 years	1,070,667	4,736 1,430 3,781	CHD Heart failure Stroke	2.16 (1.95–2.39) 2.00 (1.66–2.42) 1.41 (1.23–1.61)	–
Daly et al. (26), UK	Retrospective cohort study, <50 years	–	46,399	9,112 9,106	CHD Cerebrovascular disease	2.78 (1.37–5.66) 0.95 (0.51–1.77)	–
Tobias et al. (27), USA	Prospective cohort study, 24–44 years at baseline	25.7	89,479	612 553	CHD Stroke	1.45 (1.05–1.99) 1.10 (0.75–1.61)	Compared with women without diabetes, women with T2DM only, or both GDM and T2DM had a 4-fold elevated risk of CHD and 3-fold elevated risk of stroke. The association was not significant in women with a history of GDM but without progression to T2DM.
Retnakaran et al. (28), Canada	Prospective cohort study, Median age: 31 years	10.0	1,515,079	–	CHD	2.56 (2.21–2.95)	Among women who had GDM, the hazard ratio of CHD was much higher for women who also developed T2DM [3.54 (2.96–4.23)] than women who did not develop T2DM [1.41 (1.11–1.80)].
Goueslard et al. (29), France	Retrospective cohort study, Median age: 29 years	7	1,518,990	930 1,252	CHD Stroke	1.77 (1.43–2.18) 1.28 (1.01–1.62)	Among women who had GDM, the odds ratio of CHD was much higher for women who also developed T2DM [5.45 (2.38–12.45)] than women who did not develop T2DM [1.92 (1.36–2.71)].
Savitz et al. (30), USA	Retrospective cohort study, –	1	849,639	81 126	CHD Cerebrovascular disease	1.5 (0.7–3.1) 1.2 (0.7–2.3)	–
Carr et al. (31), USA	Cross-sectional study, 51.1	–	995	–	CHD Stroke	1.58 (1.00–2.49) 1.67 (0.87–3.22)	–

CHD, coronary heart disease, T2DM, type 2 diabetes.

TABLE 3 | Odds ratios of coronary heart disease, heart failure and stroke for women with a history of gestational diabetes mellitus compared with those without a history of gestational diabetes mellitus.

Groups		Odds ratios (95% confidence intervals)						
	Cases/N	Model 1	Model 2	Model 3	Model 4	Model 4 + hypertension	Model 4 + MetS	Model 4 + Type 2 diabetes
CHD	933/12,025	1.93 (1.25–2.97)**	1.82 (1.25–2.65)**	1.80 (1.21–2.67)**	1.82 (1.21–2.72)**	1.81 (1.21–2.69)**	1.79 (1.21–2.66)**	1.46 (0.99–2.15)
Heart failure	396/11,604	1.40 (0.79–2.47)	1.40 (0.80–2.46)	1.41 (0.80–2.49)	1.43 (0.80–2.53)	1.41 (0.79–2.50)	1.42 (0.80–2.53)	1.14 (0.64–2.05)
Stroke	536/12,025	1.41 (0.84–2.37)	1.20 (0.79–1.82)	1.19 (0.76–1.84)	1.19 (0.76–1.86)	1.19 (0.76–1.86)	1.19 (0.76–1.85)	1.07 (0.67–1.69)

***P < 0.01.*

Model 1: adjusted for age and race/ethnicity.

Model 2: adjusted for covariates in model 1 and body mass index, education, and annual family income.

Model 3: adjusted for covariates in model 2 and alcohol drinking, smoking, and recreational physical activity.

Model 4: adjusted for covariates in model 3 and dietary factors (energy, fat, fiber, vitamin C, vitamin B6 and vitamin D).

and cerebrovascular disease (9 studies, 6,090,848 participants) in this analysis.

Association of GDM With CHD

Overall, the findings on a history of GDM and CHD were similar across the 4 different logistic regression models. In model 4, compared with women without GDM, the multivariable-adjusted OR (95% CI) for CHD were 1.82 (1.21–2.72) among women with a history of GDM. Further adjustment for hypertension and metabolic syndrome did not change the results materially. However, the association was attenuated after further adjustment for type 2 diabetes [1.46 (0.99–2.15)] (**Table 3**). The analysis showed that type 2 diabetes, hypertension and metabolic syndrome explained 43.90, 1.22, and 3.66% of the excess odds of CHD associated with GDM, respectively.

Associations of GDM With Heart Failure and Stroke

Women with a history of GDM had increased but not significant odds of heart failure [1.43 (0.80–2.53)] and stoke [1.19 (0.76–1.86)] compare with women without GDM, which might be caused by the relatively wide ranges of 95% CIs (**Table 3**). The analysis showed that type 2 diabetes, hypertension and metabolic syndrome explained 67.44, 4.65, and 2.33% of the excess odds of heart failure associated with GDM, respectively, and the figures were 63.16, 0.00, 0.00% for stroke.

Previously Related Studies

Among the 11 previously related studies, GDM was positively associated with the risk of CHD in 9 studies, while the association was statistically not significant in the other two studies (**Table 2**). GDM was associated with an increased risk of heart failure in all of the 4 studies (**Table 2**). A significant association was found between GDM and cerebrovascular disease in 3 studies, while the association was statistically not significant in the other 5 studies (**Table 2**). The random-effect model combining results from this study with those from previously related studies yielded ORs (95% CIs) of 1.81 (1.60–2.05) for CHD (I^2= 72.6%), 1.66 (1.25–2.21) for heart failure (I^2= 88.6%), and 1.25 (1.07–1.46) for cerebrovascular disease (I^2= 77.8%) (**Figure 1**). In a sensitivity analysis, the combined results from studies with higher quality scores (≥7 stars) were 1.83 (1.59–2.10) for CHD [9 studies (12–14, 25–30), 7,594,040 participants], 1.70 (1.24–2.32) for heart failure [4 studies (12, 13, 23, 25), 4,479,640 participants], and 1.24 (1.04–1.47) for cerebrovascular disease [7 studies (12, 13, 25–27, 29, 30), 6,077,828 participants].

DISCUSSION

Results from this nationally representative survey cohort showed that GDM had stronger associations with coronary heart diseases and heart failure than cerebrovascular disease, and the excess risks are attributable, in part, to type 2 diabetes. In the analysis combing results from previously related studies, we observed 81% higher odds of developing CHD, 66% higher odds of developing heart failure, and 25% higher odds of developing cerebrovascular disease for women with a history of GDM compared with women without GDM.

The biological plausibility for causality in that development of GDM can promote cardiovascular diseases are as follows: First, GDM could increase the risk of long-term complications including type 2 diabetes, metabolic syndrome and hypertension (2–6), which are detrimental to cardiovascular health. In particular, women with a history of GDM have a nearly 10-fold higher risk of developing type 2 diabetes than women without a history of GDM (2). Diabetes showed stronger associations with ischemic heart disease [relative risk (95% CI): 2.46 (2.39–2.53)] and other forms of heart disease [1.98 (1.88–2.08)] than cerebrovascular disease [1.70 (1.61–1.80) in women in US adults (32). Second, in patients with GDM, the underlying metabolic defects including chronic beta-cell dysfunction and insulin resistance could increase levels of glycemia, LDL cholesterol, blood pressure and adiposity, but decrease HDL cholesterol levels, which in together increase the risks of CHD, stroke and heart failure (8). Abnormal expression of cardiovascular diseases associated microRNAs was observed 3–11 years after delivery in women with a history of GDM (33). In addition, less favorable profiles of circulating inflammatory markers including tumor necrosis factor-α, C-reactive protein, and adiponectin in patients with GDM may also contribute to the association between a history of GDM and risk of cardiovascular diseases (34). Third, hyperglycemia exposure even

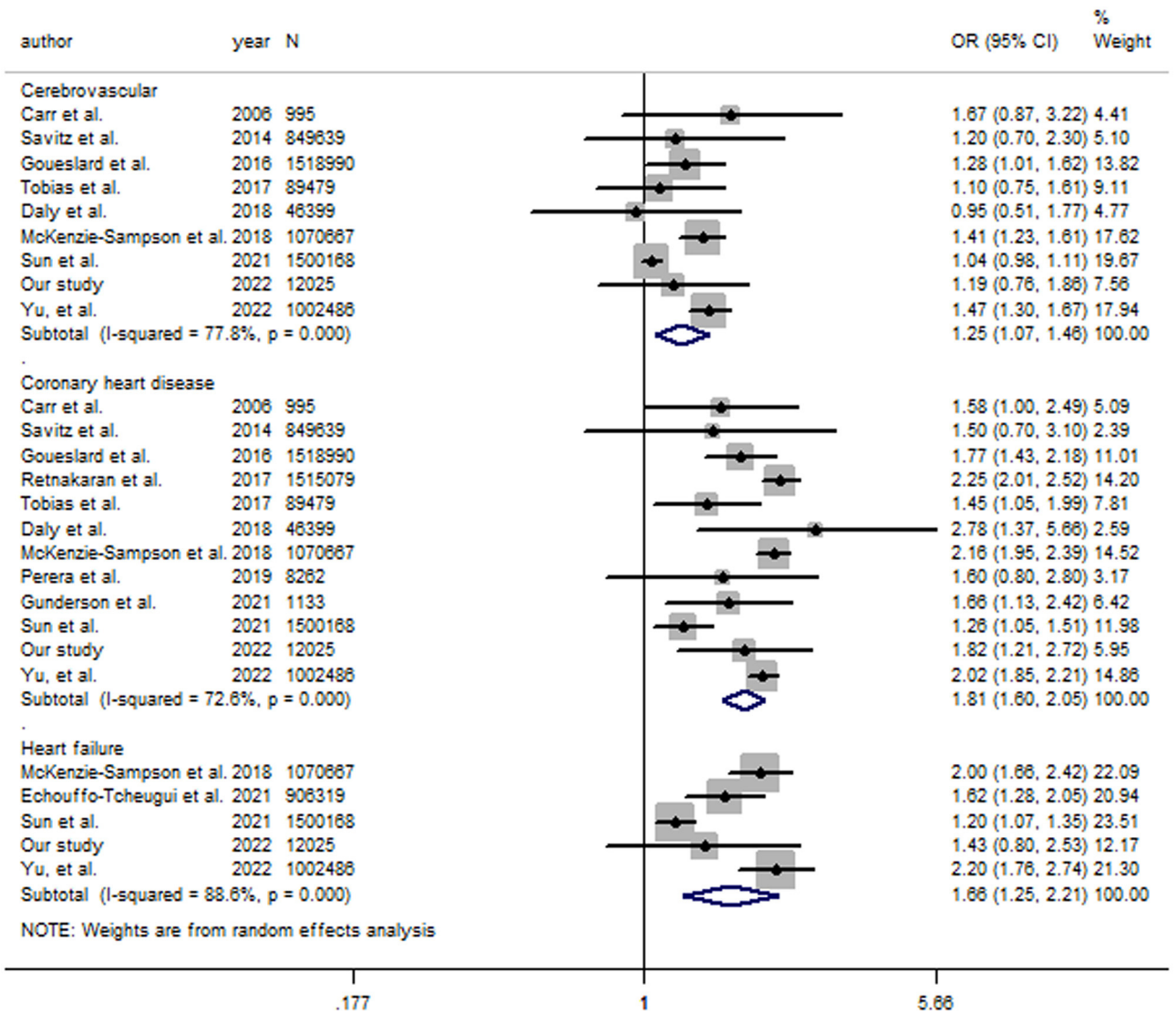

FIGURE 1 | The forest plot for gestational diabetes mellitus and risks of coronary heart disease, heart failure and cerebrovascular disease. The size of gray box is positively proportional to the weight assigned to each study, which is inversely proportional to the standard error of the OR, and horizontal lines represent the 95 % confidence intervals. OR (95% CI): Odds ratio (95% confidence interval).

in a short period could significantly induce functional cardiac impairment in women with GDM (35). In addition, a history of GDM was associated with a 2-fold higher risk of coronary artery calcification, and the association was independent of other traditional risk factors of cardiovascular diseases (14), suggesting there is a direct association between GDM itself and the development of cardiovascular diseases (10). Fourth, according to the Barker's Hypothesis, epigenetic factors may predispose to the development of cardiovascular events in offspring (36, 37). A previous meta-analysis found that offspring born to mothers with GDM have elevated systolic blood pressure, glucose and body mass index (38), and population based cohort studies also showed an elevated risk of cardiovascular disease in offspring exposed to GDM (39–41).

However, data from the 2007–2014 NHANES showed that a history of GDM was only associated with lower HDL cholesterol, and the associations with systolic or diastolic blood pressure, total cholesterol, triglycerides, or LDL-cholesterol were not significant (17). These findings indicate that HDL cholesterol maybe a key factor in the association between a history of GDM and future development of cardiovascular diseases. A recent meta-analysis of 32 prospective cohort studies found that the death risk from cardiovascular diseases was reduced by 23% (95% CI: 13–31%) with each 1 mmol/L increment in HDL cholesterol levels (42). In addition, both high levels of cholesterol efflux capacity, antioxidant capacity, and anti-inflammatory capacity of HDL were associated with lower cardiovascular disease risk, while further studies are still needed to confirm these findings (43).

However, HDL subspecies defined by the components of minor protein or lipid could exert diverse effects on the development of cardiovascular disease (44). While atheroprotective effects of HDL containing APOE or APOC1 were observed (45, 46), APOC-III-containing HDL was associated with higher carotid intima-media thickness (47) and higher risk of CHD (48) in the general population. In addition, HDL subspecies containing haptoglobin, complement C3, alpha-2 macroglobulin, or plasminogen were also associated with higher risk of CHD (45). These findings highlights the need for further studies on the associations between a history of GDM and levels of HDL subspecies in later life. In our study, the associations between a history of GDM and type-specific cardiovascular diseases remained unchanged after further adjustment for hypertension and metabolic syndrome. Our results are consistent with those from the previous study (17) showing that hypertension and metabolic syndrome do not contribute to the association between a history of GDM and type-specific cardiovascular diseases.

In this study, we found that type 2 diabetes was associated with 43.90, 67.44, and 63.16% of the excess odds of CHD, heart failure and stroke associated with GDM, respectively. A previous meta-analysis found that a history of GDM was associated with 2-fold higher risk of total cardiovascular disease [1.98 (1.57–2.50)], and incidence of type 2 diabetes did not impact the association between GDM and total cardiovascular disease in univariate meta-regression (7). However, an attenuated but significant association was found among women without type 2 diabetes [1.56 (1.04–2.32)] (7). Several recent studies have also assessed the role of intercurrent type 2 diabetes on the risk of cardiovascular disease associated with GDM. A recent large population-based prospective cohort study including 10,02,486 Danish women showed that type 2 diabetes was associated with 25.0, 64.2, and 10.1% of the excess odds of CHD, heart failure and stroke associated with GDM, respectively, suggesting that the excess risks could be partly explained by subsequent type 2 diabetes (12). Another recent large population-based retrospective cohort study including 1,500,168 Korean women found that, compared to women without GDM or type 2 diabetes, an increased risk of total CVD was observed for women who had GDM and developed type 2 diabetes during follow-up [1.74 (1.40–21.5)], while the association was not statistically significant for women with GDM only [1.06 (1.00–1.12)], suggesting that type 2 diabetes accounts for much of the excess risk (13). In addition, a population-based prospective cohort study of 1,515,079 women conducted in Canada also found stronger associations between GDM and total cardiovascular disease and CHD in women who had a history of GDM and developed type 2 diabetes during follow-up [2.82 (2.41–3.30) for total cardiovascular disease and 3.54 (0.96–4.23) for CHD] than women who had a history of GDM but did not develop type 2 diabetes during follow-up [1.30 (1.07–1.59) for total cardiovascular disease and 1.41 (1.11–1.80) for CHD] (28). In summary, the recent findings from different countries suggested that type 2 diabetes partly explains the increased risk of cardiovascular disease linked with GDM.

High between-study heterogeneity (I^2 statistic) was found in the analysis between GDM and CHD, heart failure and cerebrovascular disease, respectively. However, direction of the associations between GDM and CHD, heart failure and cerebrovascular disease are generally consistent among the included studies, and the high between-study heterogeneity could be caused by the larger risk estimates and narrow 95% CIs in several large population-based cohort studies. As shown in **Figure 1**, the magnitude of the association between a history of GDM and CHD was apparently larger in several of the large population-based cohort studies with long follow-up period [the study by McKenzie-Sampson et al. (25), N = 1,070,667, a follow-up of up to 25.2 years: 2.16 (1.95–2.39); the study by Retnakaran et al. (28), N = 1,515,079, a median follow-up of 10.0 years: 2.56 (2.21–2.95); the study by Yu et al. (12), N = 1,002,486, a median follow-up of 16.2 years: 2.02 (1.85–2.21)]. The association between a history of GDM and heart failure was also more pronounced in several of the large population-based cohort studies with long follow-up period [the study by McKenzie-Sampson et al. (25), N = 1,070,667, a follow-up of up to 25.2 years: 2.00 (1.66–2.42); the study by Yu et al. (12), N = 1,002,486, a median follow-up of 16.2 years: 2.20 (1.76–2.74)]. A stronger association was also found between a history of GDM and cerebrovascular disease in several of the large population-based cohort studies with long follow-up period [the study by McKenzie-Sampson et al. (25), N = 1,070,667, a follow-up of up to 25.2 years: 1.41 (1.23–1.61); the study by Yu et al. (12). N = 1,002,486, a median follow-up of 16.2 years: 1.47 (1.30–1.67)]. In summary, the findings available support the associations between a history of GDM and future risk of type-specific cardiovascular diseases, and the associations are more pronounced in large population-based cohort studies with long follow-up period.

There are several strengths in this study. This is a nationally representative survey cohort, and we also combined our results with those from previously related studies. In addition, we also found type 2 diabetes could partly explain the increased odds of type-specific cardiovascular disease linked with GDM. However, there are also several limitations. First, causality between GDM and risks of type-specific cardiovascular diseases cannot be determined in this study. However, we have excluded women who were diagnosed with type-specific cardiovascular diseases prior to a diagnosis of GDM from the analysis, and the positive associations between a history of GDM and type-specific cardiovascular diseases were also observed in previously prospective cohort studies. Second, there may be misclassification because a history of GDM and diagnosis of type-specific cardiovascular diseases were based on self-report. However, data from NHANES have been widely used to determine the prevalence of major diseases and risk factors for diseases (15), and the risk estimates in this analysis are generally comparable to the combined results from previously related studies. In addition, non-differential misclassification could have weakened an association. Other information including control of the glycaemia levels during the three trimesters of pregnancy are not available in our study and are also missing in the included previous studies on GDM history and risk of type-specific cardiovascular diseases, which should be considered in further studies. Third, although we have adjusted for a number of potential covariates, residual confounding arising from other

unmeasured variables could be of concern. However, as shown in **Table 3**, the associations between a history of GDM and type-specific cardiovascular diseases did not change materially across the four statistical models, suggesting the associations were independent of these covariates and supporting a direct association between GDM itself and future development of type-specific cardiovascular diseases.

Patients with GDM require anti-diabetic pharmacotherapy if the glycaemia levels cannot be maintained with diet modification, and insulin and metformin are recommended for the treatment of GDM (49–51). Results from two recent meta-analysis of randomized controlled trials suggested that metformin treatment could reduce the further risk of cardiovascular diseases (52, 53). However, over a 21-year median follow-up, neither metformin nor lifestyle interventions could reduce the risks of myocardial infarction and stroke in the DPP/DPPOS (54) (the longest and largest trial of metformin treatment for diabetes prevention). In addition, baseline metformin treatment did not provide additional cardioprotective effect associated with dulaglutide in another large trail (55). For insulin, two recent meta-analysis of randomized clinical trials showed that baseline insulin treatment was not associated with further risks of cardiovascular events or death (56, 57). As the first-line treatment, nutritional interventions have made recommendations on intakes of carbohydrate, fat, and protein (58). Although most of these clinical practice guidelines on nutritional interventions are not being of high quality (58), the nutritional interventions could significantly reduce the risk of postpartum diabetes (59). However, evidence is limited regarding diet modification and anti-diabetic pharmacotherapy including metformin treatment during pregnancy and risks of cardiovascular diseases in women with a history of GDM (60). Information for insulin, metformin and diet modification during pregnancy are not available in our study. The long-term effects of these anti-diabetic pharmacotherapies and diet modification during pregnancy on the further risks of cardiovascular diseases among women with a history of GDM deserve to be determined further.

Results from our analysis and previous studies showed that GDM provides unique opportunities for identifying women at increased risks of type-specific cardiovascular diseases (9). For the primary prevention of cardiovascular disease including CHD, stroke and heart failure, the recent Statement From the American Heart Association (61) recommends recognizing GDM when evaluating risk of cardiovascular disease, increasing physical activity, adopting a heart-healthy diet, lactation and breastfeeding, and calls for future studies of pharmacotherapy including metformin among women who previously had GDM.

In summary, data from the NHANES showed that GDM had stronger associations with CHD and heart failure than cerebrovascular disease, and the excess risks are attributable, in part, to type 2 diabetes. Combined results from this analysis with those from previously related studies showed that a history of GDM was associated with 81% higher risk of CHD, 66% higher risk of heart failure, and 25% higher risk of cerebrovascular disease.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: The datasets generated during and/or analyzed during the current study are available in the NHANES: https://www.cdc.gov/nchs/nhanes/.

ETHICS STATEMENT

NHANES was approved by the National Center for Health Statistics Research Ethics Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YM and QL designed the study. WH conducted the statistical analysis. YM, BX, LL, XH, and QL drafted the manuscript. QL made critical revisions. All authors have approved the final article.

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ORIGINAL RESEARCH
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Interactive Affection of Pre-Pregnancy Overweight or Obesity, Excessive Gestational Weight Gain and Glucose Tolerance Test Characteristics on Adverse Pregnancy Outcomes Among Women With Gestational Diabetes Mellitus

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Purpose: To examine the combined effect of pre-pregnancy overweight or obesity, excessive gestational weight gain, and glucose tolerance status on the incidence of adverse pregnancy outcomes among women with gestational diabetes mellitus.

Methods: A observational study including 5529 gestational diabetes mellitus patients was performed. Logistic regression were used to assess the independent and multiplicative interactions of overweight or obese, excessive gestational weight gain, abnormal items of oral glucose tolerance test and adverse pregnancy outcomes. Additive interactions were calculated using an Excel sheet developed by Anderson to calculate relative excess risk.

Results: Overall 1076(19.46%) study subject were overweight or obese and 1858 (33.60%) women gained weight above recommended. Based on IADPSG criteria, more than one-third women with two, or three abnormal glucose values. Preconception overweight or obesity, above recommended gestational weight gain, and two or more abnormal items of oral glucose tolerance test parameters significantly increased the risk of adverse pregnancy outcomes, separately. After accounting for confounders, each two of overweight or obesity, excessive gestational weight gain, two or more abnormal items of OGTT parameters, the pairwise interactions on adverse pregnancy outcomes appear to be multiplicative. Coexistence of preconception overweight or obesity, above recommended gestational weight gain and two or more abnormal items of oral glucose tolerance test parameters increased the highest risk for adverse pregnancy outcomes. No additive interaction was found.

Conclusions: Pre-pregnancy overweight or obesity, excessive gestational weight gain, two or more abnormal items of OGTT parameters contribute to adverse pregnancy outcomes independently among women with gestational diabetes mellitus. Additionally, the combined effect between these three factors and adverse pregnancy outcomes appear to be multiplicative. Interventions focus on maternal overweight or obesity and gestational weight gain should be offered to improve pregnancy outcomes.

Keywords: adverse pregnancy outcomes, overweight or obesity, excessive gestational weight gain, gestational diabetes mellitus, multiplicative interaction

INTRODUCTION

Gestational diabetes mellitus(GDM) is one of the common complications during pregnancy (1). In the past decades, the prevalence of gestational diabetes mellitus(GDM) has increased rapidly and caused a tremendous disease burden (2, 3). In China, the prevalence is continue climbing due to the growing number of childbearing age women, the overweight or obesity epidemic, correlated to the implementation of the "two-child policy" since October 2015 (1). The risk factor includes older age, family history of diabetes, pre-pregnancy overweight or obesity, previous GDM, excessive gestational weight gain, polycystic ovarian syndrome (PCOS) (1, 4–7). In China, the GDM has become epidemic and affects the short- and long-term health of mothers and their offspring such as hypertensive disorders of pregnancy(HDP), preeclampsia, cesarean section, shoulder dystocia for mother and large gestational age, premature, macrosomia and even increase the risks of obesity, type 2 diabetes mellitus(T2DM), and metabolic syndrome in adult life (8–15). overweight or obesity have increased rapidly across different age groups and sexes including childbearing age women which not only increase the rates of metabolic complication but also contribute to greater risks of adverse pregnancy outcomes (3, 16). Gestational weight gain is strongly associated with maternal and fetal growth health. The Institute of Medicine(IOM) introduced guidelines for gestational weight gain to lower the risks of perinatal complications in 1990 and updated in 2009 (17). Extensive research has shown the increased risk for maternal and infant adverse pregnancy outcomes with excessive gestational weight gain including HDP, GDM, large gestation age for newborns, cesarean section, macrosomia, and childhood obesity (17–19). Moreover, it has been demonstrated that there was a significantly increased risk of cesarean section, preterm delivery, macrosomia and large gestation age as the number of abnormal terms of oral glucose tolerance test(OGTT) increased (20).

On the face of these, women with GDM, overweight or obesity, and excessive gestational weight gain are all independent associated with increased risk of adverse maternal and perinatal outcomes. When co-occurrence of these three factors, maternal with overweight or obesity and excessive gestational weight gain may increase their already elevated risk of adverse maternal and perinatal outcomes, particularly in GDM women with two or three abnormal terms of glucose values on the OGTT. However, in women with GDM, the combination effect of pre-pregnancy overweight or obesity, excessive gestational weight gain and glucose tolerance status for adverse maternal and perinatal outcomes is still unknown. Hence, this study aims to evaluate the combined effect of pre-pregnancy overweight or obesity, excessive gestational weight gain, and glucose tolerance status on pregnancy outcomes among women with GDM.

MATERIALS AND METHODS

The Study Population

The observational study reviewed medical records in Fujian Maternity and Child Health Hospital of women who were diagnosed with GDM and delivery of a live singleton neonate after 28 weeks gestation between 2017 and 2021. The eligibility criteria include all women who received perinatal care and performed a 75 g OGTT between 24 and 28 weeks of gestation. We excluded those with preconception diabetes mellitus and incomplete medical records.

This was a retrospective study and was approved by the Ethics Committee of Fujian Maternity and Child Health Hospital.

Study Variables

All the medical record data were extracted into a computerized database including demographic data, obstetric data, and delivery data including age, pre-pregnancy weight, height, gravity, parity, maternal weight at each perinatal examination, and OGTT values, discharge diagnosis, gestational age at delivery and neonatal data.

pre-pregnancy body mass index(BMI) was calculated as [pre-pregnancy weight(kg)/height^2(m^2)] based on self-reported pre-pregnancy and measured height in hospital. pre-pregnancy BMI was classified as underweight and normal weight (BMI<24.0kg/m^2), overweight or obesity (BMI≥24.0kg/m^2) based on Chinese standard (21). Gestational weight gain was calculated as the difference between pre-pregnancy weight and delivery weight. The gestational weight gain was divided as above recommendations and as or below recommendations according to weight monitoring and evaluation during the pregnancy period of Chinese women (Underweight, >16.0kg; Normal weight,>14.0kg; Overweight,>11.0kg; Obesity,>9.0kg) (22). We used the OGTT result to classify the GDM group into one abnormal item and at least two abnormal items of OGTT parameters: fasting ≥5.10 mmol/L,1 h ≥10.0 mmol/L, or 2 h ≥8.5 mmol/L (23).

The main pregnancy outcomes in this study included: macrosomia, defined as a birth weight of more than 4000g (24); Large for gestational age (LGA) or small for gestational age(SGA), defined as a birth weight more than 90th or less than 10th percentile based on gender and gestational age (25); Preterm delivery, defined as gestational age at delivery<37 weeks but >28 weeks; Full term low birth weight, defined as a gestational age ≥ 37weeks with birth weight less than 2500g; hypertensive disorders of pregnancy(HDP), defined as blood pressure ≥140/90 mmHg that occurred after 20 weeks gestation but without proteinuria (26). Other pregnancy outcomes were cesarean section and composite outcome. Composite outcome was defined as either one of macrosomia, LGA, SGA, preterm delivery, full term low birth weight, HDP, and cesarean section.

Statistical Analysis

Data of maternal demographic and obstetrical and neonatal outcomes were tested for normal distribution and shown as median (inter-quartile range, IQR) for continuous variables as the abnormal distribution, number (percentage) for categorical variables.

Binary logistic regression was used to analyze the effect of overweight or obesity/excessive gestational weight gain/at least two abnormal items of OGTT parameters on the pregnancy outcomes and multiplicative interactions, expressed resulted as odds ratio(OR) and 95% confidence intervals(95%CI). For all outcomes except preterm delivery, the adjustment OR was based on the maternal age, gestational age, infant sex, gravity, and parity. For preterm delivery, the adjustment OR was based on the maternal age, infant sex, gravity, and parity. Multiplicative interactions among individual risk factor was carried out by adding two or more product terms to the regression model while statistical significance indicates the multiplicative interactions. Additive interactions were calculated using an Excel sheet prepared by Anderson to calculate the following three indices with their 95% CIs: relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and interaction index (synergy index, SI) (27). The 95% CI of RERI and AP include "0" and the 95% CI of SI include "1" indicate that there is no summation interaction. We firstly performed a logistic regression model to calculate the regression coefficients and covariance matrix for each two of factors and then they were input the Excel sheet to calculate RERI, AP, SI and their 95% CIs. Statistical analysis was performed using IBM SPSS Statistics 22. 0 software.

RESULTS

Basic Characteristics of the Participants

A total of 8850 pregnant women with GDM received prenatal examinations and delivery at Fujian Provincial Maternity and Children's Hospital between 2017 and 2021. We excluded 3321women from the following: 58 pregnant women who terminated the pregnancy before 28 weeks, 212 women with multiple pregnancies, 18 women with stillbirth, 340 women without gestational weight value before delivery, and 2693 women who didn't undergo a complete oral glucose tolerance test. Of the remained 5529 GDM women, the median maternal age was 31 years, pre-pregnancy weight was 54kg;12.41% were underweight, 68.31% were normal weight, 18.09% were overweight, and 1.37%were obese. Overall, more one-third of women were of greater gravidity, more than 3 times. Of the 5529 GDM women, 47.98% were multiparity. According to the Chinese gestational weight gain guidelines (22), 14.74% of women gained weight below recommended, 51.65% f women gained weight as recommended and 33.60% of women gained weight above recommended. As for glucose tolerance status, our study group consisted of 59.54%, 31.33%, and 9.13% women with one, two, or three abnormal glucose values, respectively. More than 37% of women are delivered by cesarean section. The characteristics of the mothers and neonates are described in **Table 1**. Due to the small number of obese GDM women, we merged overweight and obese GDM women into the same group and analyzed these parameters as just one variable.

Association of Overweight or Obesity, Excessive Gestational Weight Gain, Abnormal Items of OGTT With Adverse Pregnancy Outcomes

The association between overweight or obesity, excessive gestational weight gain, two or more abnormal items of OGTT parameters, and adverse pregnancy outcomes were analyzed by binary logistic

TABLE 1 | Basic characteristics of the participants (n = 5529).

Variables	All participants
Maternal age (median[IQR],Years)	31[28,35]
Pre-pregnancy Weight (median[IQR],Kg)	54[49.5,60]
Body mass index category (N,%)	
Underweight	686 (12.41)
Normal weight	3767 (68.13)
Overweight	1000(18.09)
Obesity	76 (1.37)
Gravidity	
1	1972 (35.67)
2	1679 (30.37)
≥3	1878 (33.97)
Parity (N,%)	
Primiparity	2876 (52.02)
Multiparity	2653 (47.98)
Gestational age at delivery (median[IQR],Weeks)	39[38,40]
Gestational weight gain category by Chinese guideline (N,%)	
Below recommended	815 (14.74)
As recommended	2856 (51.65)
Above recommended	1858 (33.60)
Birth weight (median[IQR],g)	3300[3032.5,3570]
Glucose tolerance status (N,%)	
One abnormal item	3292 (59.54)
Two abnormal items	1732 (31.33)
Three abnormal items	505 (9.13)
Model of delivery (N,%)	
Vaginal birth	3463 (62.63)
Cesarean delivery	2066 (37.37)
Infant sex (N,%)	
Boy	2981 (53.92)
Girl	2548 (46.08)

regression and is shown in **Table 2**. Women with overweight or obesity had an increased relative risk of macrosomia (aOR:1.83,95% CI:1.39~2.40), LGA(aOR:1.59,95%CI:1.36~1.85), HDP (aOR:2.73,95%CI:2.15~3.46), cesarean section(aOR:1.58,95% CI:1.38~1.82) and composite outcome(aOR:1.82,95%CI:1.57~2.10). Compared to women with gestational weight gain follow or below recommendations, women with gestational weight gain above recommendations was associated with an increased risk of macrosomia(aOR:2.24,95%CI:1.75~2.88), LGA(aOR:1.73,95% CI:1.52~1.98), HDP(OR:1.87,95%CI:1.49~2.36), cesarean section (aOR:1.49,95%CI:1.32~1.68) and composite outcome (aOR:1.59,95%CI:1.41~1.79), but decreased the risk of preterm delivery(aOR:0.76,95%CI:0.59~0.99). There also have an association between at least two abnormal items of OGTT parameters and perinatal outcomes. The aOR of the association for macrosomia was 1.31(95%CI:1.02~1.68), for LGA was 1.16 (95% CI:1.02~1.32), for HDP was 1.48(95%CI:1.18~1.85).

Pairwise Interaction of Overweight or Obesity, Excessive Gestational Weight Gain and Abnormal Items of OGTT on Adverse Pregnancy Outcomes

Pairwise interaction analysis showed the multiplicative interactions were observed between overweight or obesity with gestational weight gain above recommendations and macrosomia(aOR:3.58,95% CI:2.48~5.16), LGA(aOR:2.67,95%CI:2.15~3.31), HDP (aOR:3.97,95%CI:2.84,5.54), cesarean section(aOR:2.27,95% CI:1.85~2.78) and composite outcome(aOR:2.97,95%CI:2.36~3.73). In addition, there was a positive multiplicative interactions between overweight or obesity with at least two abnormal items of OGTT parameters and macrosomia(aOR:2.05,95%CI:1.39~3.04), LGA (aOR:1.72,95%CI:1.39~2.12),HDP(aOR:3.72,95%CI:2.69,5.12), cesarean section(aOR:1.59,95%CI:1.30~1.93) and composite outcome(aOR:1.94, 95%CI:1.57~2.39). Similar multiplicative interactions of gestational weight gain with two or more abnormal items of OGTT parameters and macrosomia (aOR:3.17,95% CI:2.19~4.58), HDP(aOR:2.90,95%CI:2.06~4.09), cesarean section (aOR:1.57,95%CI:1.31~1.89) and composite outcome(aOR:1.77, 95%CI:1.46~2.13) (**Table 3**).

When each two of overweight or obesity, excessive gestational weight gain, two or more abnormal items of OGTT parameters exist at the same time, no additive interaction was found for adverse pregnancy outcomes. However, neither multiplication interaction nor additive interaction was noticed in preterm delivery, SGA, and full-term low birth weight (**Tables 3** and **4**).

Coexist Interaction of Overweight or Obesity, Excessive Gestational Weight Gain and Abnormal Items of OGTT on Adverse Pregnancy Outcomes

Compared to underweight or normal, gestational weight gain as or blew recommendations and with only one abnormal term of OGTT pathological values pregnant women, women with overweight or obesity, gestational weight gain above recommendations and with two or more abnormal items of OGTT parameters had highest risks of macrosomia (aOR:4.52,95%CI:2.60~7.84), LGA(aOR:3.19,95%CI:2.33~4.37), HDP(aOR:7.60, 95%CI:4.78~12.08), cesarean section(aOR:2.56, 95%CI:1.89,3.47) and composite outcome(aOR:3.75, 95% CI:2.63,5.34), after controlling the confounding factors.

Furthermore, gestational weight gain as or below recommendations among overweight or obesity women also increased relative risk of macrosomia[(aOR:2.12, 95%CI:1.19,3.78) and (aOR:2.01, 95%CI:1.13,3.73)], LGA[(aOR:1.50, 95%CI:1.12,2.02) and (aOR:1.44, 95%CI:1.12,1.94)], HDP[(aOR:3.91, 95% CI:2.29,5.96) and (aOR:4.11, 95%CI:2.41,6.34)], cesarean section [(aOR:1.55, 95%CI:1.19,2.00) and (aOR:1.42, 95%CI:1.10,1.83)], and composite outcome[(aOR:1.61, 95%CI:1.24,2.09) and (aOR:1.67, 95%CI:1.28,2.15)], regardless of OGTT pathological values. Moreover, gestational weight gain as or below recommendations among underweight or normal women with two or more abnormal items of OGTT parameters was associated with increased risk of macrosomia(aOR:1.52, 95%CI:1.01,2.29), LGA (aOR:1.21, 95%CI:1.01,1.46), HDP(aOR:1.84, 95%CI:1.26,2.70), but

TABLE 2 | Association of overweight or obesity, excessive gestational weight gain and glucose tolerance status with adverse pregnancy outcomes[a].

Category	Macrosomia	LGA	Preterm delivery[b]	HDP	SGA	Cesareansection	Full term low birth weight	Composite outcome
Pre-pregnancy BMI category (kg/m^2)								
Underweight or Normal (<24.0)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00(Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Overweight or Obese (≥24.0)	1.83 (1.39,2.40)	1.59 (1.36,1.85)	0.95 (0.70,1.29)	2.73 (2.15,3.46)	0.80 (0.49,1.31)	1.58 (1.38,1.82)	0.72 (0.37,1.40)	1.82 (1.57,2.10)
Gestational weight gain category								
As or below recommended	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Above recommended	2.24 (1.75,2.88)	1.73 (1.52,1.98)	0.76 (0.59,0.99)	1.87 (1.49,2.36)	0.70 (0.65,1.04)	1.49 (1.32,1.68)	0.64 (0.36,1.16)	1.59 (1.41,1.79)
Glucose tolerance status								
One abnormal item	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
At least two abnormal items	1.31 (1.02,1.68)	1.16 (1.02,1.32)	1.26 (0.99,1.60)	1.48 (1.18,1.85)	0.95 (0.66,1.37)	1.04 (0.93,1.17)	0.84 (0.50,1.38)	1.09 (0.97,1.22)

Data are showed as OR(95%CI).

BMI, body mass index; LGA, large for gestational age; SGA, small for gestational age; HDP, Hypertensive disorders of pregnancy; [a] For all outcomes except preterm delivery were adjusted for maternal age, gestational age, infant sex, gravity, and parity. [b] adjusted for on the maternal age, infant sex, gravity, and parity.

TABLE 3 | Pairwise interaction of overweight or obesity, excessive gestational weight gain and glucose tolerance status on adverse pregnancy outcomes[a].

Category		Macrosomia	LGA	Preterm delivery[b]	HDP	SGA	Cesarean section	Full term low birth weight	Composite outcome
Pre-pregnancy BMI category(kg/m)	**Gestational weight gain category**								
Underweight or Normal (<24.0)	As or below recommended	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)
	Above recommended	2.15 (1.60,2.89)	1.58 (1.36,1.84)	0.63 (0.46,0.87)	134 (1.44,2.57)	1.03 (0.58,1.81)	1.39 (1.21,1.60)	0.81 (0.43,1.54)	1.44 (1.26,1.65)
Overweight or Obese (≥24.0)	As or below recommended	1.68 (1.12,2.52)	1.35 (1.10,1.66)	0.72 (0.48,1.09)	3.03 (2.19,4.19)	0.79 (0.51,1.22)	1.43 (1.20,1.72)	1.01 (0.48,2.13)	1.55 (1.29,1.87)
	Above recommended	3.58 (2.48, 5.16)	2.67 (2.15,3.31)	1.02 (0.68,1.54)	3.97 (2.84,5.54)	0.42 (0.17,1.05)	2.267 (1.85,2.78)	0.276 (0.07,1.17)	2.970 (2.36,3.73)
Pre-pregnancy BMI category(kg/m^2)	**Glucose tolerance status**								
Underweight or Normal (<24.0)	One abnormal item	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)
	At least two abnormal items	1.43 (1.07,1.92)	1.16 (0.99,1.34)	1.17 (0.90,1.53)	1.34 (1.00,1.78)	0.95 (0.64,1.42)	1.02 (0.90,1.17)	1.02 (0.59,1.76)	1.05 (0.93,1.20)
Overweight or Obese (≥24.0)	One abnormal item	2.20 (1.52,3.19)	1.66 (1.34,2.04)	0.75 (0.47,1.20)	2.52 (1.78,3.57)	0.78 (0.40,1.54)	1.60 (1.33,1.94)	1.14 (0.51,2.53)	1.78 (1.46,2.17)
	At least two abnormal items	2.05 (1.39,3.04)	1.72 (1.39,2.12)	1.31 (0.89,1.94)	3.72 (2.69,5.12)	0.80 (0.40,1.57)	1.59 (1.30,1.93)	0.36 (0.11,1.22)	1.94 (1.57,2.39)
Gestational weight gain category	**Glucose tolerance status**								
As or below recommended	One abnormal item	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)	1.00(Ref.)
	At least two abnormal items	1.41 (0.99,2.00)	1.19 (1.01,1.40)	1.19 (0.90,1.57)	1.64 (1.21,2.23)	0.93 (0.61, 1.41)	1.08 (0.94, 1.25)	1.01 (0.58, 1.77)	1.13 (0.99, 1.30)
Above recommended	One abnormal item	2.33 (1.66,3.26)	1.74 (1.47,2.07)	0.72 (0.50,1.02)	2.08 (1.50,2.87)	0.69 (0.42, 1.14)	1.53 (1.31, 1.78)	0.89 (0.44, 1.77)	1.63 (1.40, 1.89)
	At least two abnormal items	3.17 (2.19,4.58)	2.09 (1.71,2.55)	1.01 (0.69,1.49)	2.90 (2.06, 4.09)	0.65 (0.35, 1.23)	1.57 (1.31, 1.89)	0.31 (0.09, 1.04)	1.77 (1.46, 2.13)

Data are showed as OR(95%CI).

BMI, body mass index; LGA, large for gestational age; SGA, small for gestational age; HDP, Hypertensive disorders of pregnancy; [a] For all outcomes except preterm delivery were adjusted for maternal age, gestational age, infant sex, gravity, and parity. [b] adjusted for on the maternal age, infant sex, gravity, and parity.

do not effect on cesarean section(aOR:1.10, 95%CI:0.94,1.28) and composite outcome(aOR:1.13, 95%CI:0.98,1.32) (**Table 5**).

DISCUSSION

With the current epidemic of GDM, the public health of GDM is becoming more apparent in China. The incidence of GDM in China reached 8% (1), which is extremely harmful to maternal and child health. Therefore, the focus on the intervention of GDM is of great importance to reduce the risk of adverse perinatal outcomes. We found that pre-pregnancy overweight or obesity, above recommended gestational weight gain, and two or more abnormal items of OGTT parameters significantly increase the risk of adverse pregnancy outcomes, separately. After accounting for confounders, each two of overweight or obesity, excessive gestational weight gain, two or more abnormal items of OGTT parameters, the pairwise interactions on macrosomia, LGA, HDP, cesarean section, and the composite outcome appear to be multiplicative. Furthermore, coexistence of pre-pregnancy overweight or obesity, above recommended gestational weight gain and two or more abnormal items of OGTT parameters increase the highest risk for macrosomia, LGA, HDP, cesarean section, and composite outcome.

Overweight or obesity status before pregnancy in women of reproductive age influence not only the occurrence of GDM but also adverse perinatal outcomes. Growing studies has shown the higher pre-pregnancy BMI was an independent risk factor for LGA, HDP and cesarean section (28, 29), and when combined with GDM, acting as the most major determinant for macrosomia and LGA (30–32). This also accords with our finding, which also showed significant association with higher rate of HDP and composite outcome, after adjusting for the potential confounding variables.

Excessive gestational weight gain has been proved to be linked with adverse perinatal outcomes among GDM patients (33–35). We also found the similar results: exceeding the Chinese guideline (22) was linked with higher odds for macrosomia, LGA, HDP, cesarean section and composite outcome. Increased adipose tissue breakdown and circulating free fatty acids in third trimester may be transported through the placenta, promoting a pro-inflammatory environment with fetal metabolic programming consequences for the offspring (36–39). Alone or combined GDM and maternal obesity are independently associated with poor pregnancy outcomes. Maternal lipids may play a more important role in the fetal programming of infant obesity in the diabetic intrauterine environment (40). In the present study, we note that excessive gestational weight gain and overweight or

TABLE 4 | Additive interaction of overweight or obesity, excessive gestational weight gain and glucose tolerance status on adverse pregnancy outcomes.

	Iterm1	Iterm2	Additive interaction		
			RERI (95%CI)	AP (95%CI)	SI (95%CI)
Macrosomia	Pre-pregnancy overweight or obese(≥24.0)	Gestational weight gain above recommendations	0.58(-2.47,3.63)	0.171 (-0.50,0.84)	1.32 (0.45,3.88)
	Pre-pregnancy overweight or obese(≥24.0)	At least two abnormal items of Glucose tolerance	-0.86(-1.86,0.69)	-0.29 (-1.30,0.73)	0.64 (0.12,3.57)
	Gestational weight gain above recommendations	At least two abnormal items of Glucose tolerance	0.44(-2.30,3.17)	0.14(-0.55,0.82)	1.25 (0.42,3.75)
LGA	Pre-pregnancy overweight or obese(≥24.0)	Gestational weight gain above recommended	0.74(-1.27,2.76)	0.28(-0.14,0.67)	1.80 (1.043.097)
	Pre-pregnancy overweight or Obese(≥24.0)	At least two abnormal items of Glucose tolerance	-1.57(-1.94,-1.20)	-12.20 (-39.68,15.28)	0.88 (0.19,4.06)
	Gestational weight gain above recommendations	At least two abnormal items of Glucose tolerance	-0.10(-1.03,0.84)	-0.06 (-0.68,0.56)	0.88 (0.19,4.06)
Preterm delivery	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	Gestational weight gain above recommendations	0.66(-0.22,1.54)	NA	NA
	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	At least two abnormal items of Glucose tolerance	0.39(-0.73,1.52)	0.299 (-0.13,0.73)	NA
	Gestational weight gain above recommendations	At least two abnormal items of Glucose tolerance	-0.17(-0.44,0.10)	-3.39(-6.21,-0.58)	1.22 (0.85,1.75)
HDP	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	Gestational weight gain above recommendations	0.02(-3.09,3.13)	0.01(-0.77,0.78)	1.01 (0.35,2.86)
	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	At least two abnormal items of Glucose tolerance	0.87(-2.38,4.11)	0.23(-0.34,0.81)	1.47 (0.58,3.69)
	Gestational weight gain above recommendations	At least two abnormal items of Glucose tolerance	0.87(-2.47,4.20)	0.23(-0.37,0.83)	1.47 (0.55,3.91)
SGA	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	Gestational weight gain above recommendations	-0.75(-1.34,2.81)	0.48(-0.08,1.04)	2.62 (0.25,27.69)
	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	At least two abnormal items of Glucose tolerance	0.06(-0.68,081)	0.08(-0.75,0.90)	0.77 (0.01,49.04)
	Gestational weight gain above recommendations	At least two abnormal items of Glucose tolerance	0.04(-0.40,0.48)	0.06(-0.51,0.63)	0.90 (0.21,3.80)
Cesarean section	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	Gestational weight gain above recommendations	0.44(-1.11,1.99)	0.19(-0.25,0.64)	1.53 (0.82,2.88)
	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	At least two abnormal items of Glucose tolerance	-0.04(-0.80,0.71)	-0.03 (-0.54,0.49)	0.93 (0.22,4.00)
	Gestational weight gain above recommendations	At least two abnormal items of Glucose tolerance	-0.04(-0.82,0.75)	-0.03 (-0.56,0.51)	0.94 (0.21,4.34)
Full term low birth weight	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	Gestational weight gain above recommendations	-0.55(-1.27,0.18)	-1.97 (-6.90,2.96)	4.04 (0.03,544.94)
	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	At least two abnormal items of Glucose tolerance	-0.79(-1.56,-0.03)	-2.18 (-6.89,2.53)	-4.03(NA)
	Gestational weight gain above recommendations	At least two abnormal items of Glucose tolerance	-0.59(-1.06,-0.11)	-1.89 (-5.88,2.10)	6.53 (0.01,20.15)
Composite outcome	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	Gestational weight gain above recommended	0.98(-1.39,3.35)	0.33(-0.07,0.73)	1.99 (1.28,3.10)
	Pre-pregnancy body mass index Overweight or Obese(≥24.0)	At least two abnormal items of Glucose tolerance	0.10(-1.03,1.23)	0.05(-0.46,0.57)	1.12 (0.41,3.07)
	Gestational weight gain above recommendations	At least two abnormal items of Glucose tolerance	0.01(-0.97,0.98)	0.004 (-0.54,0.55)	1.01 (0.29,3.55)

NA, Not Applicable; LGA, large for gestational age; SGA, small for gestational age; HDP, Hypertensive disorders of pregnancy; RERI, relative excess risk; AP, attributable proportion; SI, synergy index.

obesity have higher risks on adverse pregnancy outcomes than maternal glucose characters. According to Pedersen's hypothesis, elevated maternal glucose levels would increase fetal insulin production, leading to increased fetal growth and obesity (41). The result of HAPO showed excessive gestational weight gain was linked with increased fetal insulin production but no maternal glucose levels (42). Gestational weight gain may also affect fetal certain metabolic factors which can drive excess fetal growth. The HAPO study found than excess gestational weight gain increased fetal c-peptide (42). A prospective observational study conducted in Dublin found each 1kg increase in gestational weight gain was associated with a 0.039ng/ml increase in c-peptide and 0.024mmol/l decrease in cholesterol (40). Plasma c-peptide reflects the insulin secretory activity of pancreatic beta cells and the its higher level in cord blood was related to maternal insulin sensitivity, weight and adiposity maker (43–45).

Excessive gestational weight gain leads to increased insulin resistance and islet β-cell depletion, so that β-cells cannot secrete enough insulin to compensate for insulin resistance caused by pregnancy, leading to the occurrence of GDM. Adequate weight

TABLE 5 | Coexist interaction of overweight or obesity, excessive gestational weight gain and glucose tolerance status on adverse pregnancy outcomes[a].

Pre-pregnancy BMI category(kg/m^2)	Gestational weight gain category	Glucose tolerance status	Macrosomia	LGA	Preterm delivery[b]	HDP	SGA	Cesarean section	Full term low birth weight	Composite outcome
Underweight or Normal (<24.0)	As or below recommended	One abnormal items	1.00(Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
		At least two abnormal items	1.52 (1.01,2.29)	1.21 (1.01,1.46)	1.13 (0.83,1.52)	1.84 (1.26,2.70)	0.97 (0.61,1.54)	1.10 (0.94,1.28)	1.24 (0.67,2.29)	1.13 (0.98,1.32)
	Above recommended	One abnormal items	2.22 (1.49,3.32)	1.63 (1.34,1.98)	0.62 (0.42,0.93)	2.58 (1.74,3.82)	0.85 (0.50,1.44)	1.49 (1.25,1.78)	1.19 (0.56,2.54)	1.55 (1.34,1.84)
		At least two abnormal items	3.37 (2.15,5.26)	1.84 (1.44,2.34)	0.75 (0.46,1.22)	2.53 (1.57,4.08)	0.65 (0.30,1.39)	1.37 (1.10,1.71)	0.39 (0.09,1.68)	1.45 (1.17,1.80)
Overweight or Obese (≥24.0)	As or below recommended	One abnormal items	2.12 (1.19,3.78)	1.50 (1.12,2.02)	0.51 (0.26,1.03)	3.91 (2.29,5.96)	1.24 (0.60,2.60)	1.55 (1.19,2.00)	1.70 (0.69,4.23)	1.61 (1.24,2.09)
		At least two abnormal items	2.01 (1.13,3.73)	1.44 (1.12,1.94)	1.00 (0.60,1.67)	4.11 (2.41,6.34)	0.82 (0.34,1.95)	1.42 (1.10,1.83)	0.43 (0.10,1.89)	1.67 (1.28,2.15)
	Above recommended	One abnormal items	4.48 (2.71,7.4114)	2.7313 (2.040,3.66)	0.83 (0.45,1.53)	3.66 (2.17,6.15)	0.15 (0.02,1.12)	2.20 (1.67,2.90)	0.33 (0.04,2.54)	2.74 (2.04,3.68)
		At least two abnormal items	4.52 (2.60,7.84)	3.19 (2.33,4.37)	1.38 (0.80,2.38)	7.60 (4.78,12.08)	0.70 (0.25,1.99)	2.56 (1.89,3.47)	0.27 (0.35,2.11)	3.75 (2.63,5.34)

Data are showed as OR(95%CI).

BMI, body mass index; LGA, large for gestational age; SGA, small for gestational age; HDP: Hypertensive disorders of pregnancy; [a] For all outcomes except preterm delivery were adjusted for maternal age, gestational age, infant sex, gravity, and parity. [b] adjusted for on the maternal age, infant sex, gravity, and parity.

gain may be positive for perinatal outcomes among women with GDM. There is no consensus on the appropriate range of weight gain during pregnancy for GDM. Although Landon et al. observed parallel reductions of gestational weight gain and pre-eclampsia (46), reducing gestational weight gain has not been proven to reverse GDM-related complications (47). Thus, preventing excess gestational weight gain should be a important goal and feasible interventions for GDM.

Hyperglycemia is linked with adverse pregnancy outcomes. Maternal hyperglycemia allows for increased placental transfer of glucose and (fetal) beta-cell prohormones to the fetus, which leads to fetal hyperinsulinemia, causing fetal metabolic reprogramming that can lead to fetal overgrowth and/or obesity and so on (48). Feng et al (20) observed consistent trends between the number of abnormal OGTT parameters and odds of cesarean delivery, preterm delivery, and neonatal complications. Zhou et al (49) also found that the increasing number of abnormal OGTT parameters, the increased frequencies of LGA, and neonatal hypoglycemia. Compare with one abnormal items of OGTT parameters, patients with two or more abnormal items of OGTT parameters may suffer more serious glucose metabolic homeostasis disruptions and insulin sensitivity (20, 50). Our data presented patients with two or more abnormal items of OGTT parameters were of greater likelihood of adverse pregnancy outcomes, compared with patients with only one abnormal item of OGTT parameters. This indicated that more attention needs to be paid to strict management of hyperglycemia including diet control and exercise and pharmacological glucose-lowering is needed to prevent adverse pregnancy outcomes. However, overly strict glycemic control may often lead to SGA offspring, to severe diabetes. Our study showed no association between overweight or obesity, excessive gestational weight gain, two or more abnormal items of OGTT parameters, and SGA, and full- term birth weight. This may be because our participant received medical nutrition therapy after diagnosis, including interventions such as diet, exercise, and insulin therapy, these interventions result in good glycemic control so that they do not progress to severe uncontrolled diabetes. Previous studies have noted that GDM may result in SGA and preterm delivery and other neonatal complications (10, 20). Severe diabetes or overly strict severe diabetes or overly tight control may lead to SGA offspring. An observational study involved 2037 GDM women revealed average HbA1c levels in third trimester was a new risk factor for HDP in GDM women a new association between mean HbA1c levels and excessive weight gain and HDP has been established (47). Our data showed the strongest influence on HDP was exerted pre-pregnancy overweight or obesity, followed by excessive gestational weight gain. It may therefore be speculated that insulin resistance appears to be a key causative factor in HDP (51). Hyperglycaemia and various adipose tissue cytokines may be the mediators of systemic endothelial hypertensive vasculopathy (52).

There are complex relationships between overweight or obesity, gestational weight gain, maternal hyperglycemia, and adverse pregnancy outcomes, especially the interaction of them. Interaction analysis includes multiplicative interactions and additive interactions interaction analysis (53). Previous studies mainly focus on the association between overweight or obesity,

and excessive gestational weight gain with adverse pregnancy outcomes, few studies evaluating the combined effect of pre-pregnancy overweight or obesity, excessive gestational weight gain and glucose tolerance status on pregnancy outcomes. An observational study examined the relative impact of a maternal factor on birth weight showed that pre-pregnancy BMI, and gestational weight gain was close with birth weight (54). A recently published literature found pre-pregnancy overweight or obesity increased the risk of macrosomia and LGA births independently and partly mediated by GDM (55). Black M H and colleagues conducted a retrospective study of 9,835women and revealed that pre-pregnancy overweight or obesity accounts for 23.3% of LAG in women with GDM and 21.6% in women without GDM (56). A large population-based study in Florida explored the adjusted population-attributable fraction of LGA as a result of the mutual effect of BMI, excessive gestational weight gain, and GDM and they discovered overweight and obesity, excessive gestational weight gain, and GDM all are associated with LGA, and excessive gestational weight gain has the greatest potential to reduce LGA risk (57). However, these studies mainly focus on neonatal birth weight-related outcomes, other adverse pregnancy outcomes, especially those related to the mother, were not addressed.

Our findings regarding fetal overgrowth are consistent with the above studies. We also found the association with adverse maternal outcomes. The mechanisms of pre-pregnancy overweight or obesity and excessive gestational weight gain are probably may be due to abnormal distribution of adipose tissue, which further contribute to impaired maternal metabolism, and an unhealthy intrauterine environment (58–60). Thus, pre-pregnancy overweight or obesity, excessive gestational weight gain, and GDM are inextricably linked. In our study, the high independent effects of excessive gestational weight gain on fetal overgrowth exceed that of pre-pregnancy overweight or obesity and two or more abnormal items of OGTT parameters, while the independent effect on HDP, cesarean section, and the composite outcome was the greatest for pre-pregnancy overweight or obesity. It is worth noting that the combination of each two and all have a greater impact than either one alone and the all combination was of the greatest. Previous studies also confirmed similar result (61–63).

Overweight or obese women may more likely to gain excessive weight, excessive gestational weight gain can aggravate insulin resistance, that is, increase the risk of developing GDM (64–69). However, it is important to mention that gestational weight gain as or below recommended among overweight or obese women didn't lower the risk of macrosomia, LGA, HDP, cesarean section, and composite outcome, regardless of OGTT pathological values. What's more, gestational weight gain as or below recommendations among underweight or normal women with two or more abnormal items of OGTT parameters was still associated with increased risk of macrosomia, LGA, and HDP. These findings contrast with those of previous studies which reported inadequate gestational weight gain in overweight or obese women with GDM lower risk of macrosomia (70), or do not effect on birth weight (64).

Our results presents the interplay between overweight or obesity, gestational weight gain, and GDM and their interaction with adverse pregnancy outcomes. Wherefore, pre-pregnancy overweight or obesity and gestational weight gain requires systematic monitoring and management before and during pregnancy. All women are encouraged to develop good dietary and living habits before pregnancy, especially among overweight or obese women. Observational study showed that adherence to a healthy lifestyle before pregnancy by maintaining a healthy weight, adhering to a healthy diet, regular exercise and avoiding smoking can prevent approximately 45% of GDM cases (71). And besides, diet and lifestyle changes early in pregnancy can also prevent GDM. A meta-analysis showed that lifestyle modification (diet, physical activity, or both) initiated before the 15^{th} week of gestation reduced the risk of GDM (72). Totally, the focus of GDM prevention efforts should be on the preconception phase or early pregnancy to achieve the desired reduction in the prevalence of GDM and the attendant pregnancy complications (48). After the diagnosis, the treatment of GDM is mainly to control the blood glucose level with target by dietary modification and promotion of physical activity to prevent fetal overgrowth and pregnancy complications (73–75). In addition to hyperglycemia, excessive gestational weight gain is also associated with fetal overgrowth and pregnancy complications in both healthy and GDM pregnant women (76, 77). Weight management services are recommended before conception to provide advice on weight optimization. In contrast with pre-pregnancy overweight or obesity, prevention of excessive gestational weight gain may be more feasible. Pregnancy offers a unique challenging time for women to be to informed of the long-term implications of overweight or obesity and excessive gestational weight gain on themselves and their fetal future health from obstetricians and midwives, help them take preventive and interventive measures to lower the risk of GDM and adverse pregnancy outcomes (78). Furthermore, women of reproductive age usually don't know their blood glucose levels and thus miss out on preconception counseling and treatment. Our results suggested that excessive weight gain has the greatest impact on adverse pregnancy outcomes, followed by pre-pregnancy overweight or obesity. Thus, Whether pre-pregnancy overweight or obesity, or in those with two or more abnormalities in glucose tolerance during pregnancy, we recommend to monitor weight gain in each antenatal visit carefully and set weight-gain goals for patients to reduce GDM risk and improve adverse pregnancy outcomes. Little is known about the optimal gestational weight gain for women with GDM, and future research should focus on determining the appropriate weight gain for women with GDM. Pharmacological treatment should be initiated when glycaemia remains after 1-2 weeks of lifestyle intervention, of which insulin is the primary medical treatment also includes metformin or sulfonylurea (48).

There are some limitations to the study. First, due to retrospective design, confirmation of causal association is limited. Second, the category of BMI we used was Chinese standard, i.e., BMI≥24 is defined as overweight and ≥28 as obesity, which is different from the international definition in the literature and will have some limitations when comparing the results of others studies. Third, women with GDM will be treated

after diagnosis and those interventions may underestimate the risk of adverse pregnancy outcomes. Although these limitations, our study is the first time to depicted the interactive association between overweight or obesity, excessive gestational weight gain, abnormal items of OGTT on adverse pregnancy outcomes. The second strength is that we adjusted for the potential mediating effect and considered results reliable.

In summary, our result demonstrates the independent multiplicative interaction but no additive interaction between overweight or obesity, gestational weight gain, and two or more abnormal items of OGTT parameters on adverse pregnancy outcomes among women with GDM. Every effort should be made for women to conceive with pre-pregnancy normal weight and reasonable gestational weight gain to reduce the risk of GDM and improve pregnancy outcomes.

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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the Fujian Maternity and Children Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

J-YY and JL contributed to study designed and critical revision of the manuscript. L-HL collected data, analyzed data, prepared and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Magnitude of cesarean-section and associated factors among diabetic mothers in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A cross-sectional study

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Background: Gestational diabetes is associated with multiple adverse pregnancy outcome as a result of unfavorable labor and delivery process with a consequent increase in obstetric interventions including cesarean-section. Even though diabetes mellitus increases the cesarean-section rate; there is no study conducted in Ethiopia. therefore, this study aimed to assess the magnitude of cesarean-section and associated factors among diabetic mothers in Tikur Ambessa Specialize Hospital, Addis Ababa, Ethiopia.

Methods: A facility-based retrospective cross-sectional study was conducted in Tikur Anbessa Specialized Hospital from 1 February to 30 April 2018 among 346 diabetic mothers. All required data were extracted from patients' charts using checklists, and incomplete records were excluded. The collected data were entered into Epi data version 4.2 and exported to SPSS version 20 for analysis. Multiple logistic regression models were fitted to identify factors associated with cesarean section. Adjusted odds ratios along with 95% CI were estimated to measure the strength of the association and declared statistical significance at a p-value <0.05.

Results: The magnitude of cesarean-section was 57.8% (95% CI: 51.7, 63.3). Pregnancy-induced hypertension [AOR: 3.35, (95% CI: (1.22, 9.20)], previous C/S [AOR: 1.62, (95% CI: (2.54, 4.83)], and fetal distress [AOR: 4.36, (95% CI: 1.30, 14.62)] were factors significantly associated with cesarean-section.

Conclusion: A considerable number of diabetic mothers gave birth by cesarean-section. Pregnancy-induced hypertension, previous cesarean-section, and fetal distress were factors more likely to increase the rate of cesarean-section. Most of the factors were modifiable by following the WHO recommendation for cesarean-section.

KEYWORDS

diabetes mellitus, cesarean-section, mothers, Tikur Anbessa, Ethiopia

Introduction

Worldwide, more than 422 million people are affected by diabetes mellitus (DM), and more in low- and middle-income countries (1). According to the International Diabetes Federation (IDF), gestational diabetes is associated with multiple adverse pregnancy outcomes where 20.9 million or 16% of live births had some form of hyperglycemia (2).

In addition, DM poses multiple risks to pregnant women and their offspring, such as preeclampsia, macrosomia, prematurity, obstructed labor, shoulder dystocia, congenital anomalies, birth injuries, and a consequent increase in obstetric interventions including cesarean-section (3, 4). Cesarean-section (CS) is a surgical procedure indicated when vaginal delivery presents a higher likelihood of adverse maternal and/or perinatal outcomes (5, 6).

Worldwide, one in five diabetic mothers give childbirths by CS (7). In Ethiopia, the rate of CS among general populations varies between regions with a range of 0.4% in Somali to 21.4% in Addis Ababa (8), with a national pooled prevalence of 29.55% (9). However, WHO recommendation for CS is 5–15% to have an optimal impact (6). Moreover, although CS is taken to relieve obstructed labor, it has complications of wound dehiscence and ulcer in addition to other complications that occur during the operative and postoperative period (10, 11).

Various characteristic features have been identified as risk factors for CS in women with DM, namely, maternal age, marital status, parity, history of stillbirth, CS scar, macrosomic infant, obstructed labor, and fetal distress (5, 12–16). Identifying the magnitude of CS and related factors among diabetic mothers is vital to generating new evidence, and developing contextual interventions. Nevertheless, there is no information regarding CS among diabetic mothers in Ethiopia. Therefore, this study aimed to assess the magnitude of CS and its associated factors among diabetes mothers in Addis Ababa, Ethiopia

Methods and materials

Study setting, design, and period

A facility-based retrospective cross-sectional study was conducted from 1 February to 30 April 2018, in the Tikur Anbessa Specialized Hospital found in Addis Ababa the capital city of Ethiopia. Tikur Anbessa is Ethiopia's largest specialized and referral public hospital. According to the 2007 statistical report of the population and housing census of Ethiopia, Addis Ababa has a total population of 3,384,569 (17). The health service coverage of the city is 52.2, and 82% of deliveries take place in public health facilities (18). There are 17 public and 25 private hospitals (19). The hospital provides diagnoses and treatment for approximately 370,000–400,000 patients per year in all wards. The diabetes center is one of the departments in the hospital services. Of a total of 800 beds, 80 were used by the department of obstetrics and gynecology during the survey (20). In the city, around 4,600 deliveries were attended each year of which 60% are operative deliveries (8).

Sample size determination

Sample size was determined using a single population proportion formula. The following assumptions were used while calculating the sample size; 95% confidence level, a margin of error (0.05) and 50% anticipated population proportion was taken since there is no published paper on assessing cesarean-section among mothers with diabetes in Ethiopia. Therefore, 422 sample size was planned to use for this study with a 10% non-respondent rate. However, since the numbers of diabetic mothers' cards with complete records were less than the planned sample size, all cards with complete records were included.

Sampling technique and study population

Tikur Anbessa Specialized Hospital was selected purposively since it is the largest public hospital with maternal health service and diabetes center/department. The required data were extracted from patient charts. First, the health management and information system (HMIS) delivery registration book, postnatal registrations, admission registration, and gestational diabetes registration in diabetes mellitus center card numbers were obtained and documents of all delivered mothers who had DM during the planned study period at obstetrics ward was searched and checked for completeness of the data. Then, cards of mothers with complete records were separated and counted.

Since the numbers of cards with complete records were less than the planned sample size, all cards of the diabetic mothers with completed records were included whereas incomplete documents were excluded.

Data collection tools and procedures

A structured checklist adapted from published studies with certain modifications was used (16, 21–23). The checklist includes information on socio-demographic characteristics, obstetric characteristics, feto-maternal outcome, and diabetes mellitus. After the card numbers were obtained, the documents of all delivered mothers who had DM during the planned study period at the obstetrics and gynecologic ward were searched and checked for completeness of the data. The data were collected through document review in the obstetrics ward from the patient chart, delivery registration book, post-natal registrations, duty report registration books, and operation logbooks. The data were extracted by two record office staff, three midwives working in the obstetrics unit, two supervisors, and the principal investigator.

Data quality control

To ensure the quality of the data before the actual data collection, a pretest was done on 5% of patient records at Zewditu Memorial Hospital. Appropriate modifications were made to the checklist and procedures after analyzing the pretest result. One-day training was given to data collectors on how to collect the data. The supervisors and the principal investigator coordinated and checked the data collection process, and daily supervision was done to ensure the completeness and consistency of the gathered information.

Data processing and analysis

The collected data was entered to Epi data version 4.2, cleaned, and transported to SPSS version 23.0 for data analysis. Descriptive statistics, frequency tables, figures, and percentages were used to summarize the data. Bi-variable analysis and multiple logistic regressions were used to test for the association between dependent and independent variables. Variables that showed an association in the bi-variable analysis with p-value < 0.25 were entered into a multiple logistic regression model. At last, the multiple logistic regression models were used after controlling for confounding factors using regression. Hosmer-Lemeshow's goodness of fit test was used to assess whether the necessary assumptions for the application of multiple logistic regression had been fulfilled. Multi-co-linearity was assessed by using standard error, and the variables were entered into the multiple models without multi-co-linearity.

TABLE 1 Socio-demographic characteristics of the diabetic mothers delivered at the Tikur Anbessa Specialized Hospital Addis Ababa, Ethiopia, 2018.

Variables	Category	Frequency ($n = 346$)	Percent (%)
Age in years	18–20	8	2.3
	20–24	24	6.9
	25–29	92	26.6
	30–34	139	40.2
	>35	83	24
Marital status	Unmarried	5	1.4
	Married	341	98.6
Occupation	House wife	174	50.2
	Gov't employees	172	49.8
Address	Addis Ababa	322	93.1
	Out of Addis Ababa	24	6.9
BMI	Normal	160	46.2
	Over weight	186	53.8

Adjusted odds ratios (AOR) were calculated with 95% CIs, and statistical significance was declared at p-value < 0.05.

Ethical considerations

Ethical clearance was obtained from the ethical review committee of Addis Ababa University, School of Nursing and Midwifery. The official letter of cooperation was taken from Addis Ababa University to Tikur Anbessa Specialized Hospital. Informed and written consent was obtained from the medical director and NICU head. To keep confidentiality, their patients were not documented; rather a code was given for each card.

Results

Socio-demographic characteristics of the mothers

In this study, a total of 346 records were reviewed. Of a total of the respondents, the majority (40.2%) were in the 30–34 years age group. Almost all (98.6%) mothers were married. Addis Ababa was the dominant residence of the mothers, accounting for 93.1%. Regarding the occupational status of the mothers, almost half of them (50.2%) were housewives (Table 1).

Obstetrics characteristics of the mothers

Regarding the parity of diabetic women, the majority (80.9%) were multipara. Nearly one out of five, (20.8%) of mothers had a history of abortion and

TABLE 2 Obstetrics history of diabetic mothers delivered at the Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia, 2018.

Variables	Category	Frequency ($n = 346$)	Percent (%)
Parity	Primipara	66	19.1
	Multipara	280	80.9
History of abortion	Yes	72	20.8
	No	274	79.2
History of CS	Yes	70	20.2
	No	276	79.8
History of stillbirth	Yes	47	13.6
	No	299	86.4
History PIH	Yes	32	9.2
	No	314	89.8
History of birth weight>4 kg	Yes	28	8.1
	No	318	90.9

CS (20.2%), respectively. Around (13.6%) of mothers had experienced a stillbirth in their previous pregnancy (Table 2).

Nearly half, (51.2%) of the labors occurred spontaneously and (30.3%) were elective CS. Pregnancy-induced hypertension (PIH) accounts for the major parts of the complications the mother developed from pregnancy to postpartum period (26.0%). The majority, (82.1%) of mothers gave birth at term, and 97.4% of delivered newborns were alive (Table 3).

TABLE 3 Current obstetrics characteristics of diabetic mothers delivered at the Tikur Ambessa Specialized Hospital in Addis Ababa, Ethiopia, 2018.

Variables	Category	Frequency ($n = 346$)	Percent (%)
Onset of labor	Spontaneus	177	51.2
	Induced	64	18.5
	Elective CS	105	30.3
GA at time of delivery	Preterm	62	17.9
	Term and above	284	82.1
Maternal Outcome	PIH	90	26.0
	Polyhydroaminus	5	1.4
	Obstructed labor	1	0.3
	Hypotyrodism/cardiac/ renal diseases	10	3.4
	Tear (traumatize labor)	7	2.0
Fetal outcome	Live birth	337	97.4
	Macrosomic baby (≥4 kg)	61	17.6
	Low birth weight (<2.99 kg)	35	10.1
	Respiratory distress	32	9.2
	Hypoglycemia	10	2.9
	IUFD /still birth	9	2.6
	Jaundice	7	2.0
	Birth injury/defect	9	2.6

PIH, Pregnancy Induced Hypertension; IUFD, Intrauterine Fetal Death.

Mode of delivery

Regarding mode of delivery, the majority (57.8%) of mothers gave birth by CS whereas the rest (42.2%) of the mothers gave childbirth by spontaneous vaginal delivery (Figure 1).

Factors associated with cesarean-section

In the bivariate logistic regression analysis, marital status, occupational status, residence, history of stillbirth, parity, history of abortion, PIH, birth weight, and fetal distress were factors significantly associated with CS. However, in multiple logistic regression mothers who have PIH were three times [AOR: 3.35, (95% CI: (1.22, 9.20)] more likely to undergo CS. Also, mothers who have a history of CS were 1.62 times [AOR: 1.62, (95% CI: (2.54, 4.83)] more likely to undergo CS than their counterparts. Mothers who have fetal distress were nearly four times [AOR: 4.36, (95% CI: 1.30, 14.62)] more likely to give birth by CS (Table 4).

Discussion

In this study, a significant number of diabetic mothers gave birth by CS. Previous CS, PIH, and fetal distress were factors significantly associated with CS.

More than half, 57.8% (95% CI: 51.7, 63.3%) of diabetic mothers gave birth by CS. This is higher than the studies conducted in South Wales (32.0%) (24), Canada (29.1%) (25), Harar (34.3%) (16), Mizan Aman (21.1%) (26), and Dessie (47.6%) (27). The possible reason is the difference in a study population, and the prevalence of primary CS high in these high-risk populations which may increase a rate of repeated CS (28). Diabetes mellitus is associated with obstructed labor and shoulder dystocia which are the most common indication of CS (12, 13, 29).

Mothers who have PIH were 3.35 times more likely to give birth by CS than mothers without PIH. This is supported by a study conducted in Addis Ababa (30) where the odds of CS increase among mothers with PIH. This implies shortening the labor process and delivery per the management protocol

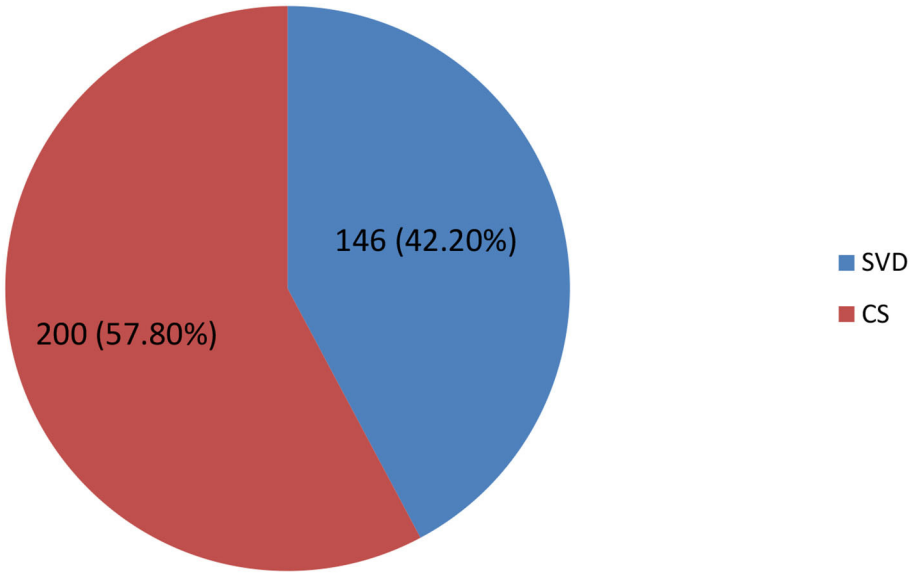

FIGURE 1
Mode of delivery among diabetic mothers at the Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia, 2018.

TABLE 4 Factors associated with cesarean-section among diabetic mothers delivered at the Tikur Ambessa Specialized Hospital in Addis Ababa, Ethiopia, 2018.

Variables	Category	COR [95% CI]	*P*-value	AOR [95% CI]	*P*-value
Marital status	Unmarried	1.00		1.00	1.00
	Married	2.95 (1.32, 26.75)	0.021	0.49 (0.02, 9.53)	0.644
Occupational status	House wife	1.00	1.00	1.00	1.00
	Gov't employee	1.30 (1.05, 2.99)	0.025	1.18 (0.53, 2.60)	0.674
Residence	Addis Ababa (AA)	2.96 (1.07, 8.12)	0.035	0.22 (0.04, 1.15)	0.074
	Outside of AA	1.00	1.00	1.00	1.00
History of stillbirth	Yes	0.53 (0.30,0.92)	0.026	1.30 (0.44, 3.84)	0.634
	No	1.00	1.00	1.00	1.00
Parity	Primipara	1.86 (1.42, 24.16)	0.028	2.92 (0.99, 8.58)	0.052
	Multipara	1.00	1.00	1.00	1.00
History of CS	Yes	0.25 (0.12, 0.46)	0.000	1.62 (2.54, 4.83)	0.001
	No	1.00	1.00	1.00	1.00
PIH	Yes	1.80 (1.38, 3.70)	0.058	3.35 (1.22, 9.20)	0.001
	No	1.00	1.00	1.00	1.00
EFW	< 4 kg	1.00	1.00	1.00	1.00
	≥ 4 kg	1.52 (1.22, 8.25)	0.021	0.49 (0.17, 1.40)	0.186
Fetal distress	Yes	2.43 (2.38, 5.47)	0.000	4.36 (1.30, 14.62)	0.007
	No	1.00	1.00	1.00	1.00

of severe preeclampsia and/or eclampsia designated to prevent perinatal morbidity and mortality (6, 31).

In a similar manner, mothers who have previous CS were more likely to give birth by CS than mothers without CS. Similar reports pointed out by Tsega et al. (16) and Gebreegziabher et al. (30) where mothers who gave previous birth by CS were more likely to give current birth by CS. The reason could be the fact that mothers who previously gave birth by CS were more likely to present with permanent indications for CS or a high risk for wound dehiscence (6, 32).

The odds of CS were four times higher among mother with fetal distress than their counterpart. This is supported by a study

conducted in Harar (3) where the odds of CS increase among mothers with the fetal distress. In fact, the fetal distress especially that occurs during first stage of labor is one of the absolute indications of CS which is recommended by WHO to save lives of the infants (6).

Strengths and limitations of the study

The study was used to generate initial data for researchers for further study. However, this study may suffer from incomplete data as it was obtained from secondary data. The other limitation is that the cross-sectional study design cannot establish a temporal relationship between the outcome and response variables.

Conclusion

This study showed CS among diabetic mothers was high. Mothers with PIH, previous CS, and fetal distress were factors significantly associated with CS. Thus, emphasis should be given to reducing CS among diabetic mothers to reduce the complication of wound dehiscence and ulcer in addition to other complications most probable to occur from CS. Increasing the quality of obstetrics care during pregnancy, intrapartum, and postnatal period among diabetic mothers is crucial to prevent complications of CS. Moreover, improving the utilization of preconception care among diabetic women is crucial in controlling PIH during the perinatal period. Also, CS should be performed based on the indication.

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.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Committee of Addis Ababa University, School of Nursing and Midwifery (aau/chs/mhnsg19/2018). Written and informed consent was taken from head of the inistitutio before data collection.

Author contributions

BE, WD, and BM: conceptualization, supervision, investigation, methodology, writing—original draft, and writing—review and editing. BB: methodology, data curation, formal analysis, and read and approved the final manuscript. TG, ER, SH, HB, IK, and AD: conceptualization, methodology, writing—original draft, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

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Correlation of body composition in early pregnancy on gestational diabetes mellitus under different body weights before pregnancy

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Objective: The prediction of gestational diabetes mellitus (GDM) by body composition-related indicators in the first trimester was analyzed under different body mass index (BMI) values before pregnancy.

Methods: This was a retrospective analysis of pregnant women who were treated, had documented data, and received regular perinatal care at the Third Affiliated Hospital of Zhengzhou University from January 1, 2021, to December 31, 2021. Women with singleton pregnancies who did not have diabetes before pregnancy were included. In the first trimester (before the 14th week of pregnancy), bioelectric impedance assessment (BIA) was used to analyze body composition-related indicators such as protein levels, mineral levels, fat volume, and the waist-hip fat ratio. The Pearman's correlation coefficient was used to evaluate the linear relationship between the continuous variables and pre-pregnancy body mass index (BMI). In the univariate body composition analysis, the association with the risk of developing GDM was included in a multivariate analysis using the relative risk and 95% confidence interval obtained from logarithmic binomial regression, and generalized linear regression was used for multivariate regression analysis. Furthermore, the area under the curve (AUC) was calculated by receiver operating characteristic (ROC) curves. The optimal cutoff value of each risk factor was calculated according to the Youden Index.

Results: In a retrospective study consisting of 6698 pregnant women, we collected 1109 cases of gestational diabetes. Total body water (TBW), protein levels, mineral levels, bone mineral content (BMC), body fat mass (BFM), soft lean mass (SLM), fat-free mass (FMM), skeletal muscle mass (SMM), percent body fat (PBF), the waist-hip ratio (WHR), the visceral fat level (VFL), and the basal metabolic rate (BMR) were significantly higher in the GDM group than in

the normal group (P<0.05). Under the pre-pregnancy BMI groupings, out of 4157 pregnant women with a BMI <24 kg/m^2, 456 (10.97%) were diagnosed with GDM, and out of 2541 pregnant women with a BMI ≥24 kg/m^2, 653 (25.70%) were diagnosed with GDM. In the generalized linear regression model, it was found that in all groups of pregnant women, pre-pregnancy BMI, age, gestational weight gain (GWG) in the first trimester, and weight at the time of the BIA had a certain risk for the onset of GDM. In Model 1, without adjusting for confounders, the body composition indicators were all positively correlated with the risk of GDM. In Model 3, total body water, protein levels, mineral levels, bone mineral content, soft lean mass, fat-free mass, skeletal muscle mass, and the basal metabolic rate were protective factors for GDM. After Model 4 was adjusted for confounders, only the waist-hip ratio was positively associated with GDM onset. Among pregnant women with a pre-pregnancy BMI <24 kg/m^2, the body composition-related indicators in Model 2 were all related to the onset of GDM. In Model 3, total body water, soft lean mass, fat-free mass, and the basal metabolic rate were negatively correlated with GDM onset. In the body composition analysis of among women with a pre-pregnancy BMI ≥ 24 kg/m^2, only Model 1 and Model 2 were found to show positive associations with GDM onset. In the prediction model, in the basic data of pregnant women, the area under the receiver operating characteristic curve predicted by gestational weight gain for GDM was the largest (0.795), and its cutoff value was 1.415 kg. In the body composition results, the area under the receiver operating characteristic curve of body fat mass for predicting GDM risk was larger (0.663) in all pregnant women.

Conclusions: Through this retrospective study, it was found that the body composition-related indicators were independently associated with the onset of GDM in both the pre-pregnancy BMI <24 kg/m^2 and pre-pregnancy BMI ≥24 kg/m^2 groups. Body fat mass, the visceral fat level, and the waist-hip ratio had a higher correlation with pre-pregnancy BMI. Total body water, protein levels, mineral levels, bone mineral content, soft lean mass, fat-free mass, skeletal muscle mass, and the basal metabolic rate were protective factors for GDM after adjusting for some confounders. In all pregnant women, the waist-hip ratio was found to be up to 4.562 times the risk of GDM development, and gestational weight gain had the best predictive power for GDM. Gestational weight gain in early pregnancy, body fat mass, and the waist-hip ratio can assess the risk of GDM in pregnant women, which can allow clinicians to predict the occurrence of GDM in pregnant women as early as possible and implement interventions to reduce adverse perinatal outcomes.

KEYWORDS

body mass index, gestational diabetes, bioelectrical impedance assessment, body composition, body fat mass

Introduction

Gestational diabetes mellitus (GDM) is diabetes diagnosed in the second or third trimester of pregnancy that was clearly overt not diabetes prior to gestation (1). GDM is an essential factor affecting maternal and infant health and is one of the most common complications during pregnancy (2). One study showed that the overall incidence of gestational diabetes has increased globally over the past decade (3). According to a 2018 meta-analysis, the prevalence of gestational diabetes in China

ranged from 13.0% to 20.9% (4). GDM increases the risk of miscarriage, obstructed labor, and cesarean section in pregnant women, as well as the risk of perinatal macrosomia, fetal growth restriction, neonatal hypoglycemia, and even the risk of type 2 diabetes in children later in life (5). Patients with GDM also have an increased risk of developing diabetes and cardiovascular disease in later years period (6).

Obesity is one of the risk factors for GDM, especially visceral obesity in pregnant women (7). In a European study, the prevalence of GDM in obese women was reported to be close to 40% (8). Body mass index (BMI) is often used as a clinical measure of body fatness. Nevertheless, it does not distinguish between body fat content and nonfat content, e.g., muscular obesity is defined as an abundance of lean tissue mass with little body fat, such as in athletes; intangible obesity is defined as an excess of body fat, i.e., obesity (9). In the state of obesity, the human body stores too much energy in the form of fat, which leads to changes in some innate immune cells in adipose tissue, promotes the occurrence of adipose tissue inflammation, induces islet β-cell dysfunction, and eventually leads to systemic insulin resistance and glucose tolerance (9, 10). This obesity-induced insulin resistance can occur at all stages of life, including during pregnancy or the postpartum period. Myo-inositol, as a dietary supplement, can reduce insulin resistance (11), and myo-inositol supplementation in early pregnancy in overweight nonobese pregnant women can significantly reduce the incidence of GDM, which can contribute to the prevention and intervention of GDM in clinical practice (12). During pregnancy, to provide energy and nutrition to the fetus, maternal energy expenditure increases, and the intestinal tract has an increased ability to absorb fat, resulting in an increase in fat content in the mother's body compared to that pre-pregnancy (13). However, excessive fat accumulation in the body and blood lipid disorders may lead to the development of diabetes (13). A study in 18 cities in China confirmed that pre-pregnancy overweight/obesity is a high-risk factor for the onset of GDM (14).

A bioelectric impedance assessment (BIA) is a simple and noninvasive method of assessing the body electrically. It provides a more accurate picture of the body's muscle, fat, and bone mass and thus determines whether a person's body composition is standard. However, a BIA cannot distinguish between maternal and fetal tissue (15, 16). It is a method for assessing the internal structure of a pregnant woman's body in the early stages of pregnancy. It has become a routine perinatal examination to analyze the composition and proportions of body components from a microscopic point of view (17). There is a strong association between high fat content, low muscle mass, and the prevalence of diabetes mellitus (18). PBF reflects the percentage of thetotal body weight accounted for by the total body fat mass. At the same time, the visceral adiposity index (VAI) is a reliable indicator of the content of visceral adipose tissue (19). These indicators are reflected in the BIA examination, and the higher the fat content is, the greater the electrical impedance (20). The physical properties, measurement variables, and clinical significance of BIAs have been well described in many previously published reports (18), and their safety has been demonstrated in many studies in patients with renal disease, such as hemodialysis and transplant patients (15). Only a few domestic and international studies have explored the effect of body composition on GDM risk through BIAs. Moreover, body fat distribution varies with ethnicity, and study indicators and conclusions are primarily inconsistent (15, 21, 22). The influence of body composition during pregnancy on GDM risk was analyzed in a retrospective study of 22,223 pregnant women in southwest China. The visceral fat level, bone mineral content, and body fat percentage were significant predictors of GDM (23). In this study, multifrequency BIAs were used to determine the body composition of pregnant women in the first trimester to further explore the effect of body composition in the first trimester on GDM risk in different prepregnancy BMI groups in the Central Plains of China.

Materials and methods

Study design and patients

This study retrospectively analyzed pregnant women who visited the Third Affiliated Hospital of Zhengzhou University from January 1, 2021, to December 31, 2021, who were treated, had documented data, and received regular perinatal care. The inclusion criteria were as follows: (1) patients for whom a 75 g oral glucose tolerance test (OGTT) was performed at 24-28 weeks of gestation before body composition analysis; (2) patients aged ≥ 18 years old; (3) patients with a singleton pregnancy; and (4) patients who did not have diabetes before pregnancy. The exclusion criteria were (1) patients with pre-pregnancy cardiovascular disease, diabetes mellitus, and thyroid abnormalities; (2) patients with twin or multiple pregnancies; (3) patients with psychiatric disorders who were unable to complete the test; and (4) patients with missing data.

The above study was approved by the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University, Henan Province (2022-143-01).

Diagnostic criteria for GDM

According to the diagnostic criteria of the IADPSG 2010 (24), subjects underwent a 75 g-OGTT at 24-28 weeks of gestation, consumed a vegetarian diet while abstaining from meat, eggs, milk, and fruit the day before the OGTT, and fasted for 8-14 hours after dinner and the following morning (no later than 9 a.m.). Three hundred milliliters of liquid containing 75 g

of glucose was taken orally within 5 minutes after drawing venous blood on an empty stomach. Venous blood was taken 1 h and 2 h after taking glucose (the time was counted from the time of drinking the glucose water), and plasma glucose was measured using the glucose oxidase method. The plasma glucose values while fasting and 1 h and 2 h after taking the glucose water were set at 5.1 mmol/L, 10.0 mmol/L, and 8.5 mmol/L, respectively. Pregnant women who met the diagnostic criteria for GDM were included in the GDM group, and those who did not were included in the normal group.

Covariates

The general data of pregnant women in the first trimester (before 14 weeks of pregnancy) were retrospectively collected, including age, height, pre-pregnancy BMI, reproductive history, weight at the time of BIA, gestational age at the time of BIA, and gestational weight gain (GWG). Direct segmental multifrequency BIA (DSM-BIA method) was performed in the first trimester of pregnancy using an Inbody J30 device (instrument measurement frequencies 5 kHz, 50 kHz, 250 kHz). All data for body composition analysis were collected by trained nursing staff in the obstetric clinic in strict accordance with the instructions for use. Before the test, the pregnant woman was asked to empty her bladder, remove her coat, shoes, socks, accessories, and metal objects, and wipe her hands and feet with a wet paper towel. The measurement was taken while the patient was standing, with her heel flush with the foot electrode, her arm semibent and away from her body, and while grasping the handle of the device and placing her thumb on the oval electrode piece. The test lasted 30 seconds and the patient remained relaxed until the end of the test. As soon as the patient stepped off the device, the device automatically printed a standard report containing the following data: total body water (TBW), protein levels, mineral levels, bone mineral content (BMC), body fat mass (BFM), soft lean mass (SLM), fat-free mass (FMM), skeletal muscle mass (SMM), percent body fat (PBF), the waist-hip ratio (WHR), the visceral fat level (VFL), and the basal metabolic rate (BMR).

Pre-pregnancy BMI was calculated as follows: pre-pregnancy weight/height ^{2} (kg/m^2). The pregnant women were classified by pre-pregnancy BMI according to the "WS/T428-2013 Adult Weight Determination" standard issued by the National Health and Family Planning Commission of the People's Republic of China in 2013 (25). Pregnant women were grouped according to the pre-pregnancy BMI classification criteria: a BMI<18.50 kg/m^2 was considered low weight before pregnancy, a BMI of 18.50-23.90 kg/m^2 was considered normal weight before pregnancy, a BMI of 24.00-27.90 kg/m^2 was considered overweight, and a BMI ≥28.00 kg/m^2 was considered obese. The number of women with a pre-pregnancy BMI<18.50 kg/m^2 and a BMI ≥28.00 kg/m^2 was small in this study, so in the low-weight and normal groups, overweight and obese pregnant women were combined into one group for analysis. Gestational weight gain (GWG) was calculated by subtracting the reported pre-pregnancy weight from the recorded weight at the time of BIA (26).

Percent body fat was calculated as follows: fat mass/body mass × 100%. The basal metabolic rate was calculated as follows = 21.6 * fat-free mass (kg) + 370. The instrument used in this study classifies visceral fat mass on a scale of 1 to 30, which is expressed as the VFL, where 1 to 9 indicates a normal visceral fat mass, 10 to 14 indicates a high visceral fat mass, 15 to 29 indicates a high-fat content, and 30 indicates super high-fat content. A visceral fat grade of 10 is equivalent to 100 cm^2 of visceral fat.

Statistical analyses

SPSS 26.0 statistical software (International Business Machines Corporation, New York, United States of America) was used for data processing and analysis. The Kolmogorov–Smirnov test (K-S test) was used to analyze whether the data were normally distributed, which was expressed as ($\bar{x} \pm s$) and compared between two groups using the two independent samples t test. Nonnormally distributed measurement data are expressed as medians (quartiles). Unordered categorical comparisons between groups were performed using the χ^2 test, and comparisons between two groups were performed using a two-independent sample nonparametric test (the Mann–Whitney U test). In the univariate analysis of body composition, the association with the risk of developing GDM was included in a multivariate analysis, using relative risks and 95% confidence intervals obtained from log-binomial regression and performing multivariate regression analysis using generalized linear regression. Linearity between continuous variables was assessed using Pearman's correlation coefficient. A correlation heatmap was used to represent the correlation of continuous variables. The narrower the graph and the darker the color, the stronger the correlation. The area under the curve (AUC) was further calculated from the receiver operating characteristic (ROC) curve. The optimal cutoff value for each risk factor was calculated according to the Youden Index, which maximizes the following equation: J = maxc {Se(c) + Sp(c) 1}, where c is the cut-off point for the sum of Se (sensitivity) and Sp (specificity) to obtain the highest value (27). After selecting the cutoff point for each marker, the sensitivity and specificity at the best cutoff value were calculated. The Hosmer–Lemeshow test was used to assess the final model fit. P<0.05 was considered a statistically significant difference.

Manuscript formatting

Description of the overall pregnant women

Initially, information was obtained for a total of 7820 pregnant women, including 324 women with twin or multiple pregnancies, 704 women with no OGTT results or missed visits, 31 women with spontaneous abortion or induced labor, 56 women with pre-pregnancy diabetes, and 7 women for whom BIA data were not available, resulting in 6698 pregnant women being included in the study (Figure 1). Table 1 shows the essential characteristics of the 6698 pregnant women, including a total of 1109 women with GDM, with a detection rate of 16.56%. It was found that the age, gravidity, weight at the time of BIA, gestational age at the time of BIA, and GWG of the GDM group were higher than those of the normal group, but the height was lower than that of the normal group. The detection rate of GDM was higher in multiparous women. Regarding body composition, TBW, protein levels, mineral levels, BMC, BFM, SLM, FMM, SMM, PBF, WHR, VFL, and the BMR were all higher in the GDM group than in the normal group. There were significant differences (P<0.05).

General information on pregnant women under different pre-pregnancy BMI groups

Under different pre-pregnancy BMI groupings, there were 4157 pregnant women with BMI <24 kg/m^2, of which 456 (10.97%) were diagnosed with GDM; in a total of 2541 pregnant women with BMI ≥24 kg/m^2, 653 (25.70%) were diagnosed with GDM.In the subgroup with pre-pregnancy BMI<24kg/m^2 or in the subgroup with pre-pregnancy BMI<24kg/m^2, the age, weight at the time of BIA, gestational age at the time of BIA, and GWG were all higher than those of the normal group, and there were statistically significant differences. See Table 2 for details.

Analysis of body composition of pregnant women under different BMI groups

Statistical analysis showed that TBW, protein levels, mineral levels, BMC, BFM, SLM, FMM, SMM, PBF, the WHR, the VFL, and the BMR of pregnant women with a pre-pregnancy BMI < 24 kg/m^2 and those with a pre-pregnancy BMI≥24 kg/m^2 were higher in the GDM group than in the normal group. In the BMI<24 kg/m^2, the BFM, PBF, WHR, and VFL of pregnant women in the GDM group were significantly different from those in the normal group (P<0.05). However, there was no significant difference in TBW, protein levels, mineral levels, BMC, SLM, FFM, SMM, or the BMR (P>0.05), as shown in Table 3.

Correlation analysis of pre-pregnancy BMI and body composition

Pre-pregnancy BMI was significantly positively correlated with TBW, protein levels, mineral levels, BMC, BFM, SLM, FMM, SMM, PBF, WHR, VFL, and the BMR (P<0.01) in the different groups. Among all pregnant women, the correlation between BMI before pregnancy and BFM was the strongest

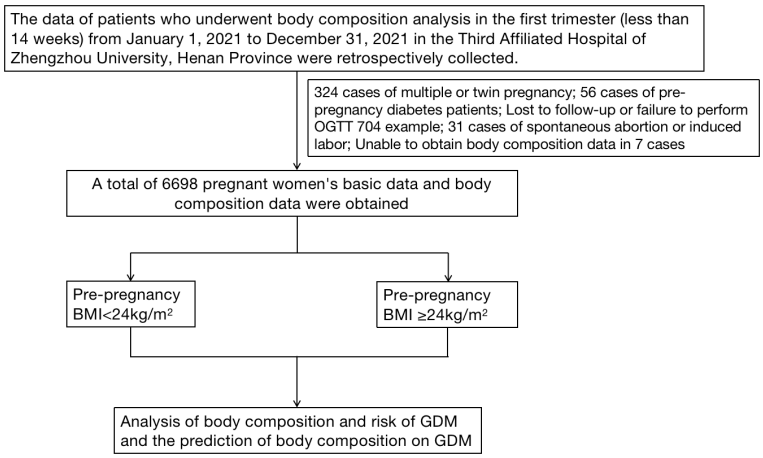

FIGURE 1
Technical route.

TABLE 1 Basic characteristics of pregnant women.

General Features	Total (N = 6698)	GDM group (N = 1109)	Normal group (N = 5589)	t/z/χ^2	*P*
Age (years)	30.20 ± 3.98	31.62 ± 4.07	29.92 ± 3.90	13.108	<0.001
Height (m)	1.61 ± 0.01	1.60 ± 0.06	1.61 ± 0.06	-3.344	0.001
Pre-pregnancy (Kg/m2)	23.41 ± 3.66	25.40 ± 4.19	23.02 ± 3.41	17.829	<0.001
Gravidity [M, (p25,p75)]	2 (1,2)	2 (1,3)	2 (1,2)	-4.689	<0.001
Parity [M, (p25,p75)]	0 (0,1)	0 (0,1)	0 (0,1)	-2.863	<0.001
Maternity history				7.264	0.007
multipara	2172 (32.43%)	398 (35.89%)	1774 (31.74%)		
primipara	4526 (67.57%)	711 (64.11%)	3815 (68.26%)		
Weight at the time of BIA (kg)	60.57± 9.88	65.36 ± 11.61	59.62 ± 9.21	15.518	<0.001
Gestational week at the time of BIA	12.15 ± 1.18	12.71 ± 1.58	12.04 ± 1.06	13.629	<0.001
GWG (Gestational weight gain,kg)	1.076± 0.36	1.41 ± 0.37	1.01 ± 0.32	34.087	<0.001
TBW (Total Body Water, kg)	29.37 ± 3.41	30.47 ± 3.83	29.16 ± 3.28	10.688	<0.001
Protein (kg)	7.79 ± 0.92	8.10 ± 1.02	7.73 ± 0.89	10.982	<0.001
Minerals (kg)	2.91 ± 0.35	3.00 ± 0.38	2.89 ± 0.38	9.118	<0.001
BMC (Bone Mineral Content, kg)	2.43 ± 0.29	2.50 ± 0.32	2.41 ± 0.28	8.992	<0.001
BFM (Body Fat Mass, kg)	20.49 ± 6.57	23.79 ± 7.69	19.84 ± 6.13	16.111	<0.001
SLM (Soft Lean Mass, kg)	37.65 ± 4.38	39.06 ± 4.91	37.37 ± 4.22	10.743	<0.001
FFM (Fat Free Mass, kg)	40.08 ± 4.66	41.57 ± 5.21	39.78 ± 4.48	10.667	<0.001
SMM (Skeletal Muscle Mass, kg)	21.52 ± 2.77	22.43 ± 3.08	21.35 ± 2.67	10.942	<0.001
PBF (Percent Body Fat, %)	33.18 ± 5.94	35.68 ± 5.88	32.67 ± 5.83	15.657	<0.001
WHR (Waist-Hip Ratio)	0.88 ± 0.05	0.90 ± 0.06	0.88 ± 0.05	13.616	<0.001
VFL (Visceral Fat Level)	9.43 ± 3.68	11.17 ± 3.94	9.08 ± 3.52	16.411	<0.001
BMR (Basal Metabolic Rate, kcal/day)	1228.50 ± 100.61	1267.91 ± 112.55	1229.29 ± 96.81	10.672	<0.001

(r=0.953), followed by that between BMI before pregnancy and the VFL (r=0.873). Among women with a BMI<24 kg/m^2 before pregnancy, BFM had the strongest correlation (r=0.812), followed by VFL (r=0.688). In women with a pre-pregnancy BMI≥24 kg/m^2, BFM was strongly correlated with pre-pregnancy BMI (r=0.884), followed by WHR (r=0.732), as shown in Figures 2, 3, 4.

Generalized linear regression of body composition and GDM risk

In the multivariate regression model, GDM was the dependent variable. The factors with statistically significant differences in the univariate analysis were included as the independent variables, and the multivariate generalized linear

TABLE 2 Comparison of general data of pregnant women with different pre-pregnancy BMI.

	N	Age (years)	Height (m)	Gravidity [M, (p25,p75)]	Parity [M, (p25,p75)]	Weight at thetime of BIA(kg)	Gestational week at the time of BIA	GWG (kg)
pre-pregnancy BMI <24kg/m^2								
GDM group	456	30.88 ± 3.94	1.61 ± 0.05	2(1,2)	0(0,1)	56.29 ± 5.56	12.75 ± 1.60	1.40 ± 0.39
Normal group	3701	29.48 ± 3.72	1.61 ± 0.05	1(1,2)	0(0,1)	54.95 ± 5.65	12.03 ± 1.07	1.00 ± 0.32
t/z		7.551	-1.615	-1.820	-0.457	4.573	9.332	21.167
P		<0.001	0.106	0.069	0.647	<0.001	<0.001	<0.001
pre-pregnancy BMI ≥24kg/m^2								
GDM group	653	32.13 ± 4.09	1.60 ± 0.56	2(1,3)	0(0,1)	71.69 ± 10.47	12.69 ± 1.56	1.42 ± 0.36
Normal group	1888	30.79 ± 4.10	1.60 ± 0.56	2(1,3)	0(0,1)	68.76 ± 7.89	12.06 ± 1.03	1.02 ± 0.32
t		7.186	-0.633	-1.721	-0.596	6.532	9.579	25.492
P		<0.001	0.527	0.085	0.551	<0.001	<0.001	<0.001

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TABLE 3 Analysis of body composition of pregnant women under different pre-pregnancy BMI.

	N	TBW (kg)	Protein (kg)	Minerals (kg)	BMC (kg)	BFM (kg)	SLM (kg)	FFM (kg)	SMM (kg)	PBF (%)	WHR	VFL	BMR(kcal/day)
Pre-pregnancy BMI <24kg/m^2													
GDM group	456	28.31 ± 2.82	7.51 ± 0.75	2.80 ± 0.29	2.34 ± 0.24	17.66 ± 3.52	36.28 ± 3.62	38.63 ± 3.84	20.67 ± 2.27	31.22 ± 4.61	0.87 ± 0.04	7.89 ± 2.33	1204.38 ± 83.05
Normal group	3701	28.10 ± 2.75	7.44 ± 0.74	2.79 ± 0.29	2.33 ± 0.24	16.62 ± 3.53	36.00 ± 3.54	38.34 ± 3.76	20.48 ± 2.23	30.05 ± 4.65	0.86 ± 0.04	7.29 ± 2.19	1198.09 ± 81.25
t		1.523	1.894	0.771	0.967	5.946	1.579	1.542	1.789	5.080	5.086	5.268	1.556
P		0.128	0.058	0.441	0.334	<0.001	0.114	0.123	0.074	<0.001	<0.001	<0.001	0.120
Pre-pregnancy BMI ≥24kg/m^2													
GDM group	653	31.98 ± 3.72	8.50 ± 0.99	3.14 ± 0.37	2.62 ± 0.31	28.06 ± 6.88	41.00 ± 4.76	43.63 ± 5.05	23.66 ± 2.97	38.80 ± 4.50	0.93 ± 0.05	13.47 ± 3.13	1312.28 ± 109.17
Normal group	1888	31.23 ± 3.24	8.30 ± 0.87	3.08 ± 0.34	2.57 ± 0.29	26.15 ± 5.16	40.03 ± 4.17	42.61 ± 4.43	23.05 ± 2.63	37.83 ± 4.25	0.91 ± 0.05	12.61 ± 2.93	1290.45 ± 95.71
t		2.462	4.585	3.443	3.231	6.512	4.612	4.544	4.613	4.935	5.223	6.142	4.541
P		<0.001	<0.001	0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

TBW, total body water; BMC, bone mineral content; BFM, body fat mass; SLM, soft lean mass; FMM, fat free mass; SMM, skeletal muscle mass; PBF, percent body fat; WHR, waist-hip ratio; VFL, visceral fat level; BMR, basal metabolic rate.

regression equation was analyzed. In the general information of pregnant women, the pre-pregnancy BMI, age, gestational weight gain (GWG) in the first trimester, and weight during BIA were all risk factors for GDM. This study found that GWG was related to a high risk of GDM. For every 1 kg increase in GWG, the risk of GDM increased by 4.08 times. This risk was higher in pregnant women with a BMI≥24 kg/m^2 before pregnancy.

In the body composition index, each index item was positively correlated with the risk of GDM when no confounding factors were adjusted. In Model 3, TBW, protein levels, mineral levels, BMC, SLM, FFM, SMM, and the BMR were protective factors for GDM ($P < 0.05$). These protective factors were not found in the subgroup of pregnant women with a pre-pregnancy BMI≥24 kg/m^2. After adjusting for confounding factors in Model 4, only the waist-hip ratio had a

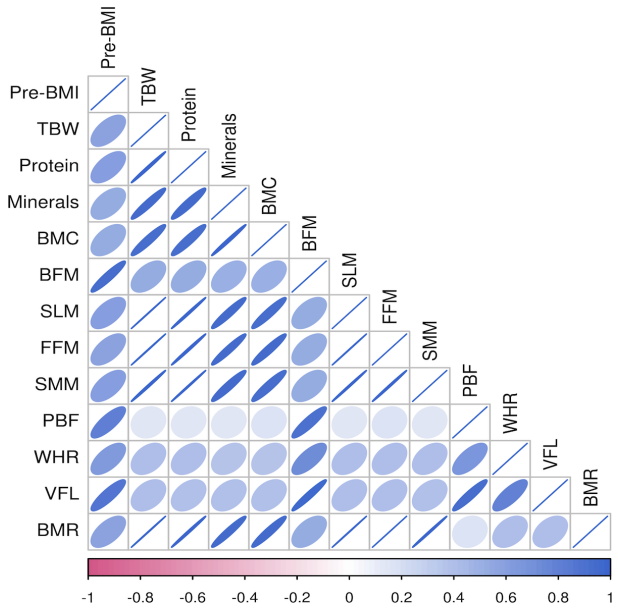

FIGURE 2
Heatmap of body composition correlations for pre-pregnancy BMI for all pregnant women.

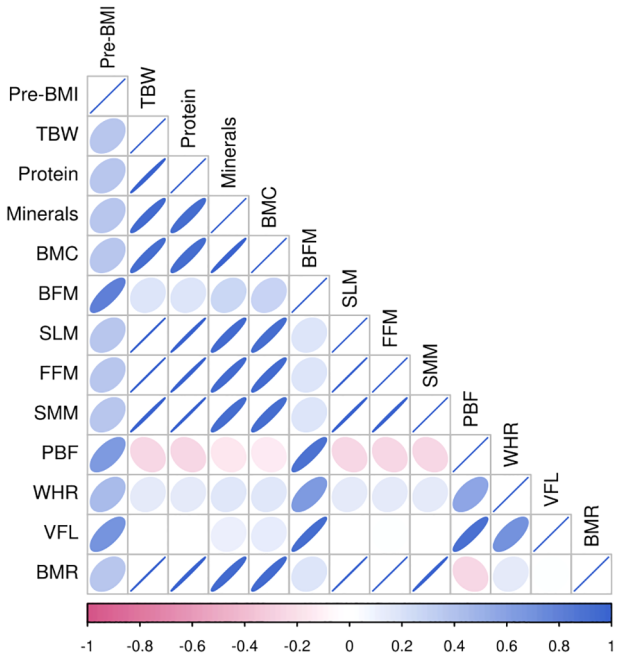

FIGURE 3
Heat map of body composition correlation in pregnant women with pre-pregnancy BMI < 24kg/m^2.

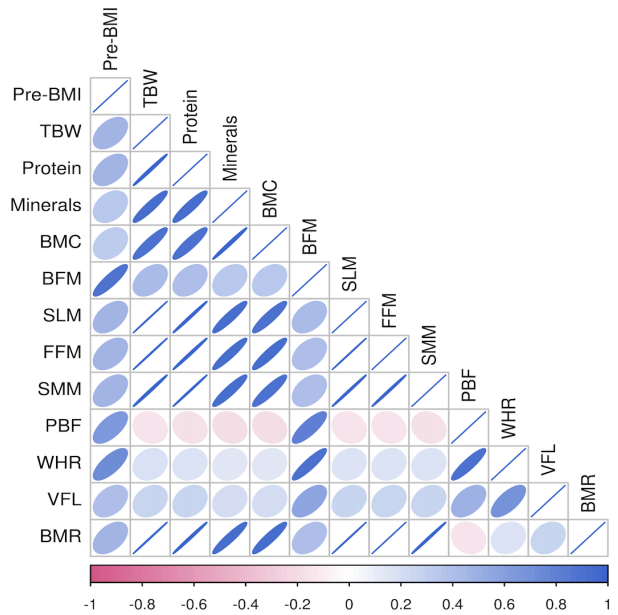

FIGURE 4
Heat map of body composition correlation in pregnant women with former BMI ≥ 24kg/m^2.

certain effect on GDM risk, and for each additional unit of the WHR, the risk of GDM increased by 4.562 times. Among pregnant women with a pre-pregnancy BMI <24 kg/m^2, the body composition-related indicators in Model 2 were all related to the onset of GDM. In Model 3, TBW, SLM, FFM, and the BMR were negatively correlated with the incidence of GDM. In Model 4, mineral levels and BMC were protective factors for GDM, and WHR led to a higher risk of GDM occurrence. For pre-pregnancy BMI≥24 kg/m^2, only in Model 1 and Model 2 was a positive correlation found between body composition and the onset of GDM. The WHR resulted in a higher risk of GDM onset during pregnancy. Body composition was not found to be associated with the risk of GDM in Model 3 or Model 4 after adjusting for confounding factors. See Table 4 for details.

Predictive value of general data and body composition for GDM under different pre-pregnancy BMI groups

The predictive value for GDM was analyzed based on the general data of pregnant women and the related body composition indicators. In the results for body composition, the area under the ROC curve of BFM for predicting GDM in all pregnant women was larger (0.663), the 95% CI was 0.645-0.680, the Youden index was 0.252, and the best cutoff value was 20.95; for the VFL, the area under the curve was 0.656, the 95% CI was 0.639-0.674, the Youden index was 0.236, and the optimal cutoff value was 10.5. Among pregnant women with a pre-pregnancy BMI <24 kg/m^2, the area under the ROC curve of BFM for predicting GDM was the largest (0.584), the 95% CI was 0.556-0.612, and the Youden index was 0.120; for PBF and the VFL, the area under the curve for both was 0.577, the Youden index was 0.118 and 0.117, respectively, and the optimal cutoff values were 32.65 and 8.5, respectively. Among pregnant women with a pre-pregnancy BMI ≥24 kg/m^2, the area under the ROC curve of BFM for predicting GDM was the largest (0.584), the 95% CI was 0.558-0.609, the Youden index was 0.143, and the best cutoff value was 28.85; for the VFL, the area under the curve was 0.656, the 95% CI was 0.553~0.604, the Youden index was 0.121, and the optimal cutoff value was 13.5; (see Tables 5, 6 for details). The results will only be reproduced in a Chinese population using the same equipment.

Discussion

In this study, the generalized linear regression model found that in all groups of pregnant women, pre-pregnancy BMI, age, gestational weight gain in the first trimester, and weight at the time of BIA were all risk factors for the onset of GDM. However, gestational weight gain in the first trimester was positively correlated with the risk of GDM.

In the body composition analysis, the body composition indicators were all positively correlated with the risk of GDM in Model 1; in Model 3, TBW, protein levels, mineral levels, BMC, SLM, FMM, SMM, and the BMR were protective factors against GDM. After Model 4 was adjusted for confounders, only WHR was positively associated with the occurrence of GDM. Among pregnant women with a pre-pregnancy BMI <24 kg/m^2, the body composition-related indicators in Model 2 were all associated with the onset of GDM. In Model 3, TBW, SLM, FMM, and the BMR were negatively correlated with GDM onset. In Model 4, mineral levels and BMC were protective factors against GDM. The WHR has a higher risk of GDM. Only in Model 1 and Model 2 was a prepregnancy BMI≥24 kg/m^2 found to be positively correlated with the onset of GDM, and there were no protective factors. In the prediction model, gestational weight gain in the first trimester had a higher predictive value for GDM, followed by pre-pregnancy BMI. Among the body composition indicators, BFM and PBF had higher predictive value for GDM in all groups of pregnant women. According to the pre-pregnancy BMI groups, the predictive risk value of body composition-related indicators for GDM needs further investigation.

With lifestyle changes, the incidence of GDM is increasing yearly, and it has become a significant public health problem in China (3). BMI is a crude marker of obesity that reflects current nutritional status but does not provide information on fat distribution. BIAs provide a more detailed assessment of body composition and compensates for the deficiencies associated with BMI (16). Previous studies have shown that BIAs are better predictors of pregnancy and postpartum outcomes than BMI (16). However, this study found that the predictive value of BMI and GWG before pregnancy in all the included pregnant women was higher than that of body composition detected by BIA, and body composition-related indicators in the first trimester had a specific predictive effect on the incidence of GDM. Pre-pregnancy BMI reflects the basic nutritional levels of women, which are closely related to the health status of the mother and fetus after pregnancy (28). A high pre-pregnancy BMI increases the risk of adverse pregnancy outcomes such as GDM, cesarean section, macrosomia, and postpartum hemorrhage (29). Pregnant women with a low BMI before pregnancy have insufficient fat reserves, poor nutritional levels, and reduced micronutrients, which can lead to iron deficiency and anemia during pregnancy (30). The pre-pregnancy BMI, as a controllable factor, suggests that women with a high BMI at the time of pregnancy should have a balanced diet, increase their amount of exercise and avoid overnutrition to reduce their body mass and reach the standard weight level as much as possible. At the same time, it is recommended that maternal and child health care institutions and hospital obstetrics and gynecology departments increase the popularization and publicity of the reasonable range of pre-pregnancy BMI for women preparing for pregnancy and scientifically guide dietary habits and

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TABLE 4 Multivariate regression analysis of different pre-pregnancy BMI groups.

Index	ALL			Pre-pregnancy BMI<24kg/m^2			Pre-pregnancy BMI ≥24kg/m^2		
	RR	95% C I	P	RR	95% C I	P	RR	95% C I	P
Pre-pregnancy BMI	1.132	1.119~1.145	<0.001	1.209	1.146~1.275	<0.001	1.073	1.047~1.099	<0.001
Age(years)	1.089	1.076~1.102	<0.001	1.086	1.065~1.108	<0.001	1.058	1.043~1.073	<0.001
GWG(kg)	4.080	2.114~6.045	<0.001	3.689	3.346~4.032	<0.001	5.193	4.540~5.846	<0.001
Weight at the time of BIA(kg)	1.041	1.037~1.046	<0.001	1.038	1.022~1.053	<0.001	1.024	1.019~1.029	<0.001
TBW(kg)									
Model 1	1.089	1.072~1.106	<0.001	1.025	0.991~1.059	0.151	1.047	1.029~1.066	<0.001
Model 2	1.136	1.119~1.154	<0.001	1.079	1.032~1.129	0.001	1.092	1.067~1.117	<0.001
Model 3	0.962	0.940~0.984	0.001	0.951	0.911~0.993	0.021	0.981	0.955~1.009	0.183
Model 4	0.996	0.966~1.026	0.778	0.986	0.936~1.039	0.596	1.002	0.968~1.037	0.910
Protein(kg)									
Model 1	1.381	1.304~1.463	<0.001	1.119	0.989~1.265	0.074	1.187	1.095~1.285	<0.001
Model 2	1.596	1.506~1.692	<0.001	1.364	1.165~1.597	<0.001	1.367	1.255~1.489	<0.001
Model 3	0.886	0.813~0.965	0.006	0.882	0.754~1.032	0.116	0.933	0.844~1.032	0.180
Model 4	1.010	0.909~1.122	0.849	1.027	0.853~1.235	0.780	1.002	0.887~1.131	0.977
Minerals(kg)									
Model 1	1.961	1.701~2.261	<0.001	1.126	0.818~1.548	0.467	1.375	1.124~1.628	0.002
Model 2	2.377	1.751~3.266	<0.001	1.797	1.165~1.597	0.010	1.763	1.291~2.407	<0.001
Model 3	0.642	0.520~0.793	<0.001	0.385	0.252~0.586	0.500	0.811	0.636~1.035	0.092
Model 4	0.966	0.721~1.293	0.816	0.496	0.287~0.855	0.012	1.107	0.818~1.499	0.510
BMC(kg)									
Model 1	2.127	1.816~2.492	<0.001	1.193	0.816~1.745	0.362	1.413	1.120~1.784	0.004
Model 2	2.506	1.766~3.577	<0.001	2.284	1.323~3.944	0.003	1.803	1.266~2.567	0.001
Model 3	0.597	0.467~0.764	<0.001	0.337	0.205~0.554	0.383	0.776	0.584~1.032	0.082
Model 4	1.018	0.727~1.427	0.916	0.491	0.255~0.945	0.033	1.146	0.815~1.613	0.433
BFM(kg)									
Model 1	1.059	1.052~1.066	<0.001	1.078	1.050~1.107	<0.001	1.036	1.025~1.047	<0.001
Model 2	1.057	1.050~1.063	<0.001	1.076	1.048~1.105	<0.001	1.039	1.031~1.047	<0.001
Model 3	1.029	1.012~1.047	0.001	1.038	1.006~1.072	0.019	0.985	0.965~1.007	0.182
Model 4	1.002	0.980~1.024	0.849	1.010	0.972~1.050	0.603	0.998	0.973~1.024	0.890
SLM(kg)									
Model 1	1.069	1.056~1.082	<0.001	1.020	0.994~1.046	0.136	1.037	1.020~1.054	<0.001
Model 2	1.104	1.091~1.118	<0.001	1.062	1.026~1.100	0.001	1.070	1.052~1.090	<0.001
Model 3	0.971	0.953~0.989	0.001	0.963	0.932~0.996	0.028	0.985	0.965~1.007	0.182
Model 4	0.998	0.975~1.021	0.842	0.992	0.952~1.033	0.687	1.001	0.975~1.028	0.924
FFM(kg)									
Model 1	1.064	1.052~1.076	<0.001	1.018	0.994~1.043	0.146	1.034	1.018~1.050	<0.001
Model 2	1.099	1.086~1.111	<0.001	1.059	1.025~1.094	0.001	1.067	1.049~1.085	<0.001
Model 3	0.972	0.955~0.988	0.001	0.963	0.933~0.994	0.019	0.986	0.966~1.006	0.167
Model 4	0.998	0.976~1.020	0.849	0.990	0.952~1.029	0.603	1.002	0.977~1.027	0.890
SMM(kg)									
Model 1	1.113	1.092~1.134	<0.001	1.036	0.994~1.079	0.091	1.059	1.031~1.087	<0.001
Model 2	1.168	1.145~1.190	<0.001	1.104	1.047~1.164	<0.001	1.110	1.079~1.142	<0.001
Model 3	0.961	0.934~0.989	0.006	0.955	0.907~1.006	0.083	0.979	0.947~1.013	0.224
Model 4	1.004	0.969~1.040	0.824	1.002	0.942~1.066	0.994	1.004	0.964~1.046	0.840
PBF(%)									
Model 1	1.073	1.063~1.084	<0.001	1.051	1.030~1.072	<0.001	1.038	1.020~1.056	<0.001

(Continued)

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TABLE 4 Continued

Index	ALL			Pre-pregnancy BMI<24kg/m^2			Pre-pregnancy BMI ≥24kg/m^2		
	RR	95% C I	P	RR	95% C I	P	RR	95% C I	P
Model 2	1.069	1.059~1.079	<0.001	1.046	1.025~1.067	<0.001	1.043	1.028~1.059	<0.001
Model 3	1.024	1.013~1.036	<0.001	1.021	1.003~1.039	0.019	1.010	0.996~1.025	0.168
Model 4	1.010	0.996~1.024	0.147	1.005	0.983~1.027	0.667	1.000	0.983~1.018	0.997
WHR									
Model 1	994.455	362.269~2729.849	<0.001	206.291	23.361~1821.689	<0.001	34.023	7.890~146.714	<0.001
Model 2	1051.493	421.458~2623.361	<0.001	272.083	31.447~2354.089	<0.001	67.603	18.049~253.205	<0.001
Model 3	4.342	1.427~13.218	0.010	13.374	2.031~88.062	0.007	1.816	0.502~6.576	0.363
Model 4	4.562	1.532~13.582	0.006	7.132	1.008~50.447	0.049	2.713	0.765~9.620	0.122
VFL									
Model 1	1.121	1.105~1.138	<0.001	1.110	1.067~1.155	<0.001	1.071	1.045~1.098	<0.001
Model 2	1.113	1.099~1.127	<0.001	1.103	1.062~1.146	<0.001	1.077	1.055~1.099	<0.001
Model 3	1.038	1.016~1.059	0.001	1.030	0.991~1.071	0.129	1.014	0.989~1.041	0.280
Model 4	1.014	0.991~1.037	0.238	0.997	0.955~1.042	0.906	1.006	0.979~1.033	0.664
BMR(kcal/day)									
Model 1	1.003	1.002~1.003	<0.001	1.001	1.000~1.002	0.142	1.002	1.001~1.002	<0.001
Model 2	1.004	1.004~1.005	<0.001	1.003	1.001~1.004	0.001	1.003	1.002~1.004	<0.001
Model 3	0.999	0.998~0.999	0.001	0.998	0.997~1.000	0.020	0.999	0.998~1.000	0.165
Model 4	1.000	0.999~1.001	0.854	1.000	0.998~1.001	0.622	1.000	0.999~1.001	0.898

RR, relative risk; CI, confidence interval.
Model 1, without adjusting for confounding factors; Model 2, adjusted for age(years), height(kg), gravidity, parity; Model 3, adjusted for weight at the time of BIA(kg), gestational week at the time of BIA, GWG; Model 4, adjusted for Model 2 +Model 3.

lifestyles for women with a high pre-pregnancy BMI to help them reduce their GDM risk.

GWG is closely related to the short-term and long-term health of mothers and babies. Excessive weight gain during pregnancy is associated with gestational hypertension, GDM, postpartum obesity, and even long-term hypertension, diabetes, and metabolic syndrome (29, 31). In this study, it was found that the GDM group gained weight faster in early pregnancy than the normal group, and GWG in the first trimester had a strong predictive ability for GDM. This study showed that weight gain in early pregnancy is closely related to GDM. Excessive weight gain in early pregnancy increases the risk of GDM by 4.080 times and is an independent risk factor for GDM. A pre-pregnancy BMI ≥24 kg/m^2 indicated an increased weight of pregnant women in the first trimester, which increased the risk of GDM by 5.193 times. People who are overweight or obese before pregnancy may have metabolic disorders before pregnancy. Weight gain in early pregnancy further worsens metabolic disorders, strengthens insulin resistance and increases the incidence of GDM (32). During the COVID-19 lockdown,

TABLE 5 Analysis of the predictive effect of general indicators under pre-pregnancy BMI on GDM.

	Classification	AUC	P	95%CI	Cutoff points	Sensitivity	Specificity	Youden index
Pre-pregnancy BMI	All	0.675	<0.001	0.657~0.692	23.43	0.665	0.606	0.271
	Pre-pregnancy BMI <24kg/m^2	0.600	<0.001	0.573~0.628	21.71	0.564	0.591	0.155
	Pre-pregnancy BMI ≥24kg/m^2	0.609	<0.001	0.583~0.634	27.53	0.478	0.715	0.193
Age(years)	All	0.617	<0.001	0.599~0.635	29.5	0.703	0.464	0.167
	Pre-pregnancy BMI <24kg/m^2	0.600	<0.001	0.573~0.626	29.5	0.651	0.509	0.160
	Pre-pregnancy BMI ≥24kg/m^2	0.591	<0.001	0.566~0.616	31.5	0.534	0.593	0.117
GWG(kg)	All	0.795	<0.001	0.779~0.812	1.415	0.564	0.921	0.485
	Pre-pregnancy BMI <24kg/m^2	0.788	<0.001	0.762~0.815	1.415	0.561	0.924	0.485
	Pre-pregnancy BMI ≥24kg/m^2	0.796	<0.001	0.774~0.817	1.415	0.567	0.915	0.482
Weight at the time of BIA(kg),	All	0.653	<0.001	0.635~0.671	62.25	0.564	0.662	0.226
	Pre-pregnancy BMI <24kg/m^2	0.564	<0.001	0.537~0.591	55.05	0.594	0.510	0.104
	Pre-pregnancy BMI ≥24kg/m^2	0.584	<0.001	0.557~0.610	73.05	0.391	0.758	0.149

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TABLE 6 Analysis of the predictive effect of different pre-pregnancy BMI lower body composition indexes on GDM.

	Classification	AUC	P	95%CI	Cutoff points	Sensitivity	Specificity	Youden index
TBW(kg)	All	0.599	<0.001	0.580~0.617	39.65	0.019	0.996	0.015
	Pre-pregnancy BMI <24kg/m^2	0.514	0.332	0.486~0.542	30.55	0.219	0.815	0.034
	Pre-pregnancy BMI ≥24kg/m^2	0.554	<0.001	0.529~0.580	32.05	0.371	0.629	0.009
Protein(kg)	ALL	0.601	<0.001	0.583~0.620	8.15	0.454	0.696	0.15
	pre-pregnancy BMI <24kg/m2	0.518	0.202	0.490~0.546	8.05	0.239	0.794	0.033
	pre-pregnancy BMI ≥24kg/m2	0.555	<0.001	0.529~0.581	8.55	0.455	0.629	0.084
Minerals(kg)	All	0.585	<0.001	0.566~0.604	3.005	0.454	0.670	0.124
	Pre-pregnancy BMI <24kg/m^2	0.505	0.722	0.477~0.533	3.115	0.145	0.877	0.022
	Pre-pregnancy BMI ≥24kg/m^2	0.541	0.002	0.515~0.567	3.225	0.391	0.677	0.068
BMC(kg)	All	0.581	<0.001	0.563~0.600	2.515	0.454	0.664	0.118
	Pre-pregnancy BMI <24kg/m^2	0.507	0.619	0.479~0.535	2.015	0.936	0.086	0.022
	Pre-pregnancy BMI ≥24kg/m^2	0.537	0.005	0.511~0.563	2.875	0.190	0.875	0.065
BFM(kg)	All	0.663	<0.001	0.645~0.680	20.95	0.626	0.626	0.252
	Pre-pregnancy BMI <24kg/m^2	0.584	<0.001	0.556~0.612	16.35	0.662	0.458	0.120
	Pre-pregnancy BMI ≥24kg/m^2	0.584	<0.001	0.558~0.609	28.85	0.377	0.766	0.143
SLM (kg)	All	0.599	<0.001	0.581~0.618	39.45	0.442	0.707	0.149
	Pre-pregnancy BMI <24kg/m^2	0.515	0.306	0.486~0.543	38.95	0.237	0.798	0.035
	Pre-pregnancy BMI ≥24kg/m^2	0.554	<0.001	0.529~0.580	40.25	0.541	0.547	0.088
FFM(kg)	All	0.598	<0.001	0.581~0.617	41.15	0.507	0.641	0.148
	Pre-pregnancy BMI <24kg/m^2	0.514	0.325	0.486~0.542	34.55	0.877	0.161	0.038
	Pre-pregnancy BMI ≥24kg/m^2	0.553	<0.001	0.528~0.579	44.05	0.429	0.658	0.087
SMM (kg)	All	0.601	<0.001	0.583~0.620	22.65	0.458	0.692	0.152
	Pre-pregnancy BMI <24kg/m^2	0.517	0.224	0.489~0.546	22.55	0.213	0.822	0.035
	Pre-pregnancy BMI ≥24kg/m^2	0.555	<0.001	0.529~0.581	24.25	0.375	0.714	0.089
PBF(%)	All	0.647	<0.001	0.629~0.665	33.75	0.657	0.568	0.225
	Pre-pregnancy BMI <24kg/m^2	0.577	<0.001	0.549~0.605	32.65	0.423	0.695	0.118
	Pre-pregnancy BMI ≥24kg/m^2	0.563	<0.001	0.537~0.588	36.95	0.669	0.447	0.116
WHR	All	0.632	<0.001	0.614~0.651	0.885	0.609	0.587	0.196
	Pre-pregnancy BMI <24kg/m^2	0.570	<0.001	0.542~0.598	0.855	0.636	0.468	0.104
	Pre-pregnancy BMI ≥24kg/m^2	0.569	<0.001	0.543~0.595	0.945	0.354	0.762	0.116
VFL	All	0.656	<0.001	0.639~0.674	10.5	0.551	0.685	0.236
	Pre-pregnancy BMI <24kg/m^2	0.577	<0.001	0.549~0.605	8.5	0.401	0.716	0.117
	Pre-pregnancy BMI ≥24kg/m^2	0.579	<0.001	0.553~0.604	13.5	0.466	0.655	0.121
BMR(kcal/day)	All	0.598	<0.001	0.580~0.617	1259.5	0.505	0.643	0.148
	Pre-pregnancy BMI <24kg/m^2	0.514	0.319	0.486~0.543	1116.5	0.875	0.162	0.037
	Pre-pregnancy BMI ≥24kg/m^2	0.553	<0.001	0.527~0.579	1300.5	0.521	0.567	0.088

AUC, area under curve.

lifestyle habits and eating patterns were affected, and outdoor activities were severely restricted. For pregnant women with GDM, weight gain during the lockdown period led to a higher BMI at delivery (33). The incidence of GDM increased during the time interval associated with the COVID-19 lockdown and in the following months (34). Therefore, paying attention to weight gain in early pregnancy and providing individualized medical nutrition therapy for patients who gain more weight in early pregnancy can reduce weight gain during pregnancy, reduce the rate of poor weight control, effectively control blood glucose and lipid levels, and reduce the incidence of maternal and infant adverse outcomes.

Different human body components have essential functions. Human body components are composed of water, protein, fat, inorganic salts, and other substances, and their proportions can reflect the nutritional status of the body to a specific extent (35). The correlation heatmap of this study showed that there was a certain correlation between body composition indicators and pre-pregnancy BMI. Staelens et al. found that the total water content was significantly increased during pregnancy (36). In this study, it was found that the TBW of pregnant women in the GDM group was higher than that in the normal group. Pregnant women with GDM may be in a hyperglycemic state for a long time, with immense osmotic pressure, and increased vascular

permeability, so the extracellular water increases accordingly. This suggests that women with GDM may have problems with polyhydramnios (37).

Protein is an essential nutrient for the health of the mother and fetus and a regulator of glucose metabolism (38). Bao proposed that high protein intake before pregnancy increases the risk of GDM (39). Insufficient protein intake during pregnancy can lead to poor fetal development, miscarriage, deformities, etc., and it is not easy for these mothers to recover after delivery (40). Dietary protein intake can reduce blood glucose levels in the body by stimulating insulin secretion, thereby affecting the blood glucose status of the body (41). Inadequate protein intake during pregnancy will lead to insufficient metabolic substrates such as amino acids, thereby affecting maternal and infant outcomes. Therefore, pregnant women should pay attention to the lack of various body components and ensure the intake of an appropriate amount of high-quality protein every day.

Minerals have the functions of maintaining cell osmotic pressure, acid-base balance, and muscle excitability (42). In different pregnancy periods, due to the other conditions of maternal weight gain, maternal tissue growth, and fetal growth, pregnant women have additional requirements for various minerals (43). Due to the physiological changes, plasma volume, and glomerular filtration rate during each pregnancy, the mineral content in plasma decreases gradually with the progression of pregnancy (44). The lack and excess of minerals can directly affect the growth and development of the fetus in pregnant women, leading to different degrees of dysfunction in pregnant women and causing miscarriage and fetal birth defects (45). Therefore, attention should be given to mineral supplementation during pregnancy, even before pregnancy. Optimal mineral supplementation can significantly reduce various pregnancy complications (46) and ensure the health of the mother and the normal development of the fetus. Currently, there is no research on the relationship between in pregnant women's body composition mineral levels and GDM risk. In this study, it was found that mineral levels had a low ability to predict the risk of GDM, and more prospective studies are needed to discuss this issue.

BMC refers to inorganic salts that make up bones and maintain bone density, in which calcium is the main component (23). The increased calcium demand during pregnancy is mainly used for the mineralization of fetal bones, so the lack of calcium in infants will lead to growth delay and bone deformation (46). Pregnant women have different degrees of calcium loss, which is evident in the third trimester of pregnancy (47). Increasing calcium intake and participating in outdoor activities during pregnancy can not only prevent bone loss in pregnant women but also ensure the normal development of the fetus (48). Zhang's research first found that bone minerals in the first trimester of pregnancy are significant risk factors for GDM (23). However, our research found that BMC was a protective factor against GDM in Model 3. The research showed that there was no difference in bone mineral content between the GDM group and the non-GDM group in early pregnancy (49), which is contrary to our research results. Therefore, BMC during pregnancy needs to be further assessed with larger sample sizes. In this study, it was found that the TBW, protein levels, mineral levels, and BMC of the pregnant women in the GDM group were higher than those in the normal group. This is consistent with Moreno's findings (50). Women with GDM have higher body weight during pregnancy, so various body components during pregnancy are also relatively increased.

SLM is determined by the addition of TBW and proteins in the body and is made up of skeletal and smooth muscle (51). Women with type 1 diabetes have lower total lean body mass and significantly less muscle area (52, 53). SMM plays a significant role in glucose homeostasis. Low skeletal muscle mass increases insulin resistance and diabetes risk (54). Maintaining the functional level of skeletal muscle is vital in maternal and fetal health. Pregnant women are faced with a reduction in skeletal muscle content caused by factors such as decreased activity and unbalanced dietary nutrition, and the risk of metabolic abnormalities caused by these factors is also worthy of attention (55). In this study, it was found that the SMM of the GDM group was higher than that of the normal group. Shin proposed that overweight women have more muscle mass, but this excess muscle mass is considered metabolically inactive because these women have insulin resistance (54). There are few studies on the correlation between skeletal muscle function indices and glucose and lipid metabolism during pregnancy. This study also found that SLM and SMM were protective factors for GDM, but their predictive risk value for GDM was not high. Therefore, further analysis of SLM and SMM with a larger sample size is required in future studies, taking the effects of physical activity and sedentary time into account.

The total body water, protein level, and muscle overlap is called FFM. FFM is a critical determinant of resting energy expenditure during pregnancy (56). Studies have reported that water and electrolytes in the human body are highly correlated with fat-free content, and 50 kHz whole-body BIA measurements are often used in conjunction with anthropometry to predict FFM (57). This study found that in pregnant women with a pre-pregnancy BMI <24 kg/m^2, when weight at the time of BIA, gestational age at the time of BIA, and GWG were included as confounding factors, it was also found that FFM and SMM were negatively correlated with the incidence of GDM. This may be related to the fact that a high FFM may be connected to endogenous glucose output and contribute to blood glucose control (56). In a prospective

cohort study in China, Wang et al. found a positive relationship between FFM and birth weight, and a woman had a FFM ≥ 40.76 kg, the risk of a birth weight over 4 kg was significantly increased by 2.47-fold (58). This may be related to pre-pregnancy obesity status, rapid fetal growth during pregnancy, and an increased TBW in the third trimester.

Adipose tissue is not only a storage area for energy but also an organ for releasing endocrine and immune signals. Therefore, the excessive accumulation of adipose tissue can affect the normal physiological functions of the body (15). After pregnancy, the intake of nutrients and calories gradually increases, the amount of exercise relatively decreases, fat accumulates, and the body fat percentage rises without any significant increase in activity (59). In our study, we found that women in the GDM group had significantly higher body fat mass (BFM) and percent body fat (PBF) than women in the normal group. A multifactorial analysis found that BFM and PBF were independent risk factors for the development of GDM ($P<0.05$), which is consistent with the findings of many studies (21, 22, 60). In Sommer's reflection in a multiethnic population, it was found that the increase in BMI and BFM was positively correlated with GDM, and an increase in BMI of 0.21 kg/week was associated with a 1.23-fold increase in the risk of GDM (22). Some studies have shown that PBF is a better predictor of GDM than BMI (59). Zhao scholars suggested that the higher risk of diabetes in the high PBF group among those with normal BMI may be related to their low insulin sensitivity index (61). Liu et al. mentioned that pregnant women with a PBF higher than 28% had a higher risk of GDM than those with a normal PBF (21). A prospective cohort study by Qing found that BFM did not change significantly in the first trimester. At the same time, body weight (BW) and BFM increased in the second trimester and were positively correlated with GDM risk (56). Some scholars have also proposed that the increase in PBF before pregnancy also impacts GDM risk (62). In this study, it was found that the BFM and PBF of the pregnant women in the GDM group were relatively higher than those of pregnant women in the normal group, which is basically consistent with previous studies. For overweight/obese pregnant women, detecting their body fat distribution and identifying metabolically healthy obesity and metabolically abnormal obesity are helpful for the early detection of GDM high-risk groups. Therefore, we must manage pregnant women with an increased pre-pregnancy BMI and abnormal BFM or PBF.

Most of the body's adipose tissue is located subcutaneously, while a small amount of adipose tissue accumulates in the abdomen (63). Subcutaneous fat has been reported to increase leptin and tumor necrosis factor alpha (TNF-α) secretion and decrease insulin sensitivity, while visceral fat can increase insulin resistance (56). Asian populations have more abdominal and visceral fat than European populations in China and South Asia (64). The excessive accumulation of abdominal fat can increase serum inflammatory factor levels, induce a chronic inflammatory response, reduce insulin sensitivity and affect pancreatic β-cell function, which in turn can lead to disorders of glucolipid metabolism (65). A mild inflammatory response is already present in normal pregnancy (7), and inflammatory factors are involved in insulin resistance and even GDM through different pathways in the body. Adipose tissue secretes many adipokines and cytokines. For example, lipocalin is positively associated with insulin sensitivity, and TNF-α and interleukin-6 (IL-6) activate the inflammatory response, thus creating a vicious cycle. The proinflammatory state of the body in GDM patients may also be associated with future type 2 diabetes and cardiovascular disease (66). Visceral fat is commonly used to describe intra-abdominal fat, including intraperitoneal fat (mesenteric and omental fat) and retroperitoneal fat, with the former flowing directly into the portal circulation and the latter into the systemic circulation. Excess visceral fat is also referred to as central or centripetal obesity (67). Excess visceral fat produces high levels of free fatty acids, increasing hepatic glycogen isogenesis and glycogenolysis, and is strongly associated with insulin resistance (68). Kim found through a cohort study that a higher visceral fat area (VFA) was an independent risk factor for type 2 diabetes (69). This study found that the VFL of pregnant women in the GDM group was significantly higher than that in the control group. Further multivariate analysis found that the VFL of pregnant women in early pregnancy was positively correlated with the incidence of GDM and had a specific predictive value for the occurrence of GDM. Zhang et al. mentioned in their study that VFL was closely associated with increased fasting glucose and HbA1c levels in GDM patients. HbA1c was closely related to elevated GDM risk and could be a risk factor for GDM (23).

Waist circumference (WC) is the body circumference at the abdominal level, which is a simple and effective indicator for evaluating central fat and has a significant predictive value in the risk of human metabolic diseases, such as hypertension, coronary heart disease, diabetes, and blood lipid disorders (70). In a Brazilian analysis of 5251 women with WC measurements at mid-gestation, it was found that a WC over 82 cm had a sensitivity of 63% and a specificity of 57% in predicting GDM (71). In a prospective cohort study conducted in China, BMI and WC were found to be associated with the development of GDM in Chinese pregnant women in early pregnancy, with a dramatic increase in the risk of GDM when the WC was ≥78.5 cm (72). The hip circumference is the horizontal perimeter of the most protruding part of the buttocks, which reflects the development of hip bones and muscles. It is also an adequate measure of hip fat (73). Snijder MB et al. prospectively found that a large hip circumference effectively reduced the risk of type II diabetes (74). The WHR is

the ratio of the WC to hip fat, another critical index used to determine central obesity. In exploring the WHR as a predictor of GDM in Asian Indians, Madhavan et al. found that a high WHR was associated with an increased risk of GDM and was associated with an increased risk of GDM; the prevalence of GDM was seven times higher in the high WHR group than in the low WHR group (WHR ≤ 0.85) (73). In this study, the WHR was found to be an independent risk factor for GDM and had a particular predictive value for GDM. Basraon also suggested that the value of the WHR in predicting GDM is comparable to that of BMI [AUC: 0.68 (BMI), 0.63 (WHR)] (75).

The BMR is the most basic energy consumption to maintain the body's life activities. Body composition changes dynamically during energy consumption. A reasonable BMR is significant for recommending dietary energy consumption during pregnancy (76). Pregnancy is a unique and complex physiological process. Due to the physiological needs of pregnancy, the body composition and the BMR of women change after pregnancy. Studies have shown that the BMR in the third trimester will increase by approximately 11% compared with that in the first trimester (77). The extra energy intake during pregnancy increases the body fat composition of pregnant women, and excessive body fat storage during pregnancy can lead to maternal obesity and other health problems (78). Under the guidance of body composition monitoring, an average body weight and body fat can be maintained, and the increase in body fat during pregnancy can be controlled to keep the body composition of pregnant women within a reasonable range. The results showed that the BMR of overweight/obese pregnant women before pregnancy was significantly higher than that of women with normal BMI before pregnancy. Therefore, a reasonable basal metabolic value and body composition status are of great significance for nutrition education before and during pregnancy and for recommending dietary energy consumption during pregnancy.

The advantage of this study is that pre-pregnancy BMI was used to group and analyze pregnant women to predict the risk of GDM. There is no such analysis at present. Medical staff should attach great importance to women with an abnormal pre-pregnancy BMI, improve pregnant women's awareness of weight control before pregnancy, and provide them with personalized guidance as soon as possible to formulate a reasonable range of weight gain. This study lacks pre-pregnancy body composition measurement data, and it is difficult to see the variation range of body composition-related indicators from pre-pregnancy to early pregnancy. Changes in body composition during pregnancy also impact pregnancy outcomes, which needs further research. Because body fat distribution is influenced by age, ethnicity, physical activity level, and total fat mass, there are differences in body composition distributions. Therefore, the index conclusions of the best GDM prediction methods in different countries and regions are still controversial. There was no further stratified analysis of age in this study, and we will gradually supplement samples in future research to further explore the influence of various factors on body composition and pregnancy outcomes.

Conclusion

In conclusion, regardless of the pre-pregnancy BMI level, all indicators of the BIA were independently related to the risk of GDM. Further analysis of the ROC curve showed that the body composition indicators of pregnant women in the first trimester had a particular predictive value for GDM. This study also found that excessive weight gain in the first trimester for GDM patients has a substantial predictive value for GDM. This suggests that medical staff should attach great importance to women with an abnormal pre-pregnancy BMI, improve pregnant women's awareness of weight control before pregnancy, and provide them with personalized guidance as soon as possible to formulate a reasonable range of weight gain. By controlling diet, encouraging exercise, and paying more attention to the regulation of pregnant women's endocrine and metabolic functions, the occurrence of GDM and perinatal complications can be prevented and controlled. In this retrospective study, single-center cohort data were used, the sample size for collection and analysis was small, and there were certain geographical limitations. It was unknown whether the pregnant women had undergone dietary intervention in the first trimester or before pregnancy. Relevant conclusions still need to be explored in a large-scale multicenter prospective cohort study. Under the circumstance of strictly controlling the interference factors, the feasibility of the results of this experiment can be further verified. Body composition standards should be formulated in line with various regions to guide clinical practice and further improve the quality of obstetric care for the birthing population.

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 study was approved by the Ethics Committee of the Third Affiliated Hospital of Zhengzhou University, Henan Province (2022-143-01). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

LXT and CRM: data acquisition and drafting of the manuscript. LXT, ZL, HYD, CTT, GYY, and LJX: acquisition and analysis and interpretation of the data. XDM and CLL: study concept and design, critical revision of the manuscript for important intellectual content, and study supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Maternal choices and preferences for screening strategies of gestational diabetes mellitus: A exploratory study using discrete choice experiment

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Aims: This study aimed to investigate maternal preferences for gestational diabetes mellitus (GDM) screening options in rural China to identify an optimal GDM screening strategy.

Methods: Pregnant women at 24–28 gestational weeks were recruited from Shandong province, China. A discrete choice experiment (DCE) was conducted to elicit pregnant women's preferences for GDM screening strategy defined by five attributes: number of blood draws, out-of-pocket costs, screening waiting-time, number of hospital visits, and positive diagnosis rate. A mixed logistic model was employed to quantify maternal preferences, and to estimate the relative importance of included attributes in determining pregnant women's preferences for two routinely applied screening strategies ("one-step": 75 g oral glucose tolerance test [OGTT] and "two-step": 50 g glucose challenge-test plus 75 g OGTT). Preference heterogeneity was also investigated.

Results: $N = 287$ participants completed the DCE survey. All five predefined attributes were associated with pregnant women's preferences. Diagnostic rate was the most influential attribute (17.5 vs. 8.0%, OR: 2.89; 95%CI: 2.10 to 3.96). When changes of the attributes of "two-step" to "one-step" strategies, women's uptake probability from full "two-step" to "one-step" significantly increased with 71.3% (95%CI: 52.2 to 90.1%), but no significant difference with the first step of "two-step" (−31.0%, 95%CI: −70.2 to 8.1%).

Conclusion: Chinese pregnant women preferred the "one-step" screening strategy to the full "two-step" strategy, but were indifferent between "one-step" and the first step of "two-step" strategies.

KEYWORDS

discrete choice experiment, gestational diabetes mellitus, patient preferences, screening methods, Chinese pregnant women

Introduction

Gestational Diabetes Mellitus (GDM) is a condition in which women without previously diagnosed overt diabetes exhibit high glucose intolerance during pregnancy, particularly during their third trimester (1). It has become an increasingly serious public health problem both in China and worldwide (1–3). In 2019, the overall prevalence of GDM was estimated at 14.8% of pregnant women in China (3), and 14.5% in rural China (4). GDM affected over two million pregnant women in China each year, with half of these women residing in rural areas (3–5). The occurrence of hyperglycemia in pregnancy is associated with worse (short-term and long-term) health outcomes for mothers as well as their offspring (6). A series of epidemiological studies indicated that women with GDM had higher risk of pre-eclampsia, premature birth, macrosomia, and type 2 diabetes after childbirth (7, 8). Their babies were also at greater risk of obesity, diabetes and metabolic syndromes later in life (9, 10).

GDM screening and subsequent treatment and management are critical for women with GDM at 24–28 weeks of gestation (1, 11). Despite a number of attempts to determine an optimal and uniform screening strategy for GDM (e.g., exploring the clinical and economic effectiveness) (12), no national consensus on the best practices and criteria for GDM screening and diagnosis exists (13). Currently, "one-step" and "two-step" are the two strategies that are commonly implemented in China and other counties. For the "one-step" strategy, a 75 g oral glucose tolerance test (OGTT) is performed to a fasting woman. Then, fasting, 1 and 2 h glucose level is measured, and the recommended diagnostic threshold is 5.1, 10, and 8.5 mmol/L, respectively. Pregnant women with any single abnormal glucose value are classified as diagnosed with GDM. While for "two-step," 50 g glucose challenge test (GCT) is firstly conducted to pregnant women (first step); if the 1-h glucose level is >7.8 mmol/L, the 75 g OGTT is then conducted to this woman next day (second step).

Some organizations including the American Diabetes Association (ADA) (1), the International Federation of Gynecology and Obstetrics (FIGO) (14) and World Health Organization (WHO) (15) recommended "one-step" strategy for women at 24–28 weeks of gestation since the diagnostic cut-off is much lower than that of the first step of the "two-step" strategy (namely 50 g GCT), which could avoid missed diagnoses (that could be also explained having higher specificity but reducing its sensitivity) and potential adverse events of hyperglycemia according to the Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO) (16). However, other international organizations such as the American College of Obstetricians and Gynecologists (17), Society of Obstetricians and Gynecologists of Canada (18), and the National Institutes of Health (19) do not support the superiority of the "one-step" over "two-step" strategy due to inadequate supporting evidence. For example, the lower cut-off value of the "one-step" strategy could result in misdiagnosis and increased risk of maternal and neonatal complications due to over-intervention and emotional stress (13, 20, 21). Furthermore, "one step" strategy asks subjects to visit hospital only one time, while "two-step" strategy might need them twice if tested positive in the first stage, which brings challenges to women living far away from a hospital. Generally, the number of blood draws of the "one-step" strategy is higher than the "two step" strategy (considering around 50% pregnant women do not need to receive the second step of "two-step" strategy). Correspondingly, the "one-step" strategy is generally costly than the "two-step." However, if women need to experience the entire two steps, they pay more than those who only experienced the first step of the "two-step" strategy. Therefore, the two strategies come with their own advantages and disadvantages.

The inconsistent criteria of GDM caused a big challenge for pregnant women (13, 22), and brought difficulties to the promotion of GDM screening and subsequent management, especially in rural China (13, 22) where the lower GDM screening acceptance and compliance exist (23, 24). Achieving a uniform strategy of GDM is of uppermost priority. Maternal preferences on GDM screening provide us with a new direction of thinking, a more favored strategy could be conducive to improve screening acceptance, compliance and uptake (25). However, most studies in this field have focused on the differences in effectiveness of various screening strategies from the clinical perspective (13, 20), none have explored preferences and choices of screening criteria from the pregnant woman's perspective. Therefore, our present study aimed to investigate pregnant women's preferences for GDM screening to identify their preferred screening option. The findings from this study

can be helpful in efficient resource allocation and healthcare decision-making processes on GDM screening in China.

Materials and methods

Validated guidelines and ethics approval

This study was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR-DOD-16009246; http://www.chictr.org.cn/index.aspx). It was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement for reporting observational studies.

Ethics approvals were obtained from the Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (Approval Number: ZS-1119).

Study setting and sampling

In present China, the screening strategy of two steps was mainly applied in rural areas. Therefore, this study was conducted in a county hospital in Shandong province of China, where two GDM screening strategies are in practice. The per capita income in this county was ∼13,242 Chinese Yuan [CNY] in 2018, which is similar to the average income in 2018 (14,600 CNY) in Chinese rural areas (26, 27). Eligible women were identified from the hospital's obstetric and gynecological outpatient department between 1st November 2016 and 31st January 2017. Women meeting the following study inclusion criteria were considered for the study: (1) clinically presenting at 24–28 weeks of gestation; (2) without overt diabetes before pregnancy (i.e., type 1 diabetes and type 2 diabetes); (3) pregnant with a single fetus; and (4) without severe comorbidities such as hypertension, renal disease, thalassemia, systemic lupus erythematosus, coeliac disease, thyroid disease and physical, or cognitive disability.

We computed a minimum sample size according to Johnson and Orme's formula: $N \geq 500^{*}c/(t^{*}a)$, in which t indicates the number of choice tasks, a indicates the number of alternatives, and c indicates the largest number of levels for any of the attributes (28–30). We also perform a *post hoc* analysis to show the changes of a sufficient sample range when the power of test changed from 0.80 to 0.90, and odds ratio of attributes from 0.1 to 4.0 with α level of 0.05. Trained nurses contacted participants, obtained their written informed consent, and arranged the first appointment.

Discrete choice experiment (DCE)

We investigated pregnant women's preferences for GDM screening using DCE, a commonly adopted stated preference technique (31–33). We hypothesized that the uptake of GDM screening strategies can be described by a set of attributes (e.g., diagnostic rate, number of blood draws). A series of choice tasks was developed to compare pairs of screening profiles featured by predefined multilevel attributes. For each choice task, participants were required to select a screening profile that they preferred to the other profile(s). Based on their repeated choices, the relative preferences for different attributes and levels were estimated.

TABLE 1 Attributes and levels.

Attribute	Level	Conceptual definitions
Number of blood draws	One blood draw Three blood draws Four blood draws	The total number of blood draws of completing GDM screening per pregnant woman
Screening waiting-time	0.5 h 2.0 h 2.5 h	Waiting time from arriving at the outpatient departments to completing GDM screening per pregnant woman
Out-of-pocket costs[#]	10 CNY 30 CNY 60 CNY 90 CNY	Out-of-pocket costs for GDM screening
Number of hospital visits	One hospital visit Two hospital visits	The total number of hospital visits of completing GDM screening per pregnant woman
Diagnostic rate	8.0% 10.5% 17.5%	The positive rate of pregnant women defined with GDM

[#]1 Chinese Yuan (CNY) = USD 0.145 on January 2020.

Attributes and levels

The initial selection of attributes was informed by the literature review (13, 34), pilot individual interviews of pregnant women, and expert interviews (obstetrics and gynecology specialists, endocrinologists, nutritionists, and public health professionals). Five attributes for the DCE were: (1) the number of blood draws (1, 3, and 4); (2) out-of-pocket costs (CNY10, CNY 30, CNY 60 and CNY 90 [1 CNY = 0.145 US Dollar on January 2020]); (3) screening waiting-time (0.5, 2, and 2.5 h); (4) the number of hospital visits (1 and 2); and (5) diagnostic rate (this attribute indicates GDM positive diagnosis rate [8.0, 10.5, and 17.5%]) (Table 1). The diagnostic rate was identified from the literature review (13, 34), and the number of blood draws, screening waiting-time, out-of-pocket costs and the number of hospital visits were identified through the pilot interviews and expert consultations.

Experimental design

With five attributes at two to four levels, a total of 216 ($3^3 \times 4 \times 2$) hypothetical screening profiles were produced, and 46,656 (216×216) choice tasks containing two screening profiles were generated. NGene was used to select a subset of these possible choice tasks with a D-efficient fractional factorial experimental design (35). The D-efficient approach retains optimal orthogonality in a fractional design, and reduces the number of necessary combinations relative to a full orthogonal design. We generated 16 screening options. An example of a DCE choice task is shown in Supplements 1, 2. Accordingly, 14 choice tasks were constructed, and divided into two survey blocks (36, 37). Respondents were randomly assigned to one of the two survey blocks that contained seven choice tasks (37). This study was designed as a forced-choice study, and participants were not allowed to opt-out. Any participants who missed one question of the choice tasks were excluded from this analysis. Further details were revealed in the questionnaires (Supplement Questionnaire).

Questionnaire development and testing

A pilot test was conducted with ten women to test the feasibility of the questionnaire. None of the participants reported any problems with the pilot test, after which the format and wording of the pilot version was refined, and the finalized version was temporarily administered by trained nurses.

The final questionnaire consisted of two sections: general characteristics (including socio-demographics [e.g., maternal age, living areas (rural areas: county and county below [county below included villages and towns]), parity [delivery times: 0 = primipara, 1 = multipara], education, household income and occupation]) and DCE section (comprising of seven choice tasks). We also set a testing question to verify the DCE result on women's preferred choice for "one-step" and "two-step" (Supplement Questionnaires).

The survey commenced with training for participants which included an introduction to the study and predefined multilevel GDM screening attributes. The meaning of diagnosis rate was explained as the positive rate, and the advantages and disadvantages of diagnosis rate was also emphasized in this training.

Statistical analysis

Participants' characteristics were presented as Numbers (N) and percentages (%) for categorical variables, and means with standard deviations (SD) for continuous data. Statistical analyses were performed in STATA version 17 (Stata Corp LP, College Station, TX, USA). Detailed description of the statistical methods was showed in Supplement 3.

Discrete choice data was analyzed using the panel mixed logistic (PML) models with maximum simulated likelihood estimation which accommodated the nature of the data (38). As each respondent completed 7 choice tasks, and that included 14 answers (also be explained 14 samples), these answers (samples) may be correlated. The PML model extends the standard conditional logistic model by allowing one or more of the parameters in the model to be randomly distributed and the coefficients in the model to vary across respondents. It also accounts for preference heterogeneity between respondents, i.e., respondents are allowed to have different preferences, and adjust the standard errors of utility estimates to account for repeated choices by the same individual.

In the analyses, all attributes were specified as random coefficients, and choice scenarios were identified using a grouping variable. Then a higher-level grouping was specified at the level of the respondent to account for multiple choice scenarios per respondent and to account for preference heterogeneity (39).

The theoretical model describing the utility of screening profiles was based on the attributes as follows:

$$U = \hat{\beta}_0 + \hat{\beta}_1 * (\text{3 blood draws}) + \hat{\beta}_2 * (\text{4 blood draws}) + \hat{\beta}_3 * (\text{CNY 30 out-of-pocket costs}) + \hat{\beta}_4 * (\text{CNY 60 out-of-pocket costs}) + \hat{\beta}_5 * (\text{CNY 90 out-of-pocket costs}) + \hat{\beta}_6 * (\text{2 hours screening waiting-time}) + \hat{\beta}_7 * (\text{2.5 hours screening waiting-time}) + \hat{\beta}_8 * (\text{2 hospital visits}) + \hat{\beta}_9 * (\text{10.5\% diagnostic rate}) + \hat{\beta}_{10} * (\text{17.5\% diagnostic rate}) + \hat{\beta}_{11}^{*} \text{attributes} * \text{individual characteristics} + \varepsilon$$

U describes the utility of a specific screening profile based on the attributes that were included in the DCE. The dependent variable represents whether a particular screening profile was chosen. The independent variables are the attribute levels that made up the screening profile (40). $\hat{\beta}_0$ represents the alternative specific constant, $\hat{\beta}_1$ to $\hat{\beta}_{10}$ are the attribute estimates that indicated the relative importance of each attribute. Difference in coefficients (as preference weights) between the most and least favorable levels of an attribute was interpreted as the relative importance of this attribute.

In this DCE model, women's characteristics were covariates. Therefore, we also assumed that individual characteristics, such as living areas, parity, education level and household income, yielded differing interaction effects on attributes (Supplement 4). $\hat{\beta}_{11}$ is the estimate for the interaction between attributes and the individual characteristics.

We further estimated the marginal probabilities when one of attributes changed from lower level to higher one and other attributes were defaulted at mean values or set at specified values. The method and mechanism of changes of probabilities calculation referred WHO's DCE guidelines (37). The formula is

based on regression coefficient ($\hat{\beta}$) of DCE (37):

$$P_i = \frac{e^{\beta' x_i}}{\sum \beta' x_j}$$

Where P_i indicates the changes of uptake probability from a screening profile j to another screening profile i. The changes of uptake probabilities of women with different characteristics were estimated as well.

The uptake probabilities for pregnant women from the least favorable attributes (8% diagnostic rate, CNY 90 out-of-pocket costs, four blood draws, two hospital visits, and 2.5 h screening waiting-time) to the most favorable attributes (17.5% diagnostic rate, CNY 10 out-of-pocket costs, one blood draw, one hospital visit, and 0.5-h screening waiting-time) were estimated. We separately optimized each attribute, and kept the remaining attributes at the least favorable (reference) levels to calculate the changes of uptake probabilities compared with the least favorable option.

We estimated the changes of women's uptake probabilities (37, 41) for the "one-step" strategy (with attributes of 17.5% diagnostic rate, CNY 30 out-of-pocket costs, three blood draws, one hospital visit, and 2-h screening waiting-time) from the first step of "two-step" strategy (with attributes of 8% diagnostic rate, CNY 10 out-of-pocket costs, one blood draw, one hospital visit, and 0.5-h screening waiting-time); and from the entire "two-step" strategy (with attributes of 8% diagnostic rate, CNY 60 out-of-pocket costs, four blood draws, two hospital visits, and 2.5-h screening waiting-time).

Results

Participant characteristics

A total of 309 pregnant women were initially recruited, and 93% ($n = 287$) of them completed the DCE survey (Figure 1 and Supplement 5). The detailed socio-demographic characteristics of these respondents are presented in Table 2. The mean age at enrollment for the included participants was 29.6 ± 5.4 years and the mean gestational week was 24.8±1.7. Over two thirds (66.9%) of the participants lived in villages and towns. The percentage of women with high school degree or above was 46.0%, 78.4% had more than one delivery experience, and a majority (72.5%) reported to have a household income ≤ CNY 60,000.

Discrete choice experiment results

Panel-mixed logistic model

The results of the panel-mixed logistic model are shown in Table 3. Five predefined attributes were associated with pregnant women's preferences. The participants preferred screening profiles that yielded a higher diagnostic rate (for example: 17.5 vs. 8.0%, OR: 2.89; 95% Confidence interval [CI]: 2.10, 3.96), reduced out-of-pocket costs (CNY 90 vs. CNY 10, OR: 0.37; 95%CI: 0.27, 0.49), shorter screening waiting-time (2.5 vs. 0.5 h, OR: 0.62; 95%CI: 0.49, 0.80), fewer hospital visits (2 vs. 1, OR: 0.71; 95%CI: 0.59, 0.85), and fewer number of blood draws (4 vs. 1, OR: 0.54; 95%CI: 0.43,0.68). The estimation of attributes did not change when we adjusted them by women's characteristics (Supplement 6), and our sample size were also sufficient to test these difference of attributes in *post hoc* analysis (Supplement 7).

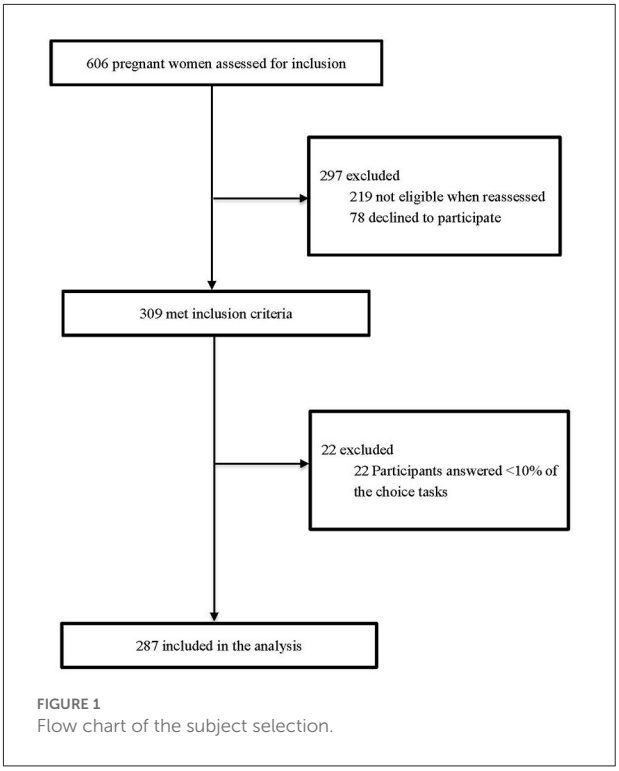

FIGURE 1
Flow chart of the subject selection.

The magnitude of differences in coefficients between the most and least favorable levels of the included attributes showed that the diagnostic rate was most influential in determining pregnant women's GDM screening preferences, followed by out-of-pocket costs, the number of blood draws, screening waiting-time and the number of hospital visits (Table 3).

Maternal changes of uptake probabilities in attributes

The changes of uptake probabilities that reflect the effectiveness of attributes on women's choice were presented in Table 4. When adjusting diagnostic rate from 8.0 to 17.5% (with other attributes set at mean values), women's uptake probabilities for this screening scenario substantially increased by 48.5% (95%CI: 36.4%, 60.6%). While the out-of-pocket cost had negative effect on the uptake probabilities when the cost

TABLE 2 Socio-demographic characteristics of respondents ($N = 287$).

Characteristic	Mean	SD
Age, years	29.6	5.4
Week of gestation, weeks	24.8	1.7
Household income, CNY[#]	52,600	35,200
Traffic cost, Yuan	11.1	29.8
Traffic time, minutes	31.9	50.5
Loss of working day, days	0.7	0.9
	N	**%**
Area of residence		
Living in the county	95	33.1
Living in the villages and towns (outside the county)	192	66.9
Parity		
Primipara	62	21.6
Multipara (≥2 times of gestation)	225	78.4
Education		
Primary school degree	11	2.8
Middle school degree	107	37.3
High school degree	38	13.2
Technical secondary school degree	46	16.0
2 year's college degree	48	16.7
4 years' university degree or above	37	12.9
Occupation		
Professional worker	26	9.1
Civil servant	11	3.8
Blue-collar worker	32	11.2
Farmer	93	32.4
Service personnel	15	5.2
Business owner	26	9.1
Unemployed	84	29.3
Household income		
≤30,000 CNY[#]	85	29.6
30,000∼60,000 CNY	123	42.9
60,000∼100,000 CNY	69	24.0
>100,000 CNY	10	3.5
Medical insurance		
New rural cooperative medical scheme	198	69.0
Urban employment medical insurance	63	22.0
Urban resident medical insurance	8	2.8
Others	18	6.3
Maternity insurance (No)	259	90.2

[#]1 Chinese Yuan (CNY) = USD 0.145 on January 2020.

increased from 10 CNY to 90 CNY (−46.3%, 95%CI: −58.0%, −34.5%). Similarly, the separate estimation of out-of-pocket costs, the number of blood draws, screening waiting-time, or the number of hospital visits showed that changes of the uptake probability changed a lot accordingly, and the variation also revealed the attributes' rank.

With the inclusion of the specific attributes of "one-step" and "two-step" strategies, the changes of women's uptake probability from the full "two-step" strategy to the "one-step" strategy was 71.3% (95%CI: 52.2 to 90.1%). Notably, the results of testing investigation were consistent with the result of DCE (Supplement 8). Finally, there was no significant changes between the uptake probabilities of the "one-step" strategy and the first step of "two-step" strategy (−31.0%, 95%CI: −70.2 to 8.1%).

Interaction effects

Table 5 shows the association between individual characteristics and the women' preferences. We found that women with higher education preferred a screening scenario with higher diagnostic rate (OR: 4.28; $P < 0.001$) and less blood draws (OR: 4.86; $P < 0.001$ for four times blood draws). A similar result was also observed for women who were primipara than those who were multipara (OR: 2.74; $P < 0.001$). But the other individual characteristics had no obvious association with women preference on attributes. Pregnant women living in villages and towns tended to prefer fewer hospital visits and lower out-of-pocket costs compared to those living in the county.

Discussion and conclusion

Discussion

This study is the first to explore pregnant women's preferences for GDM screening from a patient perspective in rural China. Of the two routinely conducted ("one-step" and "two-step") screening strategies in China, the "one-step" strategy was the overall preferred choice for pregnant Chinese women, with the diagnostic rate being the most influential attribute for pregnant women's preferences, followed by out-of-pocket costs, the number of blood draws, screening waiting-time and the number of hospital visits.

Currently, multiple screening methods exist worldwide and this major health services gap regarding an agreed screening method can lead to issues regarding the diagnosis and management of GDM. Achieving an agreement on GDM screening methods has been a major maternal healthcare challenge worldwide, especially in rural China. Rural China is confronted with a healthcare crisis in which the screening rate fails to keep pace with the incidence rate of GDM (23). Therefore, a major healthcare priority for Chinese women should be to increase GDM screening. We established that pregnant Chinese women's preference and acceptance are important factors to achieve an increased rate of GDM screening and treatment (22, 23). This study of patients'

TABLE 3 Attribute estimates of the Panel-mixed logistic model with observations = 4018.

Attributes	Coefficients (95% CI)	OR (95% CI)	Preference estimates	
			P	Relative importance
Diagnostic rate				
8.0%	0.00 (reference)	1.00 (reference)		
10.5%	0.20 (−0.04, 0.44)	1.22 (0.96, 1.55)	0.10	1
17.5%	1.06 (0.74, 1.38)	2.89 (2.10, 3.96)	<0.001	
Out-of-pocket cost[#]				
10 CNY	0.00 (reference)	1.00 (reference)		
30 CNY	−0.68 (−0.99, −0.37)	0.51 (0.37, 0.69)	<0.0	2
60 CNY	−0.82 (−1.08, −0.57)	0.44 (0.34, 0.57)	<0.001	
90 CNY	−1.00 (−1.30, −0.70)	0.37 (0.27, 0.49)	<0.001	
The number of blood draws				
1 draw	0.00 (reference)	1.00 (reference)		
3 draws	−0.69 (−1.09, −0.30)	0.50 (0.34, 0.74)	<0.00	3
4 draws	−0.61 (−0.84, −0.38)	0.54 (0.43, 0.68)	<0.001	
Screening waiting-time				
0.5 h	0.00 (reference)	1.00 (reference)		
2.0 h	−0.24 (−0.44, −0.03)	0.79 (0.64, 0.97)	0.02	4
2.5 h	−0.47 (−0.72, −0.22)	0.62 (0.49, 0.80)	<0.001	
The number of hospital visits				
1 visit	0.00 (reference)	1.00 (reference)		
2 visits	−0.34 (−0.53, −0.16)	0.71 (0.59, 0.85)	<0.001	5
Constant	−1.71 (−2.29, −1.12)	0.18 (0.10, 0.33)	<0.001	

Respondents: 287; Observations: 4018 (287*7*2).
[#]1 Chinese Yuan (CNY) = USD 0.145 on January 2020.
Model: number of blood draws, screening waiting-time, out-of-pocket cost, number of hospital visits, diagnostic rate.

preferences has provided crucial evidence for comparing various screening methods for both the Chinese and international healthcare community.

In 2011, Chinese experts and professional institutions collaborated to develop a new guideline for GDM (42). This guideline suggests that the "one-step" strategy should be adopted in the developed areas of China, whereas the "two-step" could continue to be implemented in underdeveloped areas, considering women's economic conditions and willingness to pay. Importantly, these guidelines are not in line with our study's novel findings. More specifically, we did not observe any association between household income or living areas and women's preferences regarding out-of-pocket costs. We established that household income had no influence on maternal choices, even for pregnant women with lower socio-economic status which was supported by our Supplementary Table 8. Our pilot interview highlighted that with economic development, the successful implementation of poverty-alleviation policies, and increased importance attached to pregnancy in rural China, the costs of routine check-ups during pregnancy may pose only a minor barrier to health care access (43). Furthermore, our findings suggest that pregnant women in rural China preferred a "one-step" strategy to an entire "two-step" strategy. This result is consistent with many clinical and epidemiological studies which established that the "one-step" strategy is more effective in reducing complications during pregnancy (16, 44). For example, the leading HOPA study indicated that there is no lower threshold beyond which hyperglycemia during pregnancy is unproblematic for the offspring (16), and the "one-step" strategy with higher diagnostic rate could therefore reduce missed diagnosis and concomitant maternal and newborn complications. However, if women just need to receive GDM screening with the first step of "two-step" strategy, we find that the superiority of women's preference for "one-step" strategy is not obvious. But we found a huge preference gap between women requiring to receive the first step of "two-step" strategy and the entire "two-step" strategy, which explained the high rejection rate of the full "two-step" strategy among pregnant women in rural China. our previous investigation showed that there was a concerning phenomenon that a big proportion of pregnant women with abnormal glucose value diagnosed by the first step of "two-step" strategy rejected to visit hospital

TABLE 4 Change (%) of uptake probabilities in attributes of GDM screening with observations = 4018.

Changes from baseline	Change in probability	95% CI	*P*
Diagnostic rate			
10.50%	9.8%	(−2.0%, 21.6%)	0.103
17.50%	48.5%	(36.4%, 60.6%)	0.000
Out-of-pocket cost[#]			
30 CNY	−32.7%	(−46.6%, −18.7%)	0.000
60 CNY	−39.0%	(−49.8%, −28.2%)	0.000
90 CNY	−46.3%	(−58.0%, −34.5%)	0.000
The number of blood draws			
3 times	−33.4%	(−51.1%, −15.7%)	0.000
4 times	−30.0%	(−40.2%, −19.2%)	0.000
Screening waiting-time			
2.0 h	−11.9%	(−22.0%, −1.7%)	0.023
2.5 h	−23.2%	(−35.0%, −11.4%)	0.000
The number of hospital visits			
2 visits	−17.1%	(−25.9%, −8.2%)	0.000

Respondents: 287; Observations: 4018 (287*7*2).
[#]1 Chinese Yuan (CNY) = USD 0.145 on January 2020.
The baseline level: diagnostic rate 8.0%, our-of-pocket 10 CNY, number of blood draws 1, screening waiting-time 0.5 h, number of hospital visits 1.

TABLE 5 Results of interaction estimates of individual characteristics and the participant's preferences with observations=4018.

Attributes * characteristics	Preference estimates	
	OR (95% CI)	*P*
Hospital visits *areas		
One hospital visit * Living in the county	1.00 (reference)	
Two hospital visits * Living in the villages and towns	0.76 (0.53, 1.09)	0.136
Out-of-pockets*Areas		
10 CNY[#] of out-of-pocket * Living in the county	1.00 (reference)	
30 CNY of out-of-pocket * Living in the villages and towns	0.87 (0.52, 1.42)	0.578
60 CNY of out-of-pocket * Living in the villages and towns	0.73 (0.41, 1.31)	0.293
90 CNY of out-of-pocket * Living in the villages	0.68 (0.41, 1.10)	0.120
Diagnostic rate *Parity		
8.0% * Multipara (≥2 times of gestation)	1.00 (reference)	
10.5% * Primipara	1.39 (0.88, 2.18)	0.153
17.5% * Primipara	2.74 (1.67, 4.49)	0.000
The number of blood draws * Education		
One time * High school degree below	1.00 (reference)	
Three times * University degree and above	3.33 (1.78, 6.21)	0.000
Four times * University degree and above	4.86 (2.15, 10.9)	0.000
Diagnostic rate* Education		
8.0% * High school degree below	1.00 (reference)	
10.5% * University degree and above	2.37 (1.19, 4.78)	0.015
17.5% * University degree and above	4.28 (2.02, 9.09)	0.000
Waiting time *Occupation		
0.5 h * Non-professional worker	1.00 (reference)	
2.0 h * Professional worker	1.51 (0.83, 2.72)	0.168
2.5 h * Professional worker	0.66 (0.27, 1.61)	0.364
Out-of-pocket cost*Household income		
10 CNY * ≤3,000 CNY[#]	1.00 (reference)	
30 CNY * >100,000 CNY	0.41 (0.11, 1.59)	0.201
60 CNY * >100,000 CNY	0.38 (0.07, 1.98)	0.252
90 CNY * >100,000 CNY	0.41 (0.10, 1.61)	0.207

[#]1 Chinese Yuan (CNY) = USD 0.145 on January 2020.
Model: number of blood draws, screening waiting-time, out-of-pocket cost, number of hospital visits, diagnostic rate, areas, parity, education, occupation, household income, hospital visits *areas, out-of-pockets*areas, diagnostic rate *parity, the number of blood draws * education, diagnostic rate* education, waiting time *occupation, out-of-pocket cost*household income.

again to complete the second step of "two-step" strategy in rural China. Our results implied that the promotion of "one-step" screening strategy with higher diagnostic rate may significantly enhance the uptake and compliance of GDM screening among rural Chinese women; except for those with low GDM risk, and hence, having low probabilities to continue receiving the entire "two-step" GDM screening.

Our findings regarding attributes indeed demonstrated that pregnant women preferred screening methods with a higher diagnostic rate, and other attributes including out of pocket costs, the number of blood draws, screening waiting-time and the number of hospital visits were also influential, nevertheless, not as important as the diagnostic rate. Despite women have been informed in advance that a higher diagnostic rate might lead to misdiagnosis (which may mean they are treated for a condition they do not really have, or they do not receive the proper treatment/advice regarding their true condition), they were more concerned about the adverse health consequences of missed diagnosis compared with misdiagnosis (for example, macrosomia and neonatal hypoglycemia) (16). There is a possibility that participant might not all catch the true meaning of diagnostic rate, as we could not explain all important details to them due to certain limitations surrounding the complexity of the topic. Therefore, women' screening choices might have not been fully informed (even when they were warned of the possible "misdiagnosis" or "miss diagnosis" consequences of the included screening options). However, we do not expect this limitation to materially alter our results on diagnostic rate.

We also observed that women with their first pregnancy paid more attention to diagnostic rate than those with multiple gestation. We did not find any previous studies on the association between parity and diagnostic rate preferences, but

some studies have shown a negative association between parity and screening rates (i.e., higher parity is associated with lower screening rates) (45). Psychological research during pregnancy indicated that women were more cautious and careful during their first pregnancy (46, 47), and they tended to consult more frequently before receiving a new test. In contrast, multipara paid less attention to this aspect due to their previous experience of safe childbirth (48). We suggest that this psychological phenomenon regarding pregnant women and their previous experience regarding gestation could partly explain our findings. As China now allows each family to have two children and subsequently more middle-aged women experience a second pregnancy, the incidence of GDM is likely to substantially rise in China in the next 5–10 years (49). Multipara's attention to GDM screening is important and could be improved by providing more information and education on the adverse health consequences of GDM and the subsequent benefits of improved blood glucose control.

The number of blood draws was identified as another important attribute. Our findings showed that more blood draws suggested a lower probability of pregnant women wanting GDM screening. This influence was also reflected in women's preferences for one step with a smaller number of blood draws. Some previous studies have indicated that blood draws might give rise to anxiety among pregnant women as they feel worried about the potential adverse consequences of multiple blood draws on the health of their babies (46). This finding indicates that increased consultation (such as the targeted sharing of validated information) and/or psychological counseling for pregnant women may increase rates of GDM screening. Previous studies have also shown that more psychological counseling will significantly increase these women's compliance (47).

Our study has several strengths. First, it uses DCE to elicit preferences, which takes into account patients' desires and feelings that are often ignored. Second, to improve the comprehension of DCE and the precision of parameter estimates in this study, a face-to-face pilot study was conducted in advance, and an explanation on how to complete the choice tasks as well as an example choice task were provided to the respondents. Third, even though our results are based on data from a single county in rural China and may have generalizability concerns, we do not regard it as a significant issue as women's maternal preference in rural China are not expected to materially differ from others. A report of Women's willingness on antenatal care in rural areas revealed that there are many aspects that are universal and consistent in China (50). Our preference findings of Chinese rural women have important representative value for healthcare decision-making.

This study also has some limitations. First, the investigation of the effects of various attributes using a hypothetical choice setting can result in hypothetical bias, as some hypothetical screening profiles may not exist in real-life situations. Second, our study did not consider the treatment costs deriving from false diagnoses (misdiagnosis or missed diagnosis), but we understand that these costs should be considered into policy making in the future. Third, the questionnaire was administrated and instructed by trained nurses who were familiar with participants, which may have led to some degree of response bias. Forth, compared with some nationally designated poor counties, the selected county in our study has relatively high socioeconomic and health outcomes so the generalizability of cost preference findings to pregnant women from poorer parts of rural China may be questioned, underlining the importance of conducting further studies in diverse parts of China. Finally, the preferences of women living in urban areas and other areas (west, south, and middle areas) areas are still unknown and should be investigated to enable rural vs. urban comparisons. Larger confirmatory studies with rural population are also recommended using data from multiple rural locations to validate/extend our exploratory findings.

Conclusion

Pregnant women's preferences for GDM screening were associated with several attributes, with the diagnostic rate identified as the most important when choosing a screening method from patients' perspective. Our findings suggest that compared with the entire "two-step" strategy, the "one-step" strategy (with a higher diagnostic rate, lower out-of-pocket costs, fewer number of blood draws, shorter screening wait-time and fewer hospital visits) is more suitable to the circumstances of rural Chinese pregnant women, particularly for those with high GDM risk, low socioeconomic backgrounds and living in remote locations (i.e., villages and towns). This exploratory study provided a new direction to counter the negative influence of inconsistent GDM screening methods in China. We suggest a larger confirmatory in diverse regions study to validate our exploratory findings.

Practice implications

The results provide insight that can be used to instruct the implementation of GDM screening for clinical practice, explore barriers to the promotion of GDM screening rate, and tailor screening advice based on individual characteristics that meet women' needs, especially the need to improve GDM management among people with risk factors of gestation diabetes in China.

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 Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (Approval Number: ZS-1119). The patients/participants provided their written informed consent to participate in this study.

Author contributions

TX conceptualized and designed the study, conducted the data analyses, wrote the first draft of the manuscript, and contributed to the interpretation of results. HF and AP reviewed and substantially revised the manuscript. QX, JC, and HA reviewed and edited the manuscript substantially. YJ, XG, DY, and LM contributed to the interpretation of results and critically reviewed and edited the manuscript for important intellectual content. XL contributed to the revision and improvement of the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.864482/full#supplementary-material

SUPPLEMENT 1
A list of screening strategies produced by factorial designs.

SUPPLEMENT 2
An example of a choice tasks.

SUPPLEMENT 3
Detailed description of the statistical methods.

SUPPLEMENT 4
Individual characteristic in interaction terms.

SUPPLEMENT 5
Socio-demographic characteristics of 287 included respondents and 22 excluded participants.

SUPPLEMENT 6
Attribute estimates of the Panel-mixed logistic model adjusted by women's characteristics.

SUPPLEMENT 7
Post-hoc analysis for DCE sample.

SUPPLEMENT 8
Results of interaction estimates of household income with five attributes.

SUPPLEMENT 9
Maternal preferred choice for "one-step" and "two-step" strategy.

SUPPLEMENT 10
DCE Questionnaire.

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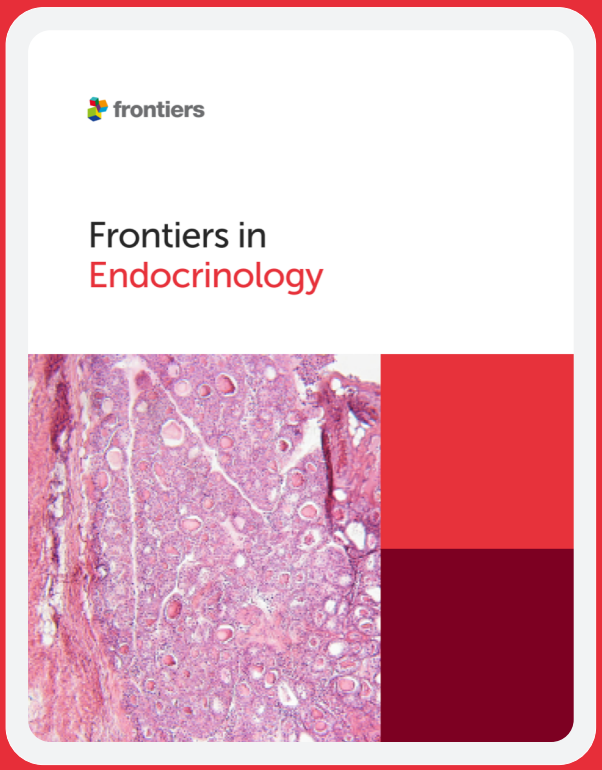

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