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Current and future trends in gestational diabetes diagnosis, care and neonatal outcomes

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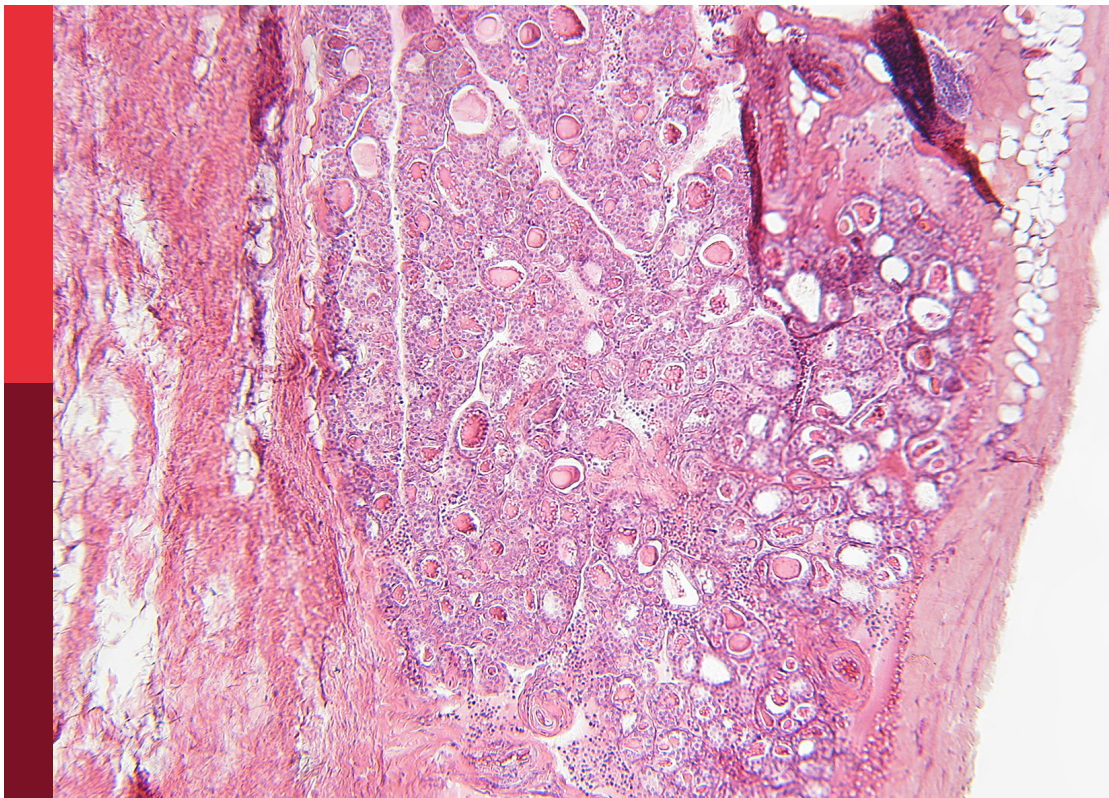

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Current and future trends in gestational diabetes diagnosis, care and neonatal outcomes

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Editorial: Current and future trends in gestational diabetes diagnosis, care and neonatal outcomes

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gestational diabetes (GDM), diabetes, newborn, neonatal hypoglycemia, neonatal care, pregnancy

Editorial on the Research Topic

Current and future trends in gestational diabetes diagnosis, care and neonatal outcomes

This Research Topic encompasses fourteen curated contributions, each covering different aspects.

Gestational Diabetes Mellitus (GDM), is defined by the World Health Organization as glucose intolerance or hyperglycemia that is first recognized or appears during pregnancy. Over the past two decades, due to lifestyle modifications and a rise in maternal age, the prevalence of GDM has increased significantly, with studies suggesting rates between 1-26%. The ever-rising incidence of GDM varies from 3% to 21.2% in Asia and 0.31% to 18% globally. In the United Arab Emirates (UAE), GDM prevalence fluctuates between 7.9% and 24.9%, with peaks of 37.7%. These variations are due to different diagnostic criteria, timing, and screening methods, with Oral Glucose Tolerance Test (OGTT) screenings typically performed around 24-28 weeks of gestation.

Bashir et al. conducted a study comparing six GDM diagnostic criteria within the Emirati population of the UAE, revealing incidence rates ranging from 8.4% to 21.5%. The most inclusive diagnostic criteria were represented by the National Institute for Health and Clinical Excellence (NICE 2015) and the International Association of Diabetes and Pregnancy Study Groups (IADPSG). On the contrary, the European Association for the Study of Diabetes (EASD 1996) and the New Zealand Society for the Study of Diabetes

(NZSSD) criteria were the least inclusive in this population. These findings emphasize the discrepancies among diagnostic criteria for GDM and highlight the need for a universal accurate set of GDM diagnostic criteria to promote consistent incidence estimates and consequent healthcare planning.

Insulin resistance, a significant factor in the development of GDM in late pregnancy, correlates with a reduced presence of butyrate-producing bacteria. A study by Liu et al. explored the composition and evolution of intestinal microbiota from the second to the third trimester in women with GDM, compared to those with normal glucose tolerance during pregnancy. The study revealed noticeably higher levels of *Scardovia* and *Propionibacterium* in the third trimester compared to the second in the control group, a pattern not observed in the GDM group. *Propionibacterium* is reported to improve insulin resistance. Taken together, these findings suggest that variances in gut microbiota may be implicated in GDM pathogenesis.

Failure to manage GDM adequately can lead to short-term and long-term adverse maternal and neonatal outcomes. Short-term maternal complications can encompass preeclampsia, cesarean section, and polyhydramnios, while long-term issues might include post-pregnancy progression to diabetes mellitus, affecting both younger and older women. Furthermore, placental health may also be influenced by maternal age. An elevated risk for placental abruption and placenta previa was identified only in younger women with GDM. However, while the risk for polyhydramnios and preeclampsia was increased in both age groups, an additive interaction of GDM and advanced maternal age was observed (Li et al.). Fetal and neonatal complications can encompass congenital malformation, neonatal death, stillbirth, macrosomia, obstetric trauma, shoulder dystocia, and neonatal hypoglycemia. Early identification and management of women at risk for GDM is crucial, as exposure to intrauterine hyperglycemia before 24–28 weeks of gestation can contribute to abnormal fetal growth and development. The impact of GDM on offspring's auxological parameter is observable at birth and may persist throughout late childhood. A study by Li et al. reported that GDM that is adequately controlled without the need for drug therapy, was associated with regular birth auxological parameters. However, the same children showed a weight gain during infancy that lagged behind compared to those of the control group.

Maternal anthropometric and metabolic factors, as well as fetal metabolic parameters, exert unique influences on the physical growth parameters of offspring during their inaugural year of life. A research study conducted by Antoniou et al. revealed that certain maternal metabolic parameters, such as high-density lipoprotein cholesterol (HDL), demonstrated a negative correlation with the physical growth measurements of offspring at birth and at 6-8 weeks. On the other hand, glycated hemoglobin (HbA1c) exhibited a positive correlation with offspring growth measurements at the one-year mark. Maternal physical anthropometric parameters, including body mass index (BMI) and fat mass, were predictors of larger physical measurements in offspring at birth. In addition, there was a positive correlation between cord blood HDL and birth weight. In contrast, cord blood insulin, C-peptide, and homeostasis model assessment-insulin resistance (HOMA-IR) demonstrated positive correlations with birth and 6-8 weeks measurements, but they were negatively associated with measurements at one year.

Li et al. created a predictive tool for GDM, employing a variety of fundamental clinical factors easily and inexpensively obtained through patient history and routine blood tests. Factors such as maternal age, blood urea nitrogen (BUN), fibrinogen to albumin ratio (FAR), blood urea nitrogen to albumin ratio (BUN/ALB), and blood urea nitrogen to creatinine ratio (BUN/Cr) were included. This model shows potential for wide application in less developed and developing countries where GDM rates are sharply increasing.

In a separate study, Hu et al. suggested the use of the extreme gradient boosting (XG boost) machine learning algorithm to predict GDM. This model employed twenty predictors incorporating demographic data, clinical attributes, and laboratory parameters. In comparison to the logistic regression (LR) model, which used only four predictors: history of GDM, age, levels of glycated hemoglobin (HbA_{1c}), and mean arterial pressure, the XG boost model demonstrated superior accuracy.

Among the glucose parameters for identifying women at risk of GDM, we would like to emphasize HbA1c, which reflects the glucose status of the preceding few weeks. High HbA1c levels and those at the upper normal limit at the time of GDM diagnosis could indicate poor glucose control during early pregnancy. Several studies have reported that adverse outcomes in early pregnancy may be predicted by elevated HbA1c. The study by Muhuza et al. confirmed that patients with HbA1c $\geq$ 5.5% at the time of diagnosis had a significantly increased risk of macrosomia, preterm delivery, pregnancy-induced hypertension (PIH), and primary cesarean section.

The GDM predictive models mentioned above, developed by Li et al. and Hu et al. could aid the clinical management of pregnant women at early gestational ages and prevent the onset of GDM in at-risk individuals through lifestyle changes, which may not be effective if initiated at later stages.

Close counseling and follow-up during pregnancy in women at risk for GDM lead to better glucose control, reduced HbA1c levels, improved health, and better pregnancy outcomes. Recently in China, the identification and treatment of women with GDM have enabled a reduction in the prevalence of macrosomia and large for gestational age (LGA), probably secondary to superior glucose control (He et al.).

Maternal dyslipidemia is a common occurrence in pregnancy. Particularly, hyperlipidemia is frequently observed in the latter half of pregnancy and is considered a necessary biologically mechanism for the fetus' energy supply. Insulin resistance and a relative lack of insulin secretion in pregnancies complicated by GDM result in higher serum triglycerides (TRG) and lower HDL-cholesterol. You et al. demonstrated that the triglyceride to high-density lipoprotein cholesterol ratio (TRG/HDL) at 10-14 weeks was positively associated with GDM, and was superior to TRG, HDL, low-density lipoprotein (LDL), and HOMA-IR for predicting GDM.

The management of GDM includes appropriate glucose control, achieved through non-pharmacological and pharmacological therapy. Continuous glucose monitoring provides glucometrics that may be more insightful that regular capillary blood glucose measurements. The study by Dingena et al. showed that there was an increased glucose variability during the day albeit within the

normal range. Interestingly, nighttime readings showed prolonged periods of lower glucose levels with relatively less glucose variability.

The primary treatment for GDM typically consists of dietary and lifestyle modifications. A study by Bashir et al. (1) suggested that 80% of women with GDM can achieve normal glucose levels through diet and lifestyle modification alone. Pharmacological therapy for GDM management is required in only 17-30% of cases, but in the study by Brzozowska et al., only 33% of GDM patients achieved an adequate glucose control with diet alone. These authors identified fasting plasma glucose as a predictor of the requirement for pharmacologic treatment, in line with factors identified in previous studies: early GDM diagnosis, a family history of diabetes, non-European ethnicity, advanced age, elevated fasting blood glucose level, HbA_{1c} at GDM diagnosis, and an elevated pre-pregnancy BMI. Continuous glucose monitoring also allow women and healthcare professionals to ascertain whether lifestyle changes are effective in achieving adequate glucose control, or whether pharmacological treatment is necessary.

Although insulin is the current standard treatment, dose titration is often challenging due to risks of glucose variability and hypo-/hyperglycemia. Frequent glucose monitoring and additional education is also a burden. Over the last 20 years, oral hypoglycemic agents (OHAs), primarily glyburide and metformin, have been used. Despite the increasing amount of evidence supporting the use of metformin for GDM (2), the American Diabetes Association (ADA) and American College of Obstetricians and Gynecologists (ACOG) still recommend insulin as the first line of treatment if glucose targets are not achieved with lifestyle interventions. This recommendation stems from the lack of evidence regarding the long-term safety of other drug treatments. On the contrary, the National Institute for Health and Care Excellence (NICE) and Canadian guidelines recommend metformin as the first line treatment. Metformin reduces hepatic gluconeogenesis and increases peripheral glucose uptake without the risk of hypoglycemia.

Several studies support the safety and efficacy of metformin use in GDM as it is associated with less weight gain and a lower risk of neonatal hypoglycemia compared to insulin. Furthermore, metformin's low cost, low risk of maternal hypoglycemia, and the lack of need for educational programs or intensive glucose control, make it an attractive therapeutic candidate (Tosti et al.).

However, metformin is not universally accepted as the first treatment option due to the lack of consistent evidence of long-term safety, including its diffusion across the placenta, resulting in comparable fetal and maternal drug levels.

Rowan et al. (3) and Paavilainem et al. (4)showed no significant differences in offspring auxological parameters during follow-up. In this study, newborns of metformin-treated mothers with GDM had superior glucose and lipid profiles at follow-up compared to those born from insulin-treated mothers with GDM. On the contrary, the meta-analysis by Tarry-Adkins et al, reported that infants that were exposed to metformin *in utero*, displayed an accelerated post-natal growth (5).

As for technology, although reports have described successful use of insulin pumps in patients with GDM, their use in this context is still sporadic. This is due to lack of clear data suggesting a superior cost-effectiveness than conventional treatments.

Beyond insulin and metformin, taurine could serve as another therapeutic alternative due to its insulin-sensitizing effect. A study conducted by Wang et al. investigated the changes in serum taurine throughout pregnancy and found that these levels were markedly lower during the first trimester in women who subsequently developed GDM. Consequently, taurine may also be used as a diagnostic marker since it has demonstrated the potential to boost insulin sensitivity, stimulate insulin secretion, and diminish inflammation and oxidative stress.

In summary, recent research has not only confirmed the increasing prevalence and potential risks of GDM but also brought forth potential predictors, management strategies, and long-term implications. This information bolsters our understanding of GDM and the multifaceted efforts required to address it effectively. Ongoing research into alternative monitoring and treatment strategies, is crucial to diversify the therapeutic options and ensure optimal care for those affected by GDM.

Author contributions

GF: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. ES: Supervision, Validation, Writing – review & editing. RC: Supervision, Validation, Writing – review & editing. FS: Writing – original draft, Writing – review & editing. MS: Supervision, Validation, Writing – review & editing. AP: Writing – review & editing, Supervision, Validation.

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.

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Incidence of gestational diabetes mellitus in the United Arab Emirates; comparison of six diagnostic criteria: The Mutaba'ah Study

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Background: For more than half a century, there has been much research and controversies on how to accurately screen for and diagnose gestational diabetes mellitus (GDM). There is a paucity of updated research among the Emirati population in the United Arab Emirates (UAE). The lack of a uniform GDM diagnostic criteria results in the inability to accurately combine or compare the disease burden worldwide and locally. This study aimed to compare the incidence of GDM in the Emirati population using six diagnostic criteria for GDM.

Methods: The Mutaba'ah study is the largest multi-center mother and child cohort study in the UAE with an 18-year follow-up. We included singleton pregnancies from the Mutaba'ah cohort screened with the oral glucose tolerance test (OGTT) at 24–32 weeks from May 2017 to March 2021. We excluded patients with known diabetes and with newly diagnosed diabetes. GDM cumulative incidence was determined using the six specified criteria. GDM risk factors were compared using chi-square and t-tests. Agreements among the six criteria were assessed using kappa statistics.

Results: A total of 2,546 women were included with a mean age of 30.5 ± 6.0 years. Mean gravidity was 3.5 ± 2.1, and mean body mass index (BMI) at booking was 27.7 ± 5.6 kg/m^2. GDM incidence as diagnosed by any of the six criteria collectively was 27.1%. It ranged from 8.4% according to the EASD 1996 criteria to 21.5% according to the NICE 2015 criteria. The two most inclusive criteria were the NICE 2015 and the IADPSG criteria with GDM incidence rates of 21.5% (95% CI: 19.9, 23.1) and 21.3% (95% CI: 19.8, 23.0), respectively. Agreement between the two criteria was moderate ($k = 0.66$; $p < 0.001$). The least inclusive was the EASD 1996 criteria [8.4% (95% CI: 7.3, 9.6)]. The locally recommended IADPSG/

WHO 2013 criteria had weak to moderate agreement with the other criteria, with Cohen's kappa coefficient ranging from (k = 0.51; p < 0.001) to (k = 0.71; p < 0.001). Most of the GDM risk factors assessed were significantly higher among those with GDM (p < 0.005) identified by all criteria.

Conclusions: The findings indicate discrepancies among the diagnostic criteria in identifying GDM cases. This emphasizes the need to unify GDM diagnostic criteria in this population to provide accurate and reliable incidence estimates for healthcare planning, especially because the agreement with the recommended criteria was not optimal.

KEYWORDS

gestational diabetes mellitus, incidence, IADPSG, diabetes, risk factors, diagnostic criteria, United Arab Emirates

Introduction

For over half a century, there have been many controversies on the standard way to screen for and diagnose gestational diabetes mellitus (GDM) among pregnant women, yet there is still no single globally acceptable guideline for this purpose. Lack of evidence, availability of resources, convenience, different expert opinions, differences between populations' risks, and many other reasons have contributed to this challenge (1, 2). The prevalence of GDM in the United Arab Emirates (UAE) ranges from 7.9% to 24.9% (3) and, in some cases, up to 37.7% (4). These variations are due to different diagnostic criteria, the timing of screening, screening methods, and sub-populations, among other factors (5).

Over the years, globally, different diagnostic criteria and recommendations for screening and diagnosing GDM have been published. Most widely used criteria include the International Association of Diabetes and Pregnancy Study Groups (IADPSG 2010) (6), World Health Organization (WHO 2013) (7), WHO (1999) (8), the American Diabetes Association (ADA 2018) (9), the Australasian Diabetes in Pregnancy Society (ADIPS 1998) (10), the National Institute for Health and Clinical Excellence (NICE 2015) (11), the Canadian Diabetes Association (CDA 2013) (12), Carpenter and Coustan criteria (C&C 1982) (13), National Diabetes Data Group (NDDG 1979) (14), European Association for the Study of Diabetes (EASD 1996) (15), New Zealand Society for the Study of Diabetes criteria (NZSSD) (16), and the International Federation of Gynecology and Obstetrics (FIGO 2015) (17).

The IADPSG is currently one of the most acceptable and widely used criteria globally because it is based on the results of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study (18), which is a multi-center, multinational, blinded prospective cohort study and is potentially one of the most generalizable regarding this topic. Some guidelines have been updated according to the IADPSG recommendations [e.g., WHO 2013, FIGO 2015, ADIPS 2017, ADA 2018 (alternate), and CDA 2013 (alternate)], although many others have not (2). Lack of a uniform standardized global guideline results in the inability to accurately combine or compare the disease burden worldwide or even at a local level and develop a simple, standardized GDM management protocol that could be applied globally (1).).

Different diagnostic criteria have been found to classify GDM differently (19–25). In the Gulf region, a recent study in Oman showed that 48.5% of patients with GDM were identified by the IADPSG (WHO 2013) criteria and only 26.4% by the former WHO 1999 criteria (26). Meanwhile, a study in Qatar showed that 21.5% of patients with GDM were identified by the WHO 2013 criteria (IADPSG) and 20.1% by the NICE criteria, with a kappa coefficient of 0.67 showing moderate agreement between the two criteria (27). The IADPSG criteria generally diagnose more patients with GDM than the other criteria (28). A study conducted in the UAE in 2005 showed that the ADIPS criteria were the most inclusive in diagnosing GDM at the time (3), while 10 years later, in a similar population, the IADPSG was found to be the most inclusive, with GDM prevalence rate ranging from 9.2% to 45.3% using different criteria (29). These studies were conducted among multi-ethnic women.

Abbreviations: GDM, gestational diabetes mellitus; DM, diabetes mellitus; IADPSG, International Association of Diabetes and Pregnancy Study Groups; NICE, National Institute for Health and Clinical Excellence; WHO, World Health Organization; ADIPS, Australasian Diabetes in Pregnancy Society; EASD, European Association for the Study of Diabetes; NZSSD, New Zealand Society for the Study of Diabetes; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; mmol/L, millimoles per liter; CI, confidence interval; BMI, body mass index; UAE, United Arab Emirates.

The effect of ethnicity on GDM has been well researched at the local and global levels showing varying GDM risks across different ethnicities (30, 31). The Emirati population, which is the local population of the UAE, has been described to have one of the highest prevalence of cardiovascular risk factors reported in the country and worldwide (32). However, very few studies have been conducted in this population to describe the effect of different diagnostic criteria on GDM incidence. This study aims to compare the incidence of GDM using the IADPSG, WHO 1999, NICE 2015, ADIPS 1998, EASD 1996, and NZSSD 2004 criteria among the Emirati population in the UAE. It also assesses the GDM risk factor distribution according to each GDM criterion and compares agreement between the different criteria used.

Materials and methods

Study design and setting

The Mutaba'ah study is the largest ongoing prospective mother and child cohort study in the UAE, recruiting women from the Emirati population during pregnancy and following them up during antenatal, birth, and postnatal periods and their children until the age of 18 years. It is being conducted in the city of Al Ain, Abu Dhabi Emirate, UAE, which has the highest proportion (30.8%) of Emirati Nationals in the country, of which women constitute 49%. Recruitment of participants is from the two major tertiary public hospitals and the largest private maternity hospital in the city. Details of the Mutaba'ah Study, including the recruitment process, have been published elsewhere (33).

Participants

This study analyzed data from the pregnant women (Mutaba'ah Mother and Child Cohort Study) recruited between May 2017 and March 2021. Those screened for GDM at 24 to 32 weeks (with at least one reading) were included in this analysis. Only singleton pregnancies were included. Those with pre-existing diabetes or fasting blood glucose (FBG) of ≥7 mmol/L and/or 2-h OGTT (oral glucose tolerance test) ≥ 11.1 mmol/L [i.e., newly diagnosed type 2 diabetes mellitus (DM) cases] were excluded.

Sample size

A minimum sample of 707 participants will allow for the detection of a true proportion (37.7%) of GDM cases identified by IADPSG criteria (4), given an 80% power and a 1% alpha error and considering a non-response rate of 20%. Estimation was done using online OpenEpi version 3.01.

Data collection and variables

Data were collected using a self-administered questionnaire and extraction from the medical records. The questionnaire was administered at 12–25 weeks of gestation to the participants by trained research assistants using a tablet containing the questionnaire link, which is directly uploaded to the study database upon completion. It assessed information including sociodemographic, past, and current pregnancy history, medical history, and other factors. The questionnaire was available in both English and Arabic versions. Medical records were used to obtain other information on the current pregnancy, including all anthropometric measurements, laboratory results (including OGTT results), and details of previous pregnancies. For this analysis, data utilized included participants age, gravidity, body weight, height, and body mass index (BMI) at booking; personal history of diagnosis with GDM; family history of type 2 DM; level of education; employment status; and OGTT results.

GDM screening and diagnosis

GDM screening in the public and private recruiting hospitals was similar. The recommendation was for all pregnant women to undergo universal screening with 75-g 2-h OGTT at 24 to 28 weeks of pregnancy during routine antenatal care (ANC) visits. At the first visit (<24 weeks), all women undergo a fasting plasma glucose (FPG) test or a HbA1C test to detect patients with pre-existing diabetes who were then co-managed with the endocrinologists. For GDM diagnosis in this study, we used six different diagnostic criteria, which are part of the most widely used in the UAE (34), and they all endorse universal one-step screening with 75-g OGTT at 24 to 28 weeks of gestation as done in the recruiting hospitals. They include IADPSG [WHO 2013/FIGO 2015/ADIPS 2017/ADA 2018 (alternate)/CDA 2013 (alternate)], NICE 2015, WHO 1999 (NICE 2008), ADIPS 1998, EASD 1996, and NZSSD 2004. Standard definitions are described in Table 1.

Statistical analysis

Data analyses were conducted in Stata statistical software version 16.1 (StataCorp LLC, College Station, TX, USA). Continuous variables were summarized using means with standard deviations (SD), whereas the categorical variables were summarized using counts and proportions. GDM risk factors and other maternal characteristics were compared using chi-square test for categorical variables and *t*-test for continuous variables. An alpha level of significance was specified at 5%.

Cumulative incidence of GDM (by the six diagnostic criteria) from May 2017 to March 2021 was calculated as the number of pregnant women with GDM (as identified by a specific diagnostic

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TABLE 1 GDM screening and diagnostic criteria.

	Population to screen	Timing of screening	Type of screening test	No. of abnormal values	Fasting plasma glucose (mmol/L)	1-h OGTT (mmol/L)	2-h OGTT (mmol/L)	3-h OGTT (mmol/L)
IADPSG/WHO 2013/FIGO 2015/ ADIPS 2017/ADA 2018 (alternate)/ CDA 2013 (alternate)	Universal screening	24–28 weeks	One step, 2 h, 75 g	≥1	5.1	10.0	8.5	-
WHO 1999/NICE 2008	Universal screening	24–28 weeks	One step, 2 h, 75 g	≥1	7.0*	-	7.8	-
NICE 2015/RCOG	Selective/ Universal screening	24–28 weeks	One step, 2 h, 75 g	≥1	5.6	-	7.8	-
ADIPS 1998	Universal screening	24–28 weeks	One step, 2 h, 75 g	≥1	5.5	-	8.0	-
EASD 1996	Universal screening	24–28 weeks	One step, 2 h, 75 g	≥1	6.0	-	9.0	-
NZSSD 2004	Universal screening	24–28 weeks	One step, 2 h, 75 g	≥1	5.5	-	9.0	-
NZSSD 2014	Universal screening	24–28 weeks	Two steps, 2 h, 75 g	≥1	5.5	-	9.0	-
CDA 2013 (preferred)	Universal screening	First visit	Two steps, 2 h, 75 g	≥2	5.3	10.6	9.0	-
ADA 2018	Universal screening	24–28 weeks	Two steps, 3 h, 100 g	≥2	5.3	10.0	8.6	7.8
C&C 1982/ACOG2013/ADA 2004	Selective screening	First visit	Two steps, 3 h, 100 g	≥2	5.3	10.0	8.6	7.8
NDDG 1979	Selective screening	First visit	Two steps, 3 h, 100 g	≥2	5.9	10.6	9.2	8.1
Modified NDDG	Selective screening	First visit	Two steps, 3 h, 100 g	≥2	5.3	10.1	8.7	7.8

*Fasting plasma glucose threshold currently falls under the updated WHO criteria for existing diabetes mellitus. IADPSG, International Association of Diabetes and Pregnancy Study Groups; NICE, National Institute for Health and Clinical Excellence; WHO, World Health Organization; ADIPS, Australasian Diabetes in Pregnancy Society; EASD, European Association for the Study of Diabetes; NZSSD, New Zealand Society for the Study of Diabetes; RCOG, Royal College of Obstetricians & Gynaecologists; ACOG, American College of Obstetricians & Gynaecologists.

criterion) divided by the total number of eligible pregnant women screened during the period multiplied by 100. Results were reported with their logit confidence intervals.

Agreements between the six diagnostic criteria were compared (in pairs) using kappa statistics. Cohen's kappa coefficient (k) for each pair was reported. P-value was significant at <0.05.

Because of the missing values of some of the OGTT readings, we conducted sensitivity analysis to check for GDM cumulative incidences stratified by the number of non-missing OGTT readings used for diagnosis, i.e., those having at least one versus those having at least two OGTT readings.

Results

A total of 2,586 pregnant women with singleton pregnancies were recruited and screened for GDM at 24 to 32 weeks of gestation during the study period. Thirty-nine patients with newly diagnosed diabetes and one patient with known diabetes were excluded. Hence, 2,546 patients were eligible to participate and included in the analyses.

Participants' characteristics

Table 2 shows the maternal characteristics. The mean (± SD) age of the cohort was 30.5 ± 6.0 years, mean gravidity was 3.5 ± 2.1 pregnancies, and mean BMI at booking was 27.7 ± 5.6 kg/m^2. Majority (94.7%) of the participants had at least a high school education, and 31.0% were employed. A fifth (20.6%) had previous GDM, and more than a quarter (29.6%) had a family history of type 2 DM. Their mean FPG was 4.6 ± 0.4 mmol/L, 1-h OGTT was 8.0 ± 1.9 mmol/L, and 2-h OGTT was 6.5 ± 1.6 mmol/L.

GDM incidence by different diagnostic criteria

Figure 1 compares the GDM cumulative incidence diagnosed by the six different criteria. The NICE 2015 and the IADPSG criteria were the most inclusive in this population, showing GDM incidence rates of 21.5% (95% CI: 19.9, 23.1) and 21.3% (95% CI: 19.8, 23.0), respectively. The EASD 1996 criteria showed the lowest GDM incidence rate of 8.4% (95% CI: 7.3, 9.6).

TABLE 2 Baseline characteristics of participants (N = 2,546).

Maternal Characteristics	Total Participants (N)[a]	Frequency [n (%)]	Mean ± SD
Age (years)	2,544		30.5 ± 6.0
Gravidity	2,546		3.5 ± 2.1
Educational status	2,345		
Primary and below		125 (5.3)	
High school		975 (41.6)	
Diploma		244 (10.4)	
Bachelors		912 (38.9)	
Postgraduate		89 (3.8)	
Employment status	2,348		
Student		219 (9.3)	
Housewife		1151 (49.0)	
Unemployed		252 (10.7)	
Employed		726 (31.0)	
Body weight (kg) at booking	2,546		69.6 ± 14.6
Height (m)	2,546		1.6 ± 0.1
BMI (kg/m^2) at booking	2,546		27.7 ± 5.6
Previous history of GDM	2,047	422 (20.6)	
Family history of type 2 diabetes	2,546	754 (29.6)	
Oral Glucose Tolerance Test (OGTT) results in mmol/L (at 24 to 32 weeks of gestation)			
Fasting plasma glucose (FPG)	1,188		4.6 ± 0.4
1-h OGTT	1,548		8.0 ± 1.9
2-h OGTT	2,443		6.5 ± 1.6

BMI, body mass index; kg, kilograms; m, meters; mmol/L, millimoles per liter.
[a]Total number of participants who had data for a particular variable.

GDM risk factors by different criteria

Table 3 shows the distribution of GDM risk factors according to the six diagnostic criteria. Compared with the non-GDM group identified by each diagnostic criterion, most of the risk factors were significantly higher among those with GDM ($p < 0.005$). An exception is seen for family history of type 2 DM using the EASD 1996 criteria ($p > 0.05$). Table 4 also shows the distribution of the GDM risk factors according to the six diagnostic criteria, but, in this instance, the comparison group was non-GDM participants identified by all six criteria. Here, also, risk factors were significantly higher among those with GDM ($p < 0.001$) across all criteria.

Agreement among the different GDM diagnostic criteria

Table 5 compares the agreement between the diagnostic criteria in pairs. Agreement between the two most inclusive criteria (NICE 2015 and IADPSG criteria) was moderate, with Cohen's kappa coefficient (k) of 0.66; $p < 0.001$. The highest agreement was between the NICE 2015 and WHO 1999 criteria (0.99; $p < 0.001$), whereas the lowest was between the NZSSD 2004 and WHO 1999 criteria (0.49; $p < 0.001$). The locally recommended IADPSG/WHO 2013 criteria had weak to moderate agreement with the other criteria, with Cohen's kappa coefficient ranging from ($k = 0.51$; $p < 0.001$) to ($k = 0.71$; $p < 0.001$).

Sensitivity analysis

Table 6 stratifies the GDM cumulative incidence by the number of non-missing OGTT readings used for diagnosis, i.e., those having at least one versus those having at least two OGTT readings. GDM incidence rate ranged from 8.4% using the EASD 1996 criteria to 21.5% using the NICE 2015 criteria among those who had at least one reading and 8.8% using the EASD 1996 criteria to 22.3% using the NICE 2015 criteria among those who had at least two readings. There was minimal change in the GDM incidence between these two groups. The NICE criteria remained the most inclusive in both groups; however, the WHO 1999 criteria were slightly more inclusive than the IADPSG criteria in the group having at least two non-missing readings [21.9 (20.2, 23.5) vs. 21.6 (20.0, 23.3), respectively].

Discussion

This study showed that GDM incidence differed among the Emirati population in the UAE, ranging from 8.4% according to

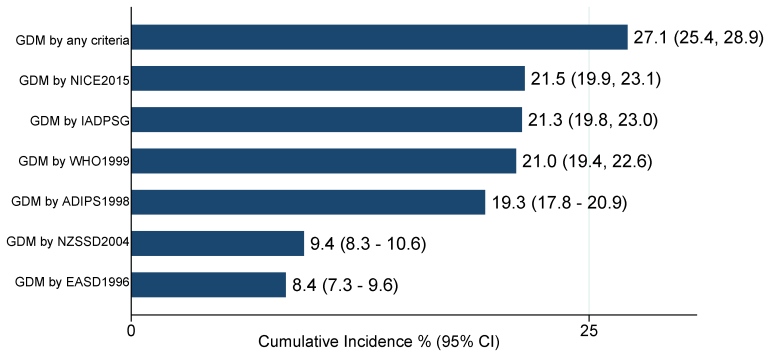

FIGURE 1
GDM cumulative incidence among pregnant women using six GDM diagnostic criteria (N = 2,546). IADPSG, International Association of Diabetes and Pregnancy Study Groups; NICE, National Institute for Health and Clinical Excellence; WHO, World Health Organization; ADIPS, Australasian Diabetes in Pregnancy Society; EASD, European Association for the Study of Diabetes; NZSSD, New Zealand Society for the Study of Diabetes.

the EASD 1996 criteria to 21.5% according to the NICE 2015 criteria. The most inclusive GDM diagnostic criteria in our study population were the NICE 2015 and IADPSG criteria (WHO 2013), whereas the EASD 1996 and NZSSD 2004 criteria were the least inclusive in this population. The study also showed GDM risk factor distribution across all criteria, with most of them being significantly higher among patients diagnosed with GDM. Agreement among the six criteria using the Cohen's kappa coefficient ranged from weak to almost perfect (Table 5).

The GDM guidelines developed by the health authorities in the UAE mainly recommend using the IADPSG/WHO 2013 criteria (36, 37). However, there was evidence that different hospitals and doctors use different criteria for GDM diagnosis in the country (34). Although recommended, the IADPSG criteria were not the most inclusive in this study. This is contrary to the previous UAE studies (3, 29), although the NICE 2015 criteria were not developed at the time that they were conducted. This is the first study in the country to assess the newer NICE criteria. Our GDM incidence by the IADPSG criteria was comparable to that found in a study in Qatar (21.5%). However, the Qatar study showed that the NICE criteria were less inclusive than the IADPSG criteria (27). The higher inclusivity of the NICE criteria was an unexpected and interesting finding in our study. The IADPSG was, however, more inclusive than the remaining four criteria.

Similar to our study, many studies (26, 28, 38–40) have found that the IADPSG criteria (new WHO 2013) identify more GDM cases than the former WHO 1999 criteria, although the increase in our study is by eight GDM cases only (Supplementary S1), and, following sensitivity analysis, the WHO 1999 was slightly more inclusive among those having at least two OGTT readings. In contrast, only a few studies (24, 41, 42) showed that the former WHO criteria diagnose more GDM cases. The IADPSG also identified more GDM cases than the Australian (ADIPS 1998), European (EASD 1996), and New Zealand (NZSSD 2004) criteria. This finding was supported by several studies, as shown in the meta-analysis conducted by Saeedi et al. (28).

Unlike in some settings (43–45), our study had shown a general reduction in the GDM incidence in the UAE using different criteria. The IADPSG criteria showed a GDM incidence of 21.3%, which was lower than the previous 37.7% (4) and 45.3% (29) shown in other studies in the country using the same criteria in previous years. Still, our GDM incidence was much higher than the regional average (13.0%) (46). GDM incidence rates were also reduced using the other diagnostic criteria compared with previous studies. The estimated criteria-specific GDM incidence applying the WHO 1999, ADIPS 1998, EASD 1996, and NZSSD 2004 was lower than that found in previous studies (4, 29) in a similar population when compared with GDM incidence by corresponding criteria. This reduction could be due to some factors and may not necessarily reflect actual GDM incidence reduction in the general population. It is important to note that the previous studies were conducted among multi-ethnic groups. In addition, in this study, we included those with at least one OGTT reading, and this could have underestimated the incidence in general. Moreover, the NICE 2015 has not been assessed in this population before.

This study also showed GDM risk factor distribution among participants. Patients with GDM (as diagnosed by any criteria) were found to be significantly older, more gravid, have higher BMI, have more history of GDM, and have a family history of type 2 DM. This is supported by studies regionally (27) and globally (47). An exception was seen in the family history of type 2 DM in the EASD 1996 criteria ($p > 0.05$). However, this was also significant when compared with non-GDM group

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TABLE 3 Risk factors distribution according to participants' GDM status (diagnosed by six criteria) N = 2546.

Variables[a]	IADPSG		NICE 2015		WHO 1999		ADIPS 1998		EASD 1996		NZSSD 2004		Any criteria	
	GDM, n = 543 (21.3%)	NO GDM, n = 2003 (78.7%)	GDM, n = 547 (21.5%)	NO GDM, n = 1,999 (78.5%)	GDM, n = 535 (21.0%)	NO GDM, n = 2,011 (79.0%)	GDM, n = 492 (19.3%)	NO GDM, n = 2,054 (80.7%)	GDM, n = 215 (8.4%)	NO GDM, n = 2,331 (91.6%)	GDM, n = 240 (9.4%)	NO GDM, n = 2,306 (90.6%)	GDM, n = 690 (27.1%)	NO GDM, n = 1,856 (72.9%)
Age, mean (SD)	32.4 (5.8)	30.0 (6.0)*	32.4 (5.7)	30.0 (6.0)*	32.4 (5.7)	30.0 (6.0)*	32.5 (5.7)	30.0 (6.0)*	33.1 (5.9)	30.2 (6.0)*	33.0 (6.0)	30.2 (6.0)*	32.1 (5.7)	29.9 (6.0)*
Gravidity, mean (SD)	3.9 (2.3)	3.4 (2.1)*	3.9 (2.2)	3.4 (2.1)*	4.0 (2.2)	3.4 (2.1)*	3.9 (2.3)	3.4 (2.1)*	4.2 (2.3)	3.5 (2.1)*	4.2 (2.4)	3.5 (2.1)*	3.9 (2.3)	3.4 (2.1)*
BMI, mean (SD) [b]	29.4 (5.6)	27.3 (5.5)*	29.0 (5.5)	27.4 (5.5)*	29.1 (5.5)	27.4 (5.5)*	29.0 (5.4)	27.4 (5.6)*	29.5 (5.4)	27.5 (5.6)*	29.5 (5.2)	27.5 (5.6)*	29.1 (5.7)	27.2 (5.5)*
Previous GDM, n (%)	203 (45.2)	219 (13.7)*	188 (41.3)	234 (14.7)*	183 (40.9)	239 (15.0)*	173 (42.1)	249 (15.2)*	86 (48.9)	336 (18.0)*	97 (49.0)	325 (17.6)*	238 (41.5)	184 (12.5)*
FHx of DM, n (%) [c]	194 (35.7)	560 (28.0)*	201 (36.8)	553 (27.7)*	194 (36.3)	560 (27.9)*	184 (37.4)	570 (27.7)*	73 (34.0)	681 (29.2) ¥	91 (37.9)	663 (28.8)*	251 (36.4)	503 (27.1)*

[a]Column percentages were reported for the categorical variables; see Table 2 for missingness of variables. *P-value < 0.005 and ¥P-value > 0.05. Chi-square test was used for categorical variables and t-test for continuous variables. [b] BMI, body mass index; [c] FHx, family history of type 2 diabetes mellitus. IADPSG, International Association of Diabetes and Pregnancy Study Groups; NICE, National Institute for Health and Clinical Excellence; WHO, World Health Organization; ADIPS, Australasian Diabetes in Pregnancy Society; EASD, European Association for the Study of Diabetes; NZSSD, New Zealand Society for the Study of Diabetes.

diagnosed by all criteria. In general, EASD 1996 and NZSSD 2004, the two least inclusive criteria, identified more participants with higher GDM risk factors. This is likely because they employ more strict criteria (higher cutoff for 2-h OGTT), hence identifying higher-risk patients.

Assessing the criteria compatibility, the IADPSG and NICE 2015 criteria together identified 400 (15.7%) patients with GDM in our population. This is in close agreement with the 14% identified in another regional study using the same two criteria (27). Furthermore, in our study, the NICE 2015 criteria diagnose more cases with the former WHO 1999 and ADIPS 1998 criteria than with the IADPSG criteria (Supplementary S1). This might be partially attributed to the fact that, among the six criteria that we assessed, only the IADPSG criteria utilizes the 1-h OGTT for diagnosis.

Cohen's kappa coefficient showed that the criteria with the highest agreement were the NICE 2015 and WHO 1999 criteria, and the lowest were the NZSSD 2004 and WHO 1999 criteria. The NICE 2015 and IADPSG (the two most inclusive criteria) had only moderate agreement (0.66). This is like the study in Qatar where these two criteria had a kappa coefficient of 0.67 (27). The IADPSG, the locally recommended criteria, had weak to moderate agreement with the other criteria. This has mostly been the case in previous studies in the country (3, 29). These discrepancies were concerning, especially if different doctors and hospitals in the country use different GDM diagnostic criteria. GDM incidence across the country could not be combined accurately. We recommend further studies to assess the criteria commonly used by doctors in the country.

GDM incidence as diagnosed by any of the six criteria collectively was 27.1%. Following comparison of this with each criterion separately, the percentage of GDM cases missed by each of the six criteria was noted (Supplementary S2). The two most inclusive criteria, the NICE 2015 and IADPSG criteria, missed 20.7% and 21.3% of GDM cases diagnosed by the other criteria combined, whereas the two least inclusive, the NZSSD 2004 and EASD 1996 criteria, missed up to 65.2% and 68.8% GDM cases, respectively. Studies have shown that missing GDM cases could lead to increase burden of adverse perinatal outcomes (24, 48, 49). Although increase workload and cost of management have been associated with using more inclusive GDM diagnostic criteria (50, 51), on the other hand, the health and economic burden of having missed GDM cases is substantial (52–54). This makes the unification of GDM diagnostic criteria a priority using the most suitable for each population.

Following the study results, we recommend the unification of GDM diagnostic criteria in the UAE population. We advise withdrawing the use of the least inclusive criteria. The NICE 2015 is currently a strong contender to the locally recommended IADPSG criteria for diagnosing GDM. It has already been adopted by some doctors probably due to its simpler protocol (no 1-h OGTT used) is its cost-effectiveness as shown in some studies (24, 55). On the other hand, the IADPSG criteria is the

TABLE 4 Risk factors distribution according to the GDM status (comparison is with no GDM by all criteria).

Variables[a]	NO GDM (all criteria)[b], n = 1856	IADPSG GDM, n = 543 (22.6%)	NICE 2015 GDM, n = 547 (22.8%)	WHO 1999 GDM, n = 535 (22.4%)	ADIPS 1998 GDM, n = 492 (21.0%)	EASD 1996 GDM, n = 215 (10.4%)	NZSSD 2004 GDM, n = 240 (11.4%)
Age, Mean (SD)	29.9 (6.0)	32.4 (5.8)*	32.4 (5.7)*	32.4 (5.7)*	32.5 (5.7)*	33.1 (5.9)*	33.0 (6.0)*
Gravidity, Mean (SD)	3.4 (2.1)	3.9 (2.3)*	3.9 (2.2)*	4.0 (2.2)*	3.9 (2.3)*	4.2 (2.3)*	4.2 (2.4)*
BMI, Mean (SD)	27.2 (5.5)	29.4 (5.6)*	29.0 (5.5)*	29.1 (5.5)*	29.0 (5.4)*	29.5 (5.4)*	29.5 (5.2)*
Previous GDM, n (%)	184 (12.5)	203 (45.2)*	188 (41.3)*	183 (40.9)*	173 (42.1)*	86 (48.9)*	97 (49.0)*
FHx of DM, n (%)	503 (27.1)	194 (35.7)*	201 (36.8)*	194 (36.3)*	184 (37.4)*	73 (34.0)*	91 (37.9)*

[a]Column percentages were reported for the categorical variables; see Table 2 for missingness of variables. [b] Women who were GDM negative using all the six criteria. *P-value < 0.001, P-value specified at 0.05 and shows comparison of a risk factor between GDM diagnosed by specified criteria and no GDM by all criteria. Chi-square test was used for categorical variables and t-test for continuous variables. IADPSG, International Association of Diabetes and Pregnancy Study Groups; NICE, National Institute for Health and Clinical Excellence; WHO, World Health Organization; ADIPS, Australasian Diabetes in Pregnancy Society; EASD, European Association for the Study of Diabetes; NZSSD, New Zealand Society for the Study of Diabetes.

TABLE 5 Comparing agreement between diagnostic criteria (in pairs) using k statistics.

	IADPSG	NICE2015	WHO 1999	ADIPS 1998	EASD 1996	NZSSD 2004
IADPSG	**1.0**					
NICE 2015	0.66	**1.0**				
WHO 1999	0.64	0.99	**1.0**			
ADIPS 1998	0.71	0.91	0.89	**1.0**		
EASD 1996	0.51	0.50	0.50	0.56	**1.0**	
NZSSD 2004	0.55	0.52	0.49	0.61	0.94	**1.0**

Cohen's kappa coefficient (k) interpretation for agreement (35); 0–0.20, none; 0.21–0.39, minimal; 0.40–0.59, weak; 0.60–0.79, moderate; 0.80–9.0, strong; >9.0, almost perfect/perfect. P-values were <0.001 for all the comparisons (k statistics). IADPSG, International Association of Diabetes and Pregnancy Study Groups; NICE, National Institute for Health and Clinical Excellence; WHO, World Health Organization; ADIPS, Australasian Diabetes in Pregnancy Society; EASD, European Association for the Study of Diabetes; NZSSD, New Zealand Society for the Study of Diabetes.
1.0 – constant.

only GDM criteria that were developed on the basis of the risk of adverse perinatal outcomes (56). Our study had shown that these two criteria were on par with each other in terms of inclusivity in GDM diagnosis among the study population and they do not have strong agreement with each other; hence, we recommend further studies to assess which criteria is most suitable for this population based on its risk of adverse outcomes.

The main strength of our study was the large representative population that increased the study power and generalizability of the findings and minimized estimate errors (57). The Mutaba'ah study is the largest prospective mother and child cohort study in the UAE, which provides data on maternal and child health from conception to adolescence. Our main limitation was that we did not have all three OGTT readings for all the participants, which

TABLE 6 GDM criteria-specific cumulative incidence stratified by the number of OGTT readings used for diagnosis.

Non-missing OGTT readings	IADPSG, n (%)	NICE 2015, n (%)	WHO 1999, n (%)	ADIPS 1998, n (%)	EASD 1996, n (%)	NZSSD 2004, n (%)	Any criteria, n (%)
Having at least 1 reading (N = 2,546)	21.3 (19.8, 23.0)	21.5 (19.9, 23.1)	21.0 (19.4, 23.0)	19.3 (17.8, 20.9)	8.4 (7.3, 9.6)	9.4 (8.3, 10.6)	27.1 (25.4, 28.9)
Having at least 2 readings (N = 2,449)	21.6 (20.0, 23.3)	22.3 (20.6, 24.0)	21.9 (20.2, 23.5)	19.9 (18.4, 21.6)	8.8 (7.7, 10.0)	9.6 (8.5, 10.9)	27.6 (25.9, 29.5)

IADPSG, International Association of Diabetes and Pregnancy Study Groups; NICE, National Institute for Health and Clinical Excellence; WHO, World Health Organization; ADIPS, Australasian Diabetes in Pregnancy Society; EASD, European Association for the Study of Diabetes; NZSSD, New Zealand Society for the Study of Diabetes.

might lead to the underestimation of incidences. In addition, those with all three could not be analyzed separately as the analysis would not be adequately powered. However, sensitivity analysis was performed among those with at least one and those with at least two readings providing for a more robust result. Prevention of adverse perinatal outcomes by different GDM diagnostic criteria was also not evaluated in this study.

Conclusions

Our findings showed discrepancies among the GDM diagnostic criteria in the UAE Emirati population, with GDM incidence ranging from 8.4% to 21.5% as diagnosed by the six assessed criteria. The NICE 2015 criteria, followed by the IADPSG/WHO 2013 criteria, were the most inclusive criteria. These two criteria had a moderate agreement (Cohen's kappa coefficient of 0.66). The locally recommended IADPSG criteria had weak to moderate agreements with the other five criteria.

This study has highlighted the need to unify GDM diagnostic criteria in this population, especially because the agreement with the recommended criteria is not optimal. Following our results, we recommend reviewing the use of IADPSG versus the NICE 2015 GDM criteria in this population. Further research is needed to assess doctors' current practice. Moreover, longitudinal data on maternal and neonatal outcomes collected within the Mutaba'ah study will explore the optimal GDM criteria based on the risk of adverse perinatal outcomes in this population.

Data availability statement

The data presented in this study can be made available on request from The Mutaba'ah Study. Approval from the research ethics committee may be required.

Ethics statement

The study was reviewed and approved by the Abu Dhabi Health Research and Technology Ethics Committee (DOH/CVDC/2022/72). The participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: MB, LA, RA-R, and FA-M. Methodology: MB, LA, IE, TL, JA, RA-R, and FA-M. Formal analysis: MB, LA, and FA-M. Investigation: MB, LA, IE, TL, RA-R, JA, and FA-M. Resources: LA, TL, JA, and FA-M. Data curation: MB and LA. Original manuscript draft preparation: MB. Manuscript review and editing: MB, LA, IE, TL, RA-R, JA, and FA-M. Visualization: MB, LA, IE, TL, RA-R, JA, and FA-M. Supervision: LA, IE, RA-R, and FA-M. Project administration: MB, LA, IE, TL, RA-R, JA, and FA-M. All authors have read and agreed to the published version of the manuscript.

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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/fendo.2022.1069477/full#supplementary-material.

SUPPLEMENTARY S1
Tables showing participants as classified by a pair of criteria.

SUPPLEMENTARY S2
Tables showing missed GDM cases by specific criteria when compared with other criteria.

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Well-controlled gestational diabetes mellitus without pharmacologic therapy decelerates weight gain in infancy

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Aim: There are no prospective longitudinal studies on the association between well-controlled gestational diabetes mellitus (GDM) without pharmacologic therapy and the physical growth of offspring in infancy. We aimed to identify the trajectories in physical growth (from 0–12 months of age) in the offspring of mothers with well-controlled GDM without pharmacologic therapy in a prospective cohort in China.

Methods: This study included 236 offspring of mothers with GDM and 369 offspring of mothers without GDM. Mothers with GDM were not on pharmacologic therapy. The length and weight of infants were measured at 0, 1, 3, 6, and 12 months. Linear mixed-effect models and linear mixed-effect models were applied.

Results: The fully adjusted model showed that the weight-for-age z-score (WAZ), length-for-age z-score (LAZ), and BMI-for-age z-score (BMIZ) were similar at birth for the GDM and control groups. However, subsequent increases in WAZ and BMIZ for the GDM group lagged the increases for the control group at the subsequent periods of observation, 0–1, 0–6, and 0–12 months.

Conclusions: Well-controlled GDM without pharmacologic therapy may normalize physical growth of offspring at birth and decelerate their weight gain in infancy. Whether glycemic control can mitigate the long-term effects of GDM on the growth trajectory in offspring remains unclear.

KEYWORDS

gestational diabetes mellitus, growth, offspring, lifestyle management, glucose control

1 Introduction

Gestational diabetes mellitus (GDM) is defined as diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation (1). Globally, approximately one in six infants are exposed to hyperglycemia *in utero*, with 14% being born to mothers with GDM (2). After adopting new diagnostic criteria for GDM (outlined by the International Association of Diabetes and Pregnancy Study Group (2010), IADPSG2010), the prevalence of GDM was 12.8%–16.7% due to regional differences in mainland China (3). More and more women are becoming overweight and obese because of lifestyle changes, such as sedentary lifestyle, lack of exercise, and changes in eating habits. Therefore, the prevalence of GDM is expected to continue to increase.

GDM may affect the short- and long-term health of the mother, including an increased risk for hypertensive disorders of pregnancy and cesarean section delivery, as well as an increased risk of developing type 2 diabetes in the future (4). However, the relationship between GDM and offspring health has attracted the most attention. GDM may have a significant "cross-generational effect," with offspring exposed to GDM being at the risk for adverse outcomes such as macrosomia, fetal hypoglycemia, cardiometabolic disorders, and type 2 diabetes (4). These adverse offspring outcomes may be due to an abnormal intrauterine environment triggered by maternal hyperglycemia (5). In recent years, the short-term outcomes of offspring of mothers with GDM (OGDM) have been improved by anti-glycemic therapy, with a decrease in the incidence of macrosomia and large for gestational age (LGA) has been reduced (6, 7). With regards to GDM management, pharmacologic therapy is required in only 17-30% of cases (8–10). Lifestyle management is one of the most important intervention for GDM management and is prioritized. Yet, there is little research available on whether well-controlled GDM without pharmacologic therapy can reduce fetal overgrowth to provide appropriate guidance for the management of pregnant women with GDM.

Sidell et al. noted that offspring exposed to GDM without pharmacologic therapy had a lower body mass index (BMI), compared to offspring not exposed to GDM as controls, at 6–24 months of age. However, the relationship between the BMI of offspring in early life, from 0 to 6 months of age, and maternal glycemic control in pregnancy has not been investigated (11). A previous study did report that the BMI in OGDM increased slowly at 0–6 months of age, compared to a control group of offspring not exposed to GDM, but with a rapid increase at 48-72 months of age. However, this study combined mothers with mild GDM, GDM, medicated GDM, and unmedicated GDM. As well, maternal glycemic control in pregnancy was not mentioned in the study (12).

Abnormal intrauterine environments during pregnancy have a profound impact on the growth of children of all ages, as well as on adult health (13). Therefore, it is necessary to conduct longitudinal studies with mother and child cohorts to provide stronger information for offspring intervention targets. Accordingly, our aim in this study was to clarify the effects of well-controlled GDM, without pharmacologic therapy, on the physical growth of offspring at birth and on their growth trajectories in the first year of life, adjusting for pre-pregnancy maternal BMI, gestational weight gain, and other confounders. Findings of our study may provide powerful theoretical guidance for rapid response to GDM and, thus, has public health and clinical significance.

2 Material and methods

2.1 Study population and design

The study was approved by the institutional review board of our institution. The study protocol has been published (14). This prospective cohort study using data was based on the birth cohort data from a secondary hospital in Chongqing, China. The

Abbreviations: GDM, gestational diabetes mellitus; OGDM, offspring of mothers with gestational diabetes; OGTT, oral glucose tolerance test; LAZ, length-for-age z-score; WAZ, weight-for-age z-score; BMIZ, BMI-for-age z-score; IADPSG2010, the International Association of Diabetes and Pregnancy Study Group (2010); T2D, type 2 diabetes; SMBG, self-monitor of blood glucose; FBG, fasting blood glucose; BG, blood glucose; BF, body fat percentage.

study sample included the offspring of mothers with well-controlled GDM without pharmacologic therapy (GDM group) and the offspring of mothers without GDM (control group), recruited at birth between June 2019 and June 2020. Within 48 hours of delivery, mothers and their offspring who volunteered to participate in this study were included in the GDM and control groups according to the inclusion and exclusion criteria and gave written informed consent. Mothers completed a questionnaire, within 48 h of delivery, to record the following information: maternal height, pre-pregnancy weight reported at the first prenatal assessment at about 8 weeks of gestation, prenatal weight, level of education, average monthly household income, and mode of delivery; and offspring sex, gestational age, date of birth, birth weight, recumbent birth length, and Apgar score. Post-natal assessments of the offspring were conducted at post-natal months 1, 3, 6, and 12, and included recumbent length and weight as anthropometric data and disease status; the feeding pattern from post-natal 0-6 months was also recorded.

2.2 Inclusion and exclusion criteria

All pregnant women who regularly visited the outpatient obstetrics department were offered a 75-g 2-h oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. The inclusion criteria were as follows: term delivery, singleton fetus, and no history of perinatal asphyxia or serious diseases affecting offspring growth and development. All pregnant women who regularly visited the outpatient obstetrics department were offered a 75-g 2-h oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. The exclusion criteria were as follows: mothers without OGTT results; mothers who have received drugs interfering with glucose homeostasis before and during pregnancy; mothers age > 35 years; mothers with diseases, such as severe systemic disease, pre-pregnancy diabetes, severe infectious diseases, hypertension in pregnancy, intrahepatic cholestasis of pregnancy, severe anemia in pregnancy; and offspring with diseases affecting metabolism and growth.

2.3 Blood glucose monitoring in mothers with GDM

GDM was diagnosed according to the 75-g 2-h OGTT at 24–28 weeks of gestation (IADPSG2010 criteria): blood glucose ≥5.1 mmol/L (fasting) or ≥10.0 mmol/L (60 min) or ≥8.5 mmol/L (120 min) (15). Pregnant women with GDM who received lifestyle management without pharmacologic therapy received individualized meal plans and instructions for physical activity and self-monitoring of blood glucose. they were asked to perform self-monitoring of blood glucose (SMBG) throughout the day at least once a week (SMBG comprised peripheral fasting blood glucose (FBG) and 2-h postprandial plasma glucose (2hPBG) a total of four times) in accordance with Chinese guidelines (16) and report their blood glucose (BG) values to doctors at each visit. If the women had poor adherence to SMBG, they were required to visit the hospital regularly (once every 2–4 weeks; i.e., intermittent SMBG) to have their FBG and 2hPBG monitored. We obtained HbA1c values from medical records, and good glycemic control was defined as a blood glucose value < 20% of the recommended target (fasting BG ≤5.3 mmol/L, 2-h postprandial plasma glucose ≤6.7 mmol/L) and HbA1c < 6.5% at each test.

2.4 Anthropometric measurement at birth and during infancy

The anthropometric measurement methods have been reported (14). Briefly, the recumbent length and weight of the offspring at birth, 1, 3, 6, and 12 months were measured by nurses following a standardized procedure and using professional examination instruments. We used the world health organization software to calculate the length-for-age z-scores (LAZ), weight-for-age z-scores (WAZ), and BMI-for-age z-scores (BMIZ) at each of the 5 measurement time points.

2.5 Statistical analysis

Statistical analyses were conducted using SAS (r) Proprietary Software 9.3 (TS1M0). BMI was calculated as weight divided by the square of height (kg/m^2) and gestational weight gain as weight on admission for delivery minus pre-pregnancy weight (kg). Continuous variables are presented as the mean ± standard deviation and categorical variables as a count and percentage. Quantitative data between the GDM and control group were compared using a t-test (normally distributed data) or Wilcoxon rank sum test (non-normally distributed data), with qualitative and ordinal data compared using the chi-squared and Wilcoxon rank sum tests, respectively.

After adjusting for confounders, three general linear models were constructed to evaluate the effect of GDM on WAZ, LAZ, and BMIZ at birth. Confounders were adjusted as follows: Model 1: maternal height (m), level of education (secondary, high school, bachelor, or postgraduate level), average monthly household income (CNY <5000, 5,000–9,999, 10,000–14,999, 15,000–19999, and >20,000), gestational age (days), delivery method (cesarean delivery, yes/no), sex (male, yes/no) and feeding patterns (exclusive breastfeeding at 1, 3, and 6 months of age, yes/no); Model 2: Model 1+ pre-pregnancy BMI (kg/m^2); and Model 3: Model 2+ gestational weight gain (kg).

A repeated-measures analysis of variance (ANOVA) for WAZ, LAZ, and BMIZ was performed. When the data passed Mauchly's test of sphericity, a two-way ANOVA analysis was used; otherwise, the Greenhouse–Geisser correction was needed. Repeated

measurements were described as the mean ± standard error of mean (SEM) and the trajectories of WAZ, LAZ, and BMIZ were plotted. Linear mixed-effect models consider the internal correlation of repeated measurements of variables and consider data with missing values (17). In these models, the Z score was the dependent variable, with group (GMD versus control) and the follow-up time points set as the fixed effects, each offspring as a random effect, and confounding factors (maternal height, level of education, average monthly household income, gestational age, cesarean delivery, sex, pre-pregnancy BMI, gestational weight gain, and feeding patterns) as covariates. The interaction effects (time × group) were included in the model. We used the maximum likelihood estimation to fit the model. The Akaike information criterion was calculated to fit different covariance models, and the UN structure was selected. The associations between GDM and the physical growth trajectories of OGDM were analyzed longitudinally using linear mixed-effect models and controlling for the abovementioned covariables. Analyses were performed with three models. The adjustments of covariates were consistent with those of confounders in the general linear model. The regression coefficients (β estimates) and associated 95% confidence intervals (CI) were described. Statistical significance was set at $P < 0.05$.

3 Results

3.1 The descriptive characteristics parameters in two groups

This prospective cohort study included data for 283 offspring of mothers in the GDM group and 429 offspring of mothers in the control group. Of these, 107 infants were excluded due to death (n=2), missing contact information (n=20), diseases affecting metabolism and growth (n=33), and relocation from the study area (n=52). Consequently, 605 offspring (236 in the GDM group and 369 in the control group) were analyzed. The participant flow chart is shown in Figure 1. The follow-up rates of 605 offspring at 1-month (32.38 ± 3.76 days), 3 months (95.42 ± 10.20 days),6 months (184.39 ± 11.20 days), and 12 months (373.08 ± 17.14 days) months was 91.6% (554 person-visits), 85.0% (514 person-visits), 80.2% (485 person-visits), and 70.6% (427 person-visits), respectively.

The descriptive characteristics for the GDM and control groups are shown in Table 1. Mothers with GDM had a higher rate of cesarean delivery (48.94% vs. 35.16%, $p<0.001$) and higher pre-pregnancy BMI (27.48 ± 3.51 kg/m^2 vs. 26.93 ± 3.66 kg/m^2, $p<0.05$) compared with those of the control groups. In contrast, the characteristics of sex, gestational age, feeding patterns, maternal height, gestational weight gain, level of education, and average monthly household income did not different significantly in both groups.

3.2 Glucose data during pregnancy in mothers with GDM

GDM was diagnosed at a mean 24.57 ± 0.94 weeks of gestation. The mean values of fasting glycaemia at OGTT, 1-h glycaemia at OGTT, and 2-h glycaemia at OGTT were 5.25 ± 0.36 mmol/L, 9.22 ± 1.99 mmol/L, and 7.88 ± 1.57 mmol/L, respectively. Target levels of fasting and postprandial blood glucose for *good* glycemic control were achieved in 228 of 236 women (96.6%) in the GDM group, as follows: 4.72 ± 1.41 mmol/L for fasting and 5.63 ± 1.83 mmol/L for postprandial. The mean HbA1c of mothers with GDM in late pregnancy was 4.6 ± 1.7% (30 ± 12mmol/mol).

3.3 Anthropometric data of the offspring

In the fully adjusted general linear model, WAZ (p=0.29), LAZ (p=0.74), and BMIZ (p=0.25) of OGDM were not different

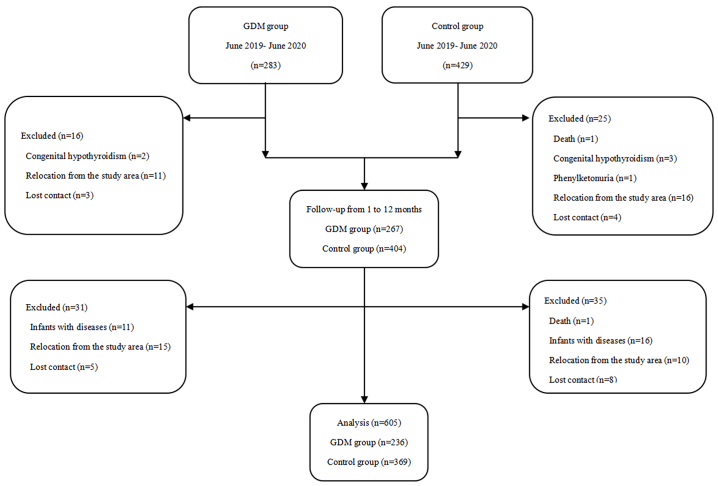

FIGURE 1
Participant flow chart.

TABLE 1 Descriptive characteristics of the GDM and control groups.

Variables (percentage of missing data for each characteristic)	GDM group (*N*= 236)	Control group (*N*= 369)	*P*
Offspring characteristics			
Male (n, %)	128 (52.24)	190 (51.49)	0.51
Breastfeeding (n, %)			
1 month (8.43%)	143 (63.56)	210 (63.83)	0.95
3 month (15.04%)	160 (74.40)	226 (74.60)	0.87
6 month (19.83%)	131 (68.23)	199 (67.92)	0.94
Gestational age (days) (0.99%)	275.12 ± 5.74	275.95 ± 7.73	0.22
Maternal characteristics			
Height (m) (1.49%)	1.60 ± 0.20	1.58 ± 0.05	0.70
Pre-pregnancy BMI (kg/m^2) (1.49%)	27.48 ± 3.51	26.93 ± 3.66	0.006
Gestational weight gain (kg) (1.32%)	14.73 ± 4.83	15.37 ± 4.30	0.09
Level of education (n, %)(3.47%)			0.74
Middle school level	39 (16.81)	50 (13.81)	
High school level	57 (24.57)	103 (28.45)	
Bachelor level	134 (57.76)	200 (55.25)	
Postgraduate level	2 (0.86)	9 (2.49)	
Caesarean delivery (n, %) (0.99%)	115 (48.94)	128 (35.16)	<0.001
Average monthly household income, ¥ (CNY) (n, %) (4.46%)			0.93
<5000	29 (12.95)	40 (11.30)	
5000- 9999	109 (48.66)	187 (52.82)	
10000- 14999	64 (28.57)	87 (24.58)	
15000- 19999	15 (6.70)	28 (7.91)	
>20000	7 (3.13)	12 (3.39)	

Values are mean ± SD, or n (%).
GDM, gestational diabetes mellitus; BMI, body mass index.
GDM group: offspring of mothers with well-controlled gestational diabetes mellitus without insulin.
Control group: offspring of mothers without GDM (control group).
Statistical significance was set at $P < 0.05$.

between offspring in the GDM group and control group (Table 2). The trajectories of Z-scores for WAZ, LAZ, and BMIZ, using the mean ± SEM values reported in Table 3, are plotted for the period of 0-12 months of age in Figure 2 for both groups. The trajectories for WAZ, LAZ, and BMIZ were not different between the GDM and control group over the period of 0-4 months, with a significant deviation for the GDM group, from the control group, becoming apparent after 4 months of age. As shown in Figure 2, the Z-score for all three variables, WAZ, LAZ, and BMIZ, were lower for the GDM than control group at 6 and 12 months of age.

The results of the linear mixed-effect, fully adjusted, model showed different trajectories of Z-scores for the GDM and control groups (Table 4). Compared to the control group, the increases for the GDM group were significantly less than for the control group over the periods of 0–1, 0–6, and 0–12 months, respectively, for WAZ (p=0.04, p=0.02, and p=0.003) and BMIZ (p=0.008, p=0.04, and p=0.01). Of note, the trajectory of the Z-scores for WAZ, LAZ, and BMIZ was not different between the GDM and control group over the 0–3-month period, as was the Z-score trajectory of LAZ over the 0-12 month period. Furthermore, the regression coefficients (βestimates) of the interaction effects (time × group) increased gradually for WAZ and BMIZ at 1, 6, and 12 months of age.

4 Conclusions

The novel contribution of our observational study is the longitudinal reporting of an association between well-controlled GDM without pharmacologic therapy and the physical growth of offspring in the first year of life. We found that WAZ, LAZ, and BMIZ of OGDM were not amplified at birth, but that a period of "catch-down" growth followed. The lag became more pronounced with age between the two groups. These observations were independent of pre-pregnancy BMI, gestational weight gain, and other maternal and infant factors. Our findings support an association between well-controlled GDM and a slower rate of physical growth of offspring, at least up to 12 months of age, the end point of the period of observation in our study.

The Similar physical growth measures at birth between the GDM and control group was consistent with those of previous

TABLE 2 The general linear model's parameter outcome comparison of Z scores at birth in both groups.

Outcomes	Model	GDM vs. control group		
		β	SE	*P*
WAZ	Model 1	-0.08	0.06	0.22
	Model 2	-0.06	0.06	0.37
	Model 3	-0.07	0.06	0.29
LAZ	Model 1	-0.03	0.07	0.65
	Model 2	-0.02	0.07	0.78
	Model 3	-0.02	0.07	0.74
BMIZ	Model 1	-0.09	0.07	0.21
	Model 2	-0.07	0.07	0.33
	Model 3	-0.08	0.07	0.25

Data are presented as β and SE.
GDM, gestational diabetes mellitus; WAZ, weight-for-age z-scores; LAZ, length-for-age z-scores; BMIZ, BMI-for-age z-scores.
GDM group: offspring of mothers with well-controlled gestational diabetes mellitus without insulin.
Control group: offspring of mothers without GDM.
Model 1: adjusted for maternal height (m), level of education (secondary, high school, bachelor, or postgraduate level), average monthly household income (CNY, <5000, 5000–9999, 10000–14999, 15000–19999, or >20000), gestational age (days), delivery method (cesarean delivery, yes/no), sex (male, yes/no), and feeding patterns (exclusive breastfeeding at 1, 3, and 6 months of age, yes/no).
Model 2: Model 1+ adjusted for pre-pregnancy BMI (kg/m^2).
Model 3: Model 2+ adjusted for gestational weight gain (kg).
Statistical significance was set at $P < 0.05$.

studies (18, 19). Of note, although Ignell et al (18) reported similar birth weight and length between offspring of mothers with GDM and the control group without GDM in a British sample, maternal glycemic control was not described. In their study, Au et al. (19) further reported a body fat (BF) percentage for offspring of mothers with GDM and those without GDM. In both studies, however, maternal interventions included a combination of lifestyle management and lifestyle management + pharmacologic therapy. Moreover, between-group comparisons were not adjusted for pre-pregnancy BMI and gestational weight gain. In contrast, a systematic review reported significantly greater infant adiposity associated with GDM compared to non-GDM (20); however, this review included infants of all pregnant women with diabetes, including those with type 1 and 2 diabetes and GDM. A recent 2018 systematic review identified that dietary modification interventions might reduce the birth weight of offspring (21). However, most of the studies included in this review had small sample sizes (≤100 participants), with few studies having slightly stronger evidence for reported outcomes. Overall, while existing research indicates important findings on the effects of diabetes in pregnancy and birth weight and adiposity, studies on the associations between GDM without pharmacologic therapy and the physical growth of offspring at birth are still lacking. Our study addresses this gap, with findings that well-controlled GDM without pharmacologic therapy, might normalize the physical growth at birth in infants.

TABLE 3 Outcomes of Z scores in the two groups at different ages ($\bar{X}$ SE).

		WAZ	LAZ	BMIZ
0 m	GDM group	0.12 ± 0.05	0.44 ± 0.06	-0.15 ± 0.06
	Control group	0.04 ± 0.04	0.43 ± 0.04	-0.27 ± 0.04
1 m	GDM group	0.00 ± 0.06	-0.04 ± 0.06	0.02 ± 0.06
	Control group	0.01 ± 0.06	-0.08 ± 0.08	0.08 ± 0.04
3 m	GDM group	0.36 ± 0.07	0.24 ± 0.07	0.30 ± 0.07
	Control group	0.34 ± 0.06	0.23 ± 0.06	0.28 ± 0.05
6 m	GDM group	0.28 ± 0.07	0.14 ± 0.07	0.27 ± 0.08
	Control group	0.35 ± 0.06	0.19 ± 0.06	0.33 ± 0.06
12 m	GDM group	0.08 ± 0.06	-0.21 ± 0.07	0.26 ± 0.07
	Control group	0.22 ± 0.06	-0.06 ± 0.06	0.35 ± 0.06

GDM, gestational diabetes mellitus; WAZ, weight-for-age z-scores; LAZ, length-for-age z-scores; BMIZ, BMI-for-age z-scores.
GDM group: offspring of mothers with well-controlled gestational diabetes mellitus without insulin.
Control group: offspring of mothers without GDM.

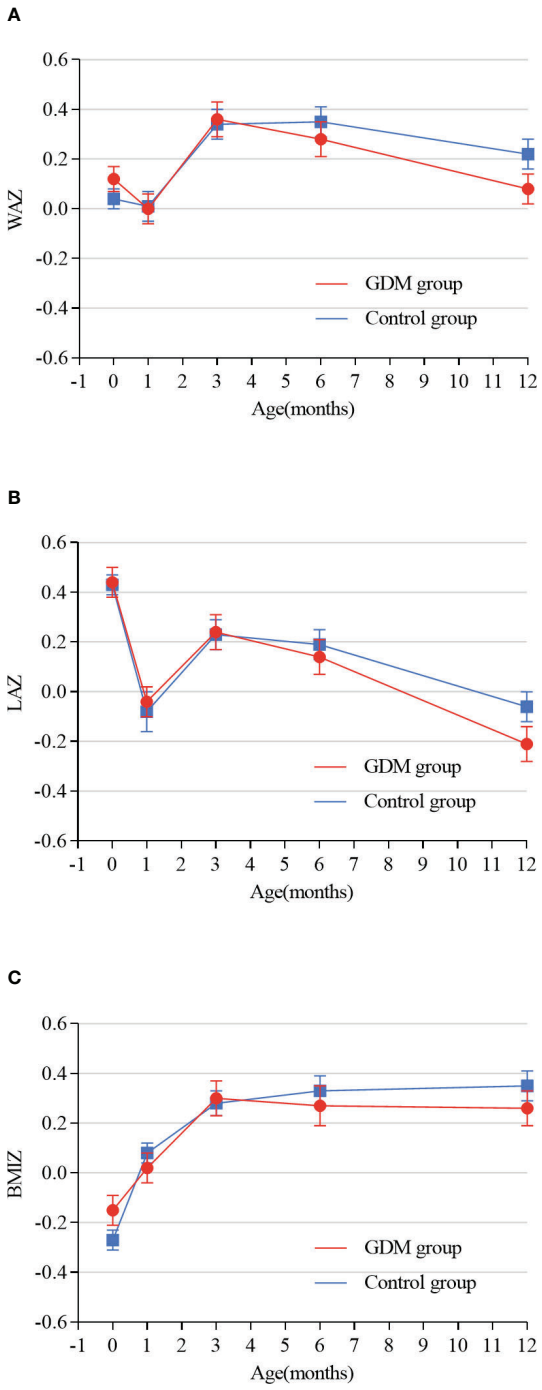

FIGURE 2
(A–C) shows the trajectories of Z-scores from birth to 12 months of age for the GDM and control groups. WAZ weight-for-age z-scores, LAZ: length-for-age z-scores, BMIZ: BMI-for-age z-scores; GDM group: offspring of mothers with well-controlled gestational diabetes mellitus without insulin. Control group: offspring of mothers without GDM.

At 0–1 month of age, we did identify a deceleration was observed in the increase of WAZ and BMIZ in OGDM compared to those of the control group, which may be a new finding. In their cross-sectional, rather than longitudinal, observational study, Logan et al. reported that weight and length SDS were significantly lower for OGDM than for a non-GDM control groupt at approximately two weeks of age (22). Conversely, Uebel et al. reported a higher fat mass for offspring of obese mothers

TABLE 4 Linear mixed-effect models of Z-scores.

	Model 1		Model 2		Model 3	
	β(95%CI)	*P*	β(95%CI)	*P*	β(95%CI)	*P*
WAZ						
GDM group	0.11 (-0.02 to 0.24)	0.09	0.09 (-0.03 to 0.22)	0.15	0.10 (-0.03 to 0.23)	0.12
1 m	-0.03 (-0.11 to 0.17)	0.66	0.03 (-0.11 to 0.17)	0.66	0.03 (-0.11 to 0.17)	0.65
3 m	0.35 (0.21 to 0.50)	<0.01	0.36 (0.22 to 0.50)	<0.01	0.36 (0.22 to 0.50)	<0.01
6 m	0.38 (0.23 to 0.53)	<0.01	0.38 (0.24 to 0.53)	<0.01	0.39 (0.24 to 0.53)	<0.01
12 m	0.19 (0.08 to 0.29)	<0.01	0.19 (0.08 to 0.29)	<0.01	0.19 (0.08 to 0.29)	<0.01
GDM group × 1 m	-0.14 (-0.28 to -0.01)	0.04	-0.14 (-0.28 to 0.01)	0.04	-0.15 (-0.28 to -0.01)	0.04
GDM group × 3 m	-0.12 (-0.28 to 0.04)	0.13	-0.13 (-0.28 to 0.03)	0.12	-0.13 (-0.29 to 0.03)	0.12
GDM group × 6 m	-0.20 (-0.37 to -0.03)	0.02	-0.20 (-0.37 to -0.03)	0.02	-0.20 (-0.37 to -0.03)	0.02
GDM group × 12 m	-0.25 (-0.41 to -0.09)	0.00	-0.25 (-0.42 to -0.09)	0.00	-0.25 (-0.42 to -0.09)	0.00
LAZ						
GDM group	0.07 (-0.07 to 0.21)	0.36	0.06 (-0.08 to 0.20)	0.44	0.06 (-0.08 to 0.20)	0.42
1 m	-0.56 (-0.72 to -0.40)	<.01	-0.56 (-0.72 to -0.40)	<.01	-0.56 (-0.72 to -0.40)	<.01
3 m	-0.27 (-0.42 to -0.11)	0.00	-0.27 (-0.42 to -0.11)	0.00	-0.27 (-0.42 to -0.11)	0.00
6 m	-0.30 (-0.45 to -0.14)	0.00	-0.30 (-0.45 to -0.14)	0.00	-0.30 (-0.45 to -0.14)	0.00
12 m	-0.50 (-0.60 to -0.40)	<.01	-0.50 (-0.60 to -0.40)	<.01	-0.50 (-0.60 to -0.40)	<.01
GDM group × 1 m	-0.02 (-0.18 to 0.13)	0.76	-0.02 (-0.18 to 0.13)	0.75	-0.03 (-0.18 to 0.13)	0.75
GDM group × 3 m	-0.02 (-0.18 to 0.13)	0.79	-0.02 (-0.18 to 0.13)	0.77	-0.02 (-0.18 to 0.13)	0.77
GDM group × 6 m	-0.10 (-0.25 to 0.06)	0.22	-0.10 (-0.25 to 0.06)	0.22	-0.10 (-0.25 to 0.06)	0.22
GDM group × 12 m	-0.16 (-0.31 to -0.00)	0.05	-0.15 (-0.31 to 0.00)	0.05	-0.15 (-0.31 to 0.00)	0.05
BMIZ						
GDM group	0.12 (-0.02 to 0.27)	0.10	0.11 (-0.04 to 0.26)	0.14	0.12 (-0.03 to 0.27)	0.12
1 m	0.48 (0.32 to 0.63)	<.01	0.48 (0.32 to 0.63)	<.01	0.48 (0.32 to 0.63)	<.01
3 m	0.69 (0.52 to 0.85)	<.01	0.69 (0.53 to 0.85)	<.01	0.69 (0.53 to 0.85)	<.01
6 m	0.74 (0.57 to 0.91)	<.01	0.75 (0.58 to 0.92)	<.01	0.75 (0.58 to 0.92)	<.01
12 m	0.63 (0.51 to 0.75)	<.01	0.63 (0.50 to 0.75)	<.01	0.63 (0.50 to 0.75)	<.01
GDM group × 1 m	-0.21 (-0.37 to -0.06)	0.01	-0.21 (-0.37 to -0.06)	0.01	-0.21 (-0.37 to -0.06)	0.01
GDM group × 3 m	-0.17 (-0.36 to 0.02)	0.09	-0.17 (-0.36 to 0.02)	0.08	-0.17 (-0.36 to 0.02)	0.08
GDM group × 6 m	-0.21 (-0.41 to -0.01)	0.04	-0.21 (-0.41 to -0.01)	0.04	-0.21 (-0.41 to -0.01)	0.04
GDM group × 12 m	-0.25 (-0.45 to -0.06)	0.01	-0.25 (-0.45 to -0.05)	0.01	-0.25 (-0.45 to -0.05)	0.01

Data are presented as β and 95% CI.
The interaction effects (time × group) were included in the model.
GDM, gestational diabetes mellitus, WAZ: weight-for-age z-scores, LAZ: length-for-age z-scores; BMIZ, BMI-for-age z-scores; CI, confidence interval.
GDM group: offspring of mothers with well-controlled gestational diabetes mellitus without insulin.
Control group: offspring of mothers without GDM.
Model 1: adjusted for maternal height (m), level of education (secondary, high school, bachelor, or postgraduate level), average monthly household income (CNY, <5000, 5000- 9999, 10000-14999, 15000- 19999, >20000), gestational age (days), delivery method (cesarean delivery, yes/no), sex (male, yes/no) and feeding patterns (exclusive breastfeeding at 1, 3, and 6 months of age, yes/no).
Model 2: Model 1+ adjusted for pre-pregnancy BMI (kg/m^2).
Model 3: Model 2+ adjusted for gestational weight gain (kg).
Statistical significance was set at $P < 0.05$.

with GDM being an independent risk factor for offspring obesity (23). However, the sample size of this study was small and only included women with obesity who had GDM. In our study, we identified a deceleration in the increase in WAZ and BMIZ for OGDM over the period of 0-6 months of age, compared to the control group. This is consistent with the findings of Sidell et al. Who reported that the BMI of OGDM was significantly lower than that of offspring of healthy mothers over the period of 0–6 months of age (11). However, Sidell et al. did not include mothers with GDM. Furthermore, our study identified a deceleration in the increase in WAZ and BMIZ over the period of 0-12 months of age for the GDM compared to the control group. Ignell et al. (18) similarly reported that increases in weight and skinfold thickness were significantly lower over the period of 3-12 months of age in OGDM compared to a control group. However, in contrast to our findings, another study reported that the increases in weight and

skinfold thickness was significantly greater from 0-3 months of age and the increase in length was significantly less over the 0-12 month age period (24). A more recent, 2022, study reported offspring of mothers treated for GDM gained more weight in infancy compared to the infants born to mothers with gestational impaired glucose tolerance and healthy mothers (25). However, these studies, included mothers with treated and untreated GDM, did not describe glycemic control during gestation, and did not describe lag in postnatal growth trajectory in OGDM. Of note, the growth trajectories of OGDM in early life were similar to those of individuals who experience obesity rebound in childhood and type 2 diabetes in adulthood (26, 27). Therefore, the age at which "catch-down" weight among OGDM becomes most pronounced remains to be clarified. To address this specific issue, we are continuing the follow-up of our sample to determine if and when a "catch-up" period of growth occurs in OGDM with a longer period of observation.

The mechanisms by which offspring normalize weight at birth and subsequently experience periods of "catch-down" growth are unclear. The strict diagnostic criteria for GDM proposed in the IADPSG2010 guideline resulted in more pregnant women with elevated BG values being identified and treated with aggressive glycemic control. The diagnosis and treatment of mild GDM reportedly reduce the risk for macrosomia and LGA (28), and another study found BF was similar at birth between the well-controlled GDM and control groups (19). Although our study population consisted of mothers who had met the diagnostic criteria for GDM, their BG values were closer to those of mild GDM and were more likely to be controlled at normal levels without pharmacologic therapy. Therefore, our results support the perspective that maternal exposure to lower glucose and good glycemic control may normalize the birth weight of their offspring. Furthermore, gestational weight gain is associated with accelerated fetal growth accelerated fetal growth (29). In our study, gestational weight gain, limited by lifestyle management, was similar between the GDM and control group, which reduced the risk of a higher birth weight in offspring overall. It is important to note that antidiabetic medications may alter fetal growth. A systematic review and meta-analysis of 33 studies found that among the offspring of mothers taking insulin, glyburide, and metformin, those of mothers taking glyburide were the heaviest and those of mothers taking metformin were the lightest (30). In addition, a study in the United States reported that the offspring of mothers using insulin and glyburide as antidiabetic medications had higher birth weights compared to offspring of mothers not receiving any antidiabetic medications (31). Metformin and glyburide cross the placenta and may affect the short-term growth of offspring through specific mechanisms (32). Combined with our findings, we conclude that the growth of offspring unexposed to antidiabetic medications may escape the possible potential adverse effects of the drugs.

After adjusting for the most important confounders (maternal BMI and gestational weight gain) and avoiding possible interference by anti-glycemic drugs, we found that good glycemic control during gestation did not completely protect offspring of mothers with GDM from effects of an adverse intrauterine environment during infancy, from 0-12 month. Therefore, other factors related to hyperglycemia during pregnancy, besides abnormal metabolism induced by hyperglycemia, can affect the growth of offspring. Leptin, a protein encoded by obesity genes, is mainly synthesized and secreted by body fat and is proportional to body fat mass. It regulates eating behavior and energy metabolism (33). OGDM reportedly have higher birth weight and cord blood leptin levels than those of the control group (34, 35). Two other studies found that although there was no significant difference in birth weight between the GDM and control groups, cord blood leptin levels were still higher in the GDM group, which may be related to the relative increase in BF of OGDM (36, 37). Therefore, cord blood leptin levels were higher for the GDM group regardless of amelioration of the classic macrosomic phenotype under maternal glycemic control during gestation.

Clinical and animal studies have found that offspring with high leptin levels do not develop the same "leptin resistance" early in life as adults with obesity who have high leptin levels (34, 35, 38, 39). Parker et al. supported that higher cord leptin levels were associated with slower weight gain from 0–6 months (35). Kaar et al. suggested that cord leptin levels were negatively correlated with weight gain in the first year of life (34). Our study found similar growth trajectories for OGDM. Therefore, we hypothesized that the growth trajectories of OGDM may result from feedback regulation developed *in utero*, with high *in utero* leptin levels in particular slowing down the early postnatal weight gain of OGDM by regulating feeding behavior and metabolism. Further studies are needed to confirm the exact associations between cord blood leptin levels and growth trajectories of OGDM who have a normal birth weight.

Few studies have shown that a higher intake of breast milk is associated with slower and less weight gain in OGDM, over the period of 0-12 months, and that breastfeeding is associated with a lower risk of childhood obesity (40), These findings may be related to lower concentrations of ghrelin and adiponectin in breast milk (41). We collected information on exclusive breastfeeding (yes/no) at three time points in our study sample, and they were all similar. Associations between breastfeeding and weight gain in OGDM need to be further explored.

Our study is unique and meaningful. To date, no prospective longitudinal studies have shown the associations between well-controlled GDM without pharmacologic therapy and the physical growth of offspring at 0-12 months of age. Data on blood glucose monitoring have confirmed that most mothers with GDM can achieve good glycemic control without

pharmacologic therapy (8–10). Therefore, our study on the growth trajectories of most OGDM (exposed to relatively low levels of hyperglycemia *in utero*) has practical significance. Furthermore, this study considered possible confounders, particularly pre-pregnancy BMI and gestational weight gain, to confirm the independent effect of GDM on the physical growth of offspring.

The limitations of our study need to be acknowledged. First, our study population comes from a secondary regional hospital in developing regions of the country, with relatively low economic family income and maternal education levels. To maximize the reliability and adherence of SMBG, intermittent monitoring was used by some mothers with GDM through regularly scheduled hospital visits. We strictly screened out well-controlled GDM from the SMBG and medical records. However, compared with frequent SMBG, intermittent SMBG might have resulted in the identification of a smaller number of mothers whose glycemic control was lower than expected. The status of glycemic control requires careful interpretation. Second, we did not have data on cord blood leptin levels and body fat of offspring, and we plan to clarify the associations in another study. Finally, the study lacked groups of OGDM of mothers who received pharmacologic therapy for GDM management to investigate whether there were differences in growth trajectories between OGDM who received different therapies and the offspring with mothers without GDM. In our future study, longitudinal follow-up and continuous attention will be paid to clarify the physical growth pattern of OGDM and provide references for clinical intervention strategies for mothers with GDM.

In conclusion, well-controlled GDM without pharmacologic therapy may normalize the physical growth of offspring at birth and decelerate weight gain in infancy. Continued follow-up will help assess the growth trajectories of offspring and whether good glycemic control alleviates the long-term effects of GDM on offspring. This may provide data support for the most accurate medical monitoring and health management for pregnant women with GDM and their offspring.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board, Children's Hospital of Chongqing Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

CL and LC conceived and designed. LC, YC, YYL, TY, ZW, HP, YZ, YH, TS and YF implemented the study. CL, YC, and YYL acquired and analyzed data. CL and LC drafted the manuscript. JC, YFL, and TL reviewed and revised the manuscript. BP and CL carried out statistical analysis. All authors approved the final version of the manuscript. LC is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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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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Observational assessments of the relationship of dietary and pharmacological treatment on continuous measures of dysglycemia over 24 hours in women with gestational diabetes

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Objectives: Studies that use continuous glucose monitoring (CGM) to monitor women with gestational diabetes (GDM), highlight the importance of managing dysglycemia over a 24-hour period. However, the effect of current treatment methods on dysglycemia over 24-hrs are currently unknown. This study aimed to characterise CGM metrics over 24-hrs in women with GDM and the moderating effect of treatment strategy.

Methods: Retrospective analysis of CGM data from 128 women with GDM in antenatal diabetes clinics. CGM was measured for 7-days between 30-32 weeks gestation. Non-parametric tests were used to evaluate differences of CGM between periods of day (morning, afternoon, evening, and overnight) and between treatment methods (i.e., diet alone or diet+metformin). Exploratory analysis in a subgroup of 34 of participants was performed to investigate the association between self-reported macronutrient intake and glycaemic control.

Results: Glucose levels significantly differed during the day (i.e., morning to evening; P<0.001) and were significantly higher (i.e., mean blood glucose and area under the curve [AUC]) and more variable (i.e., SD and CV) than overnight glucose levels. Morning showed the highest amount of variability (CV; 8.4% vs 6.5%, P<0.001 and SD; 0.49 mmol/L vs 0.38 mmol/L, P<0.001). When comparing treatment methods, mean glucose (6.09 vs 5.65 mmol/L; P<0.001) and AUC (8760.8 vs 8115.1 mmol/L.hr; P<0.001) were significantly higher in diet +metformin compared to diet alone. Finally, the exploratory analysis revealed a favourable association between higher protein intake (+1SD or +92 kcal/day) and lower mean glucose (-0.91 mmol/L p, P=0.02) and total AUC (1209.6 mmol/L.h, P=0.021).

Conclusions: Glycemia varies considerably across a day, with morning glycemia demonstrating greatest variability. Additionally, our work supports that individuals assigned to diet+metformin have greater difficulty managing glycemia and results

suggest that increased dietary protein may assist with management of dysglycemia. Future work is needed to investigate the benefit of increased protein intake on management of dysglycemia.

KEYWORDS

GDM, continuous glucose monitoring, glycemia, diet, metformin, protein, myfood24, glucose

1 Introduction

Pregnancy induces a natural state of insulin resistance (IR) to shuttle a greater proportion of maternal nutrients to the infant for growth and development (1). However, in 5-18% of all UK pregnancies (2, 3) this metabolic shift leads to uncontrolled and unhealthy increases in blood glucose (1, 4–6), known as gestational diabetes mellitus (GDM). GDM occurs when women not previously known to have diabetes develop hyperglycemia during pregnancy, risking the health of mother and growing offspring (5, 7). Moreover, GDM is associated with increased risk of pre-eclampsia, preterm delivery, and type 2 diabetes (T2DM) in later life (8); while offspring exposed to GDM *in utero* are at increased risk of abnormal birth weight, birth injury, mortality, and obesity and T2DM in later life (7–9). Treatment aims to control maternal glucose levels and mitigate adverse pregnancy outcomes and long-term maternal and offspring health risks (10).

The first line of treatment for GDM typically consists of dietary and lifestyle education (1, 11). Diets focussing on low glycaemic index (GI) foods and reduced overall carbohydrate intake are most common for the management of GDM (1, 3) but no consensus on the best nutritional approach has been agreed (12, 13). In the UK, clinical recommendations focus on improving carbohydrate quality and reducing overall carbohydrate intake (3, 6). While replacing simple carbohydrates with higher-quality carbohydrates and lower overall carbohydrate intake can help to control glucose levels, its effectiveness on managing dysglycemia is not consistent between populations (13), with meta-analyses demonstrating high levels of heterogeneity (>60%) of low GI diets on fasting and post-prandial glucose levels (14). This may be because trials often prescribe specific low-GI nutrients to be consumed at defined times over a 24-hour period, while real-life meals are often mixtures of foods consumed at various points throughout the day (15–17). Previous research has demonstrated that dietary protein can attenuate the subsequent rise in the postprandial glucose response (PPGR) (18, 19). However, free living individuals consume meals that consist of mixed macronutrients consumed at different times of the day, suggesting that a single measure of post-prandial glucose (PPG) may be inadequate to characterise the full effect of diet on dysglycemia.

Randomised controlled trials suggest that 80% of women with GDM can achieve normal glucose levels through diet and lifestyle modification alone (20). However, where management of dysglycemia is more difficult, pharmacological therapy may be needed. Metformin, an oral antihyperglycemic drug, has been used as a secondary line therapy for glycemic control in T2DM for decades (21, 22). In women with GDM, the UK clinical guidelines also recommend metformin as secondary-line therapy in the management of dysglycemia (3), with added benefits linked to reduced gestational weight gain, maternal hypertensive disorders, macrosomia, neonatal hypoglycemia, and intensive care unit admissions (3). Current evidence suggests no difference in standard maternal measures of glycaemia or neonatal outcomes after delivery in women treated with either diet or metformin (23).

However, maternal glucose is dynamic, glucose tolerance and insulin sensitivity vary over a 24-hour period (24, 25), and emerging evidence suggests that glycaemic spikes and patterns rather than single measures of glycaemia may be more indicative of poor dysglycemic management and provide novel information regarding maternal and offspring health risks (26). These details are captured using continuous glucose monitors (CGM), which repeatedly record glucose measures in close succession (minutes) over a specific period of time (days or weeks), and offer detailed records of glucose dynamics (27). The capabilities of CGM recently demonstrated novel associations between CGM-defined markers of dysglycemia at (i) 12-weeks' gestation with infant health outcomes [i.e., preterm birth: OR = 1.52 (1.08, 2.13); large-for-gestational age: OR = 1.49 (1.06, 2.08)] and (ii) 24 -week gestation with maternal outcomes [pre-eclampsia: OR = 1.98 (1.17, 3.37)] (28). This suggests that CGM can (i) offer new information regarding the association between dysglycemia, and maternal and offspring health, and (ii) be used to inform and direct care more accurately and at an earlier point of pregnancy. Interestingly, CGM has not yet been used to evaluate the relationship between lifestyle treatment with or without metformin to glucose spikes and variability over a 24-hour period in women with GDM, which could offer novel insights regarding treatment strategies (i.e., diet or diet+metformin) as mediators of dysglycemia across the day in GDM pregnancies. Therefore, this study aimed to determine key time points during the day of disrupted glucose control, and the relationship of treatment and dietary mediators to this disrupted glucose control in a diverse population of pregnant women with GDM.

Abbreviations: AUC, Area under the curve; BMI, Body Mass Index; CGM, Continuous glucose monitoring; CV, Coefficient of variation; GDM, Gestational diabetes mellitus; GI, Glycemic index; iAUC, Incremental area under the curve; NICE, National Institute for Health and Care Excellence; OR, Odds ratio; PPG, Postprandial glucose; PPGR, Postprandial glucose response; RDI, Recommended daily intakes; SD, Standard deviation; SMBG, Self-monitored blood glucose; T2DM, Type 2 diabetes mellitus; TAR, Time above range; TBR, Time below range; TIR, Time in range.

2 Methods

2.1 Study design

Secondary retrospective analysis of an observational cohort of 162 pregnant women with GDM (2). Of 162 women, 128 had complete participant data and < 30% missing CGM data across the 7 days (Supplementary Figure 1). CGM data was collected between 16/01/2014 and 23/08/2016 at the earliest convenient time point (typically 30-32 weeks) following GDM testing and diagnosis between 26-28 weeks gestation. All women provided written informed consent. The study was approved by the Yorkshire and Humber Regional Ethics Committee (13/YH/0268) and NHS Health Research Authority (NRES) Committee South Central–Oxford C (14/SC/1267).

2.2 Study participants

Participants were between 18 and 45 years of age, had a singleton pregnancy, recruited from antenatal diabetes clinics in Leeds Teaching Hospitals Trust and were diagnosed with GDM according to National Institute for Health and Care Excellence (NICE) guideline criteria — i.e., fasting glucose ≥5.6 mmol/L (≤100.8 mg/dL) and/or 2-h glucose ≥7.8 mmol/L (≥140.4 mg/dL) after a 75-g oral glucose tolerance test at ~26 weeks of gestation (3). As per clinical guidelines, all women were advised to aim for self-monitored blood glucose (SMBG) targets: fasting glucose ≤5.3 mmol/L and 1-h post meal ≤7.8 mmol/L (2, 28). Women were treated with diet and lifestyle modifications as first-line therapy and with metformin and/or insulin as second-line therapy. NICE guidelines state that if blood glucose targets are not achieved with diet and lifestyle changes within 1 to 2 weeks, metformin will be offered (3). All women with GDM attending the antenatal diabetes clinic at Leeds Teaching Hospital Trust were invited to participate. Exclusion criteria included having a physical or psychological disease likely to interfere with the conduct of the study, and not speaking English.

2.3 Continuous glucose monitoring (CGM)

The CGM device used was iPro2 (Medtronic). The CGM data was calibrated by simultaneous SMBG using approved and standardized blood glucose meters and test strips (Contour XT; Bayer) (26). Data was anonymised using a unique identification number for each participant and was downloaded *via* CareLink (Medtronic) for analysis. The device measures glucose levels every 5 minutes over a 24-hour period, providing 288 measures every day for 7 days. To analyse mean glycemic control over a 24-hr period, the individual timepoint measurements were averaged across 7 days. This provided 288 average measures of glucose over a 24-hr period.

To analyse key time points across the 24-hr day, the CGM glucose data was analysed by dividing the data into four equal periods of six hours (e.g., morning 06:00-11:55, afternoon 12:00-17:55, evening 18:00-23.55, and overnight 00:00-05.55). These windows were chosen so that the morning, afternoon, and evening time periods include pre- and post-prandial glucose levels, and the overnight time-period monitors a sleep cycle and a sustained fasted state. To evaluate dysglycemia, our primary outcome of interest was coefficient of variation (CV). However, additional indices were examined for the full 24hr hours and for each period, including: mean glucose levels, standard deviation (SD), area under the curve (AUC) and incremental area under the curve (iAUC), which quantifies the deviation of glucose levels from baseline over given length of time, and the percentage of time spent within the pregnancy glucose target range (TIR; 3.5–7.8 mmol/L [70.2– 140.4 mg/dL]), time spent above (TAR; >7.8 mmol/L [≥140.4 mg/dL]) and below (TBR; <3.5 mmol/L [≤ 70.2 mg/dL]) target range (27).

2.4 Nutritional data

In an exploratory analysis, complete nutritional information was available in a subgroup of 34 of the 128 women with CGM data (Supplementary Figure 1). Average daily dietary intake was collected using an online food diary (myfood24) (29). Participants were instructed to complete the online record for 5 days. Dietary intake was recorded as mean total grams or kilocalories per day. After removal of 1 participant with an implausible total kilocalorie intake <500 kcal/day (30), the nutrient residual model was used to perform tests for linear association between individual macronutrients and glycemic measures in 33 participants (31), after adjustment for maternal age, ethnicity, parity, maternal BMI, and weeks of gestation (32, 33). Briefly, the nutrient residual model reduces confounding by using the residuals of total energy intake, which represent the difference between each individual's actual intake and the intake predicted by their total energy intake, thereby removing the variation caused by total energy intake rather than absolute intake (31). Total kilocalorie intake per day for each participant was standardised to the average energy intake per day within our study (1500 kcal/day). To assess the association of macronutrients and glycemic control, we constructed multiple variable regression models for each CGM metric (e.g., mean glucose, SD, CV, AUC, iAUC, TIR, TAR or TBR). Each model CGM model included all macronutrients — i.e., total carbohydrate intake (kcal) + total fat intake (kcal) + total energy intake (kcal) — and covariates (maternal age, ethnicity, parity, maternal BMI, and weeks of gestation). This model permits the assessment of substituting carbohydrates, fats, or proteins (reflected by total energy intake) with an isocaloric equivalent quantity of the other macronutrients. Specifically, these models examine the association of each macronutrient independently with CGM metrics, when all other variables (i.e., other macronutrients, energy, and covariates) are held constant. With three macronutrient sources of energy, when 'carbohydrates' and 'fats' are held constant, the increase in the 'calorie' variable represents an increase in 'protein' (31).

2.5 Statistical analysis

Friedman's test and pairwise Wilcoxon signed rank test were used because of visually apparent asymmetric data, with Bonferroni corrections applied for multiple comparisons between periods of the day. Recent evidence suggests a difference in effect size of 0.924

(Cohen's d) on mean glucose between diet and diet+metformin; therefore, at 80% power we required ≥ 21 participants between comparison groups (34). To assess the association between dietary macronutrients and glycaemic control, multiple variable linear regression analyses were performed and adjusted for maternal age, ethnicity, parity, maternal BMI, and gestational week. The Cook's Distance was used for influential outlier assessment. Statistical significance was set at $p<0.05$. All statistical analyses were conducted in RStudio (version 4.0.3), and all figures were created in GraphPad Prism 9.

3 Results

Over a 24-hour period, glucose measures were collected every 5 minutes, yielding a total of 288 glucose measurements per individual and a total of 36,864 glucose measurements for 128 women. In total, 34 women were excluded, due to incomplete participant data and <30% missing CGM data across the 7 days. The majority of participants self-identified as white European (61%) and managed their dysglycemia with diet alone (n=58), diet+metformin (n=51), diet+insulin (n=2), or diet+metformin+insulin (n=17). Due to small numbers and inadequate power of insulin and metformin+insulin treatment groups (i.e., <21 participants), analysis on treatment effect was limited to diet and diet+metformin groups. The average age and BMI of participants was 33 years and 30.6 kg/m^2. Approximately 30% of women, 34 out of 128 with available CGM data, used myfood24 to record their dietary intake. Participant characteristics are summarised in Table 1.

3.1 CGM analysis

An effect of "time of day" was identified for the majority of CGM metrics — including, mean glucose, SD, CV, AUC, iAUC, and TAR (Figure 1 and Table 2). Therefore, pairwise analyses were performed on all CGM metrics. For CV and SD, measures were relatively stable during the day but lowered 'overnight' (Figure 1). Conversely, glucose and total AUC increased steadily from morning to evening and dropped overnight (mean glucose and AUC; all time comparisons $P>0.001$). When focussing on measures of glycemic variability, SD and CV of glucose were greatest in the morning and steadily decreased towards the lowest levels overnight (SD; 0.49mmol/L vs 0.30mmol/L and CV; 8.41% vs 4.99%, $P<0.001$). iAUC fluctuated over the 24-hour period, with the highest levels recorded in the morning and evening (1244.5 vs 1311.6 mmol/L.min^{-1}, $P=0.87$), reductions in the afternoon (1106.0 mmol/L.min^{-1}, $P<0.001$) and recording the lowest levels overnight (604.9 mmol/L.min^{-1}, $P<0.001$). The Friedman test reported no significant differences when glucose levels were within (TIR), or below (TBR) a specific range, no differences were confirmed between times-of-day either (Figure 1 and Table 2). However, TAR significantly differs across the day and was highest during the evening (TAR evening; 4.41%, $P=0.018$).

3.2 Exploratory analysis

3.2.1 Treatment data

Our exploratory *post-hoc* analysis of treatment included 109 women (n=58 in diet subgroup and n=51 in diet+metformin). A significant association of treatment adjusted for confounders (i.e., maternal age, BMI, gestational week, parity and ethnicity) on mean glucose and AUC was found ($F(3,1)=20.2$, $P<0.001$ and $F(3,1)=22.0$, $p<0.001$, respectively), BMI and gestational week were found to be significant confounders. Both mean glucose (5.65 vs 5.97mmol/L) and total AUC (8115.1 vs 8586.1 mmol/L.min^{-1}) was higher in metformin subgroup. No interaction between time-of-day and treatment on CGM metric was found.

Our exploratory analysis of nutritional data included 34 women (Table 3). Of the 8 CGM metrics assessed, mean glucose and AUC showed significant associations with dietary mediators. To clarify, these models examine the association of each macronutrient with

TABLE 1 Participant characteristics.

Characteristics	Total group (n=128)	Nutrition measure subgroup (n=34)	Diet subgroup (n=58)	Diet+metformin subgroup (n=51)
Age (yrs)	33.0 ± 4.5	32.2 ± 5.0	32.8 ± 4.8	33.4 ± 5.1
BMI at start of pregnancy (kg/m^2)	30.5 ± 6.1	29.7 ± 5.9	28.9 ± 5.7	31.1 ± 6.4
Gestational week	31.1 ± 1.2	31.5 ± 1.2	31.1 ± 1.3	31.1 ± 1.1
Parity	1.0 ± 1.1	1.0 ± 0.6	1 ± 1.3	1 ± 0.9
Treatment				
Diet	58 (53%)	18 (53%)	58 (100%)	0
Diet+metformin	51 (47%)	16 (47%)	0	51 (100%)
Ethnicity				
White European	78 (61%)	25 (74%)	34 (59%)	27 (53%)
Ethnic minority (Black or Asian)	50 (39%)	9 (26%)	24 (41%)	24 (47%)

For characteristics, data reported as mean ± standard deviation (SD) per day of each nutrient and total energy intake. For treatment and ethnicity, number of participants (n) is reported and proportion of total participants is reported in parentheses.

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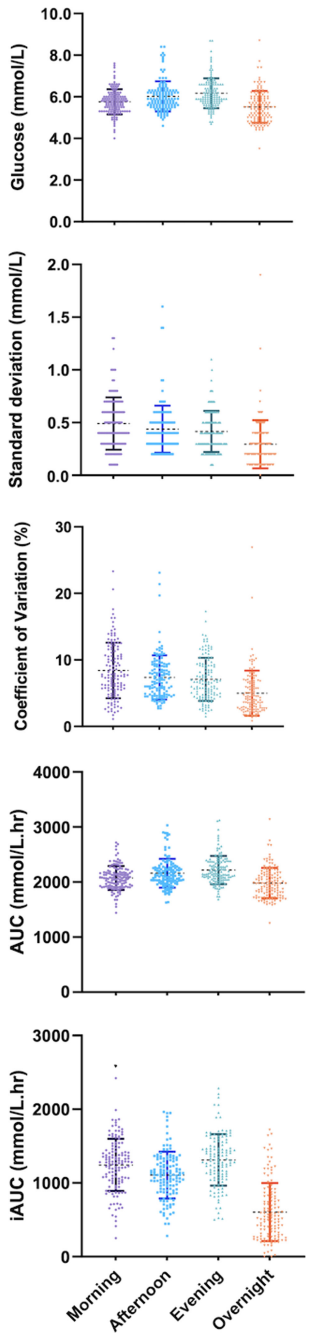

FIGURE 1
Mean 7-day measures of continuous glucose monitoring (CGM) across periods of a day for 128 women with GDM.

glycemic metrics, when the other macronutrients are held at a constant level — e.g., carbohydrates when intake of dietary fat and protein are held constant. With only three macronutrient sources of energy (i.e., carbohydrates, fats, and protein), when 'carbohydrates' and 'fats' are held constant, any increase in the 'calorie' variable represents an increase in 'protein' (31). After adjusting for known confounders (i.e., maternal age, BMI, gestational age at CGM measurement, parity, ethnicity, and treatment), an increase (+1 SD) of fats or carbohydrates associated with higher mean 24-hr glucose and AUC glucose (Table 4), while dietary protein (+1SD) associated with reduced mean 24-hr glucose (-0.91mmol/L; P=0.02) and AUC glucose (-1296 mmol/L.min^{-1}; P=0.021). A *post-hoc* analysis suggested the multiple variable model was well powered to minimize the risk of for type II errors (i.e., false negatives) for protein as a covariate (power>80%) but was not adequately powered (< 50%) to minimize the risk for fats and carbohydrates.

4 Discussion

In an observational cohort of 128 women with GDM, this study demonstrated that (i) CGM offers different methods of assessing glycemic health; (ii) measures of dysglycemia vary considerably over a 24-hour period; and (iii) distinct periods of day are prone to lower or higher levels of absolute glucose as well as glucose variability. Depending on the CGM metric used, 'morning' and 'overnight' showed to be times of greatest dysglycemia. More specifically, glucose levels were most variable during the day (morning to evening) but were stable in a healthy range (≈95% of the time), while 'overnight' showed extended periods of lower glucose levels with relatively less glucose variability. Additionally, exploratory analysis of the association between treatment type (diet vs diet +metformin), time-of-day and maternal glycemic control showed no significant interaction between treatment type and time-of-day on maternal glycemia over a mean 24h period. However, individuals assigned to diet with metformin appeared to have higher levels of dysglycemia, as reflected by elevated mean glucose and total AUC.

Current measures of dysglycemia often use fasting or mean glucose levels to evaluate glycemic control. In our analysis, we report the mean morning, afternoon, and evening glucose levels to be significantly higher compared to mean glucose levels overnight. This agrees with existing understanding of overnight glycemic control, with glucose levels typically falling overnight (35). However, recent work has speculated that glucose excursions quantify a health risk that is independent of mean glucose levels (36, 37). The proposed standard metric for glycemic variability is the CV of glucose (27, 37), which quantifies the magnitude of glycemic variability standardised to mean glucose levels. Despite seeing no difference in mean glucose levels between, afternoon, and evening, our study shows that CV steadily declines during the day reaching lowest values 'overnight' and reports that morning CV was significantly higher compared to other times-of-day. This agrees with trends observed in non-diabetic men and women (n=60) that reported significantly higher Daytime CV (06:00-21:59) compared to Overnight CV (22:00-05:59) (38) but disagrees with evidence from adolescent boys and girls (n=107; 13.1 ± 2.6 years) that suggests CV increases from early morning (06:00) and peaks from midday to late-night (12:00-23:00) (39). However, the significance in temporal CV patterns was not formally assessed for adolescents, so its importance is uncertain. Recent work suggests that diabetes CV is involved with offspring growth in the 2nd trimester in women with type-1 diabetes (40, 41), and may be an indicator of risk of future health complications associated with T2DM (including cardiovascular disease, coronary events, non-cardiovascular mortality, and total mortality) (4). Therefore, morning control of glucose variability (measured by SD and CV) may be a key point of interest for managing maternal and offspring health. Increased morning CV in this study's group of women might also be the result of a lack in

TABLE 2 Summary of measures of continuous glucose monitoring CGM over a 24-hour period.

	Daily Average	Morning (6:00-11:55)	Afternoon (12:00-17:55)	Evening (18:00-23:55)	Overnight (24:00-5:55)
Glucose (mmol/L)					
Mean ± SD	5.86 ± 0.64	5.76 ± 0.60[a]	6.02 ± 0.72[b]	6.17 ± 0.71[c]	5.51 ± 0.64[d]
95% CI	[5.75, 5.97]	[5.66, 5.87]	[5.89, 6.14]	[6.04, 6.29]	[5.38, 5.64]
Standard deviation of Glucose (mmol/L)					
Mean ± SD	0.57 ± 0.21	0.49 ± 0.45[a]	0.43 ± 0.22[b]	0.41 ± 0.20[b,c]	0.30 ± 0.22[d]
95% CI	[0.54, 0.61]	[0.45, 0.53]	[0.40, 0.47]	[0.38, 0.45]	[0.26, 0.33]
Coefficient of variation of Glucose (%)					
Mean ± SD	9.76 ± 3.36	8.41 ± 4.17[a]	7.35 ± 3.32[b]	7.08 ± 3.22[b,c]	4.99 ± 3.38[d]
95% CI	[9.18, 10.35]	[7.69, 9.14]	[6.78, 7.93]	[6.52, 7.64]	[4.40, 5.58]
Area Under the Curve of Glucose (AUC; mmol/L.min^{-1})					
Mean ± SD	8433.8 ± 913.9	2073.7 ± 216.8[a]	2160.5 ± 260.8[b]	2218.6 ± 255.8[c]	1980.9 ± 276.9[d]
95% CI	[8275.4, 8592.1]	[2036.2, 2111.3]	[2115.4, 2205.7]	[2174.3, 2262.9]	[1932.9, 2028.8]
Incremental Area Under the Curve of Glucose (iAUC; mmol/L.min^{-1})					
Mean ± SD	3606.4 ± 1034.5	1244.5 ± 354.3[a]	1106.0 ± 318.1[b]	1311.6 ± 349.0[a,c]	604.9 ± 393.1[d]
95% CI	[3427.2, 3785.6]	[1183.1, 1305.9]	[1050.8, 1161.1]	[1251.1, 1372.0]	[536.8, 673.0]
Time in Range Metrics					
TIR (% of day)	96.91 ± 9.35	98.46 ± 5.70[a]	96.03 ± 14.55[a]	95.59 ± 15.17[a]	97.57 ± 11.92[a]
TAR (% of day)	2.90 ± 9.16	1.5 ± 5.69[a]	3.97 ± 14.55[a]	4.41 ± 15.17[a]	1.71 ± 8.88[a]
TBR (% of day)	0.19 ± 2.15	0.04 ± 0.49[a]	0.0 ± 0.0[a]	0.0 ± 0.0[a]	0.72 ± 8.10[a]

All time metrics are mean measures across 7-days: TIR, time with glucose level measured within 3.5-7.8 mmol/L; TAR, time with glucose level measured above 7.8mmol/L; TBR, time with glucose level measured below 3.5mmol/L. The figures show each CGM metric and time-of-day, for visual aid.
Significant differences between times of day ($P<0.05$) for individual metrics are denoted by different superscripts (a, b, c, d).

regular routine, these women may need to get their other children ready for school and/or get ready for work and may not have time for breakfast.

Our exploratory *post-hoc* analysis of treatment effect adjusted for confounders (i.e., maternal age, BMI, gestational week, parity and ethnicity) demonstrated a significant relationship between treatment group and 2 of the 8 CGM metrics showing persistent higher mean glucose levels and total AUC in women treated with diet+metformin. Although, BMI and gestational age were found to be significant confounders, mean gestational age did not differ between treatment groups. Higher BMI and later pregnancy have been previously associated with decreased glucose control (5, 20, 42). Despite the lack of a significant relationship between metformin treatment group and other CGM metrics, it is important to note that blood glucose levels vary significantly day by day and glycemic control and variability depend on a variety of different exogenous and endogenous determinants such as, elevated insulin resistance, elevated hepatic glucose production, increased production of antagonistic hormones to insulin, sedentary lifestyle, unhealthy dietary habits and age related metabolic deterioration (42). Although metformin is the most commonly prescribed antihyperglycemic medication for diabetes in the U.K., its effectiveness in glycemic control is only now being documented. Noteworthy, metformin is only prescribed when women are failing to achieve glucose targets with diet alone; therefore, glucose levels in this group are higher. Estimates from recent trials suggest that at higher doses metformin can reduce HbA1c by 1–2% (11– 22 mmol/mol) (43), this is promising as it has been reported that a 1% reduction in HbA1c in women with GDM is associated with improved maternal and offspring outcomes (44). Furthermore, a recent study by Bashir et al. (20) found that women

TABLE 3 Nutritional intake: Average values of nutrients intake reported by random subsample of 34 participants that maintained dietary records.

	Daily intake (kcal/day) (% total kcal/day)	Daily intake (gram/day)
Protein	246 ± 92 (16%)	61 ± 26
Fats	577 ± 290 (38%)	64 ± 33
Carbohydrates	716 ± 311 (47%)	176 ± 74
Non-sugar	474 ± 208	117 ± 50
Sugar	242 ± 179	59 ± 43
Total intake	1513 ± 517	N/A

Data reported as mean intake ± standard deviation (SD) per day of each nutrient and total energy intake. Mean proportion of nutrients of total caloric intake reported in parentheses.

TABLE 4 Multivariable regression of dietary mediators (carbohydrates, fats, and protein) and glycemia stratified by outcome metric of 33 participants that maintained dietary records and had CGM metrics available.

	Mean glucose (mmol/L)		AUC (mmol/L.min^{-1})	
Variables	β (95% CI)	P-value	β (95% CI)	P-value
Age	*-0.015 (-0.05, 0.02)*	*0.38*	*-22.1 (-70.2, 25.9)*	*0.38*
Maternal BMI	*0.022 (-0.005, 0.05)*	*0.12*	*31.8 (-7.1, 70.7)*	*0.12*
Gestational week	*0.009 (-0.12, 0.14)*	*0.89*	*12.5 (-173.3, 198.3)*	*0.90*
Parity	*0.093 (-0.24, 0.28)*	*0.49*	*132.5 (-240.4, 505.3)*	*0.50*
Ethnicity	*0.22 (-0.36, 0.4)*	*0.93*	*23.2 (-526.2, 572.6)*	*0.93*
Treatment type	*0.17 (-0.08, 0.52)*	*0.17*	*315.5 (-121.5, 752.5)*	*0.17*
Adjusted carbohydrates	0.63 (0.13, 1.1)	**0.021**	887.9 (173.6, 1602.2)	**0.023**
Adjusted fats	0.49 (0.04, 0.93)	**0.043**	694.7 (48.5, 1340.8)	**0.046**
Adjusted protein	-0.91 (-0.2, -1.6)	**0.02**	-1296.0 (-265.0, -2327.0)	**0.021**

Mean glucose r^2 = 0.321, AUC r^2 = 0.318. Treatment was coded as follows: 0=diet, 1=diet+metformin. Parity was reported as having 0, 1, 2, 3, 4, 5 or 6 children. Ethnicity was coded as: 0=White and 1=Ethnic minority (e.g., Asian, Black African). CI, confidence interval. Significant associations (P<0.05) in bold.

with GDM on pharmaceutical treatment were diagnosed earlier than women on dietary treatment, and it is likely that early treatment intensification with diet and metformin has led to reduced foetal glucose levels, foetal hyperinsulinemia and macrosomia.

In our exploratory analysis, a subgroup of participants recorded their dietary intake for 3 days using myfood24 (29). According to the recommended daily intakes (RDI) set by the Diabetes Care Programmes (45), carbohydrate and protein intake are both low and the fat intake is above recommendations. Of the 8 CGM metrics assessed, mean glucose and AUC showed significant associations with dietary mediators. Our exploratory analysis off 33 women showed an increase in AUC and glucose levels associated with carbohydrate and fat intake. Various dietary carbohydrates – e.g. glucose, sucrose, cooked starches found in pastas and white bread) are readily digested and absorbed in the small intestines, this contributes to a rapid increase in blood glucose (46). Other studies have established that maternal glucose responses can be considerably influenced by the total amount of carbohydrates consumed (46). Increased dietary fat intake (high in saturated fat) has been associated with increased PPG levels and circulating fatty acids (47). Chronic increased level of circulating fatty acids have been linked to increased insulin resistance and inflammation, which are associated with risk of preeclampsia and preterm delivery (47, 48). Additionally, previous studies have demonstrated that elevated PPGRs contribute to an increased glucose transport to the foetus correlating with infant size and/or adiposity (46). Furthermore, our results showed that increasing protein intake by 1 standard deviation (while holding dietary carbohydrates and fats quantities constant) is associated with lower mean glucose and total AUC. While current positions and recommendations of major health bodies [National Health Services (UK), Canadian Diabetes Association, the American Diabetes Association, and the European Association for the Study of Diabetes] focus on replacing low-quality processed (high glycemic-index) carbohydrates with high-quality (low glycemic index) carbohydrates for diabetic patients, our analysis positions protein as an additional dietary pathway to manage gestational dysglycemia. The influence of protein on glycemia is likely to be explained by its more efficacious effect stimulating a rise in glucagon levels than glucose is in suppressing it – i.e. based on weight, protein is 10 times more efficacious than glucose in affecting the glucagon response in normal individuals (18). A previous study has concluded that substituting some of the fruit content with slowly digestible starch sources (e.g. legumes and al dente pasta, etc.), and increasing the protein content may result in a diet that is more acceptable for management of T2DM (49). Although this study was not designed to investigate interactions between carbohydrates quality consumed and time of day, future studies may be appropriately designed to investigate such an interaction and report on the importance of timing high nutritional-quality meals to manage dysglycemia.

This study has offered insight into temporal changes of dysglycemia and demonstrated the value of commonly reported CGM metrics, however, there are limitations to the study. First, although the study population was ethnically diverse, we had inadequate power to test for ethnic-specific association. Second, all women were diagnosed with GDM according to U.K. NICE criteria (3); therefore, our study population may not be representative of women diagnosed for GDM by alternative criteria (e.g., IADPSG – International Association of Diabetes and Pregnancy Study Group) (50, 51). Third, the CGM data were obtained at one time-period of gestation, which may not be representative of glycemia at other times during the pregnancy. Fourth, due to unequal number of total measurements between days and participants, we averaged the 7-days data (that was available for participants) into a 24-hr period for analysis. While this prevented us from assessing a glucose shifts over multiple days or comparing weekdays and weekends, it allowed us to identify timepoints in a 24-hour period where glucose excursions were common. Furthermore, no physical activity data was available, thus its influence on the results as a modifier could not be evaluated. Also, as participants were diagnosed for GDM and recruited at the similar times, treatment duration did not vary greatly but we acknowledge that duration of treatment may modify dysglycemia and that this may be evident in a larger sample size. Finally, dietary logs were available only for a subgroup of

participants and their mealtimes were not recorded; nonetheless, our analyses suggest future investigations of the role of dietary protein and carbohydrate quality on dysglycemia are warranted.

In summary, these results confirm that CGM is a rich source of information that could detect and quantify periods of dysglycemia. Additionally, we demonstrate that each of the metrics available to characterise CGM data, offers unique information to characterise an individual glucose profile and its variability. Therefore, demonstrating the complexity of maternal dysglycemia, which is not easily summarised by a single glycemic metric. Moreover, individuals assigned to diet with metformin appeared to have the greatest difficulty managing glycemia, suggesting the need for more directed care and follow-up may benefit this group of individuals. Finally, our exploratory analysis suggests that increased protein intake may assist with dysglycemia management, and that consideration of both protein and carbohydrate quality may provide optimal support for managing dysglycemia.

4.1 Resource Identification Initiative

To take part in the Resource Identification Initiative, please use the corresponding catalog number and RRID in your current manuscript. For more information about the project and for steps on how to search for an RRID, please click here.

4.2 Life Science Identifiers

Life Science Identifiers (LSIDs) for ZOOBANK registered names or nomenclatural acts should be listed in the manuscript before the keywords with the following format:

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For more information on LSIDs please see Inclusion of Zoological Nomenclature section of the guidelines.

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 Yorkshire and Humber Regional Ethics Committee (13/YH/0268) and NHS Health Research Authority (NRES) Committee South Central–Oxford C (14/SC/1267). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ES designed the original study protocol. CD, ES, and MZ contributed to design of secondary analysis plan. ES provided the CGM in GDM dataset. JC provided the dietary data in the dataset. CD and MZ prepared the data for analysis. CD, MZ, JC, ES, and MH contributed to the data analysis and statistical analysis. CD and MZ have primary responsibility for the final content. CD wrote the first draft of the manuscript. ES, MC, JC, and MH provided critical feedback. CD and MZ are the guarantor of this work and, as such, 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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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/fendo.2023.1065985/full#supplementary-material

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Predictors for pharmacological therapy and perinatal outcomes with metformin treatment in women with gestational diabetes

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Background: The prevalence of gestational diabetes mellitus (GDM) has been increasing in Australia and worldwide. The study aims were to examine, in comparison with dietary intervention, perinatal outcomes for women with gestational diabetes who were attending a single hospital clinic and to identify predictors for their pharmacological GDM treatment.

Methods: A prospective, observational study of women with GDM, treated with "Diet, N= 50", "Metformin, N = 35", "Metformin and Insulin, N = 46" or "Insulin, N = 20".

Findings: The mean BMI for the whole cohort was 25.8 ± 4.7 kg/m^2. The Metformin group, compared to the Diet group, had OR=3.1 (95% CI:1.13 to 8.25) for caesarean section birth (LSCS) compared to normal vaginal birth mode with no longer such a significant association after controlling for the number of their elective LSCS. The insulin treated group had the highest number of small for gestational age neonates (20%, p<0.05) with neonatal hypoglycaemia (25%, p< 0.05). Fasting glucose value on oral GTT (glucose tolerance test) was the strongest predictor for a pharmacological intervention requirement with OR = 2.77 (95CI%: 1.16 to 6.61), followed by timing of OGTT with OR=0.90 (95% CI: 0.83 to 0.97) and previous pregnancy loss with OR=0.28 (95% CI:0.10 to 0.74).

Interpretation: These data suggest that metformin may be a safe alternative treatment to insulin treatment in GDM. Raised fasting glucose on oral GTT was the strongest indicator that GDM women with BMI < 35 kg/m^2 may require pharmacological therapy. Further studies are needed to identify the most effective and safe management of gestational diabetes within the public hospital setting.

Australian New Zealand Clinical Trial Registry ANZCTR Trial Id: ACTRN12620000397910.

KEYWORDS

gestational diabetes mellitus, dietary intervention, perinatal outcomes, metformin, treatment predictors

1. Introduction

The prevalence of gestational diabetes mellitus (GDM) has been increasing in Australia and worldwide likely due to rising average maternal age and increasing obesity especially in young adults (1). In Australia, GDM is now becoming a common complication of pregnancy as it affects around 10% of pregnancies with up to 30% of pregnancies being affected by GDM in high-risk populations (2). In most cases, GDM occurs in pregnant women with impaired pancreatic function, which is insufficient to overcome the insulin resistance associated with the pregnant state.

In recent years, GDM has been diagnosed more frequently in Australia based on more stringent diagnostic criteria recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), which were endorsed by the Australasian Diabetes in Pregnancy Society (ADIPS) (2). The usual time point for GDM screening is recommended to be between 24-28 weeks of pregnancy (3). Earlier screening, recommended by these expert groups, in high risk women is desirable to enable lifestyle interventions focused on diet, physical activity, and weight control to be initiated during the first or early second trimesters of pregnancy (4).

The diagnosis of GDM carries important risks of adverse short and long-term clinical outcomes for women and their offspring. The main immediate consequences of GDM are increased risks of preeclampsia, large for gestational age (LGA) newborns, and caesarean birth, with their associated perinatal co-morbidities (5). GDM is associated with up to 10-times higher odds for the development of future maternal type 2 diabetes or prediabetes in comparison with individuals with a normoglycemic pregnancy (6). Women who are affected by GDM are not only at high risk of developing type 2 diabetes later in life, furthermore, having gestational diabetes is associated with a relative risk of 2.0 (95% CI, 1.6-2.5) for being affected by future cardiovascular disease (7).

Importantly, pharmacological treatment has been shown to improve perinatal outcomes of GDM with reductions in preeclampsia, macrosomia, shoulder dystocia and neonatal death (8). Insulin has been recommended as the first-line treatment agent for GDM in the U.S (9) while in the UK, the National Institute for Health and Care Excellence (NICE) together with Scottish and Canadian guidelines recommends that metformin, an insulin sensitizer, which reduces hepatic gluconeogenesis, and increases peripheral glucose uptake (10), may be considered as initial pharmacological glucose lowering treatment in GDM women (11). Although insulin therapy has been shown to reduce the risk of neonatal macrosomia and rate of serious perinatal outcomes such us shoulder dystocia or perinatal death (12), the benefits of insulin treatment in pregnancy often do not extend to preventing neonatal hypoglycaemia, frequently requiring intravenous glucose infusion and neonatal high-level nursery admission (13). Furthermore, gestational insulin therapy requires additional education, resources and training with the need for increased care for women throughout pregnancy and the act of injecting insulin can be stressful for some women.

At our institution, in our cohort of pregnant women with GDM, metformin has been endorsed as an alternative treatment to insulin therapy. We have therefore hypothesized that metformin use to treat GDM will result in similar pregnancy outcomes in comparison to pregnant women who are treated with insulin alone.

The present study examined perinatal outcomes for women with GDM who were treated with pharmacological interventions in comparison with dietary lifestyle changes alone while controlling for differences in baseline maternal characteristics. In particular, the primary aim was to examine the differences in composite maternal and in neonatal outcomes between four GDM treatment groups ("Diet", "Metformin", "Metformin and Insulin", "Insulin"). In addition, specific maternal and neonatal outcomes were also reported and analysed separately. The second aim of the study was to identify early clinical maternal predictors for the use of pharmacological treatment in pregnancy affected by GDM.

2. Materials and Methods

2.1. Study design

We have conducted a prospective, observational, cohort study through a review of the medical records of women with GDM in singleton pregnancy who attended the multi-disciplinary Gestational Diabetes Clinic at Sutherland Hospital, Sydney, Australia, between years 2016 to 2018. The analyzed data were consecutively extracted from electronic and from hard copies of medical records.

Weight was measured to the nearest 0.1 kg on a digital scale (TANITA, Wedderburg) and height was measured to the nearest 0.1 cm with a scale-mounted stadiometer during the first antenatal visit. BMI (kg/m^2) was calculated. Women with Type 1 and 2 pre-gestational diabetes as well as women with BMI exceeding 35 kg/m2 were excluded from the analysis, as their care was transferred to the tertiary referral centre. Furthermore, in our institution women who underwent previous lower segment caesarean sections (LSCS) were not being offered an option of vaginal birth after caesarean delivery (VBAC).

The Southern Eastern Sydney Local Health District Human Research Ethics Committee (Study Reference No. RESP/15/107) approved the study. The study was registered with Australian New Zealand Clinical Trial Registry ANZCTR Trial Id: ACTRN12620000397910. This cohort study, in accordance with the current rules of the local Research Ethics Committee, did not require the patient's informed consent.

2.2. GDM diagnosis and treatment

GDM was diagnosed, as recommended for Australian women who are at 24–28 weeks gestation, using a 75-g oral glucose tolerance test (OGTT) following an overnight fast, applying the new diagnostic criteria, introduced in 2015, of a fasting plasma glucose ≥ 5.1 mmol/L, a 1-hour plasma glucose ≥ 10 mmol/L or a 2-h plasma glucose ≥ 8.5 mmol/L, as endorsed by ADIPS (14, 15). In our institution early screening (i.e., before 24 weeks gestation) is performed in high-risk patients including those with previous GDM, or other risk factors for GDM (pre-pregnancy BMI > 30 (kg/m2), previous birth of baby with birthweight above 4000 grams, family history of diabetes or those of a high-risk ethnicity)) (16).

All women diagnosed with GDM attended two separated education sessions containing dietary and lifestyle advice in pregnancy, which were run by a Diabetes Nurse Educator and

Dietician. Women were advised to monitor their blood glucose levels (BGLs) 4 times daily using a blood glucose meter: in a fasting condition as well as at 2-hours post breakfast, lunch and dinner. Women were advised to follow a carbohydrate modified diet (30–45 grams of carbohydrate at main meals, 15–30 grams of carbohydrates at mid meals) and they were encouraged to consume low glycaemic index carbohydrates. In our institution, following Endocrinology advice, GDM women would commence on the pharmacological management when their BGLs, despite lifestyle and dietary modification, were exceeding fasting BGLs =< 5.0 and = <6.7 mmol/L 2-h postprandially. In line with NICE guidelines metformin use was discussed as first line of pharmaceutical therapy (11) together with an alternative choice of insulin treatment as dependent upon patient and physician preference. Insulin alone was a preferred treatment in high-risk women who due to their multiple risk factors underwent earlier OGTT. The insulin was commenced (insulin isophane and/or insulin aspart) based on the pattern of hyperglycaemia. Insulin doses were titrated to target fasting and postprandial BGLs by the treating Endocrinologist. The metformin group included GDM women who were prescribed metformin as the first line therapy. The initial metformin dose was 500 mg daily, which was up-titrated to 2000 mg per day (where tolerated) to aim for adequate glycaemic control. Treatment was intensified by the addition of insulin in women who did not achieve adequate glycaemic control with metformin alone.

Therefore, study patients were prospectively allocated to one of four treatment exposure groups ("Diet", "Metformin", "Metformin and Insulin", "Insulin").

2.2.1 Main primary outcome measure

The main composite study aim was to examine the differences in maternal and in neonatal outcomes between four GDM treatment groups. These perinatal outcomes were: maternal outcomes—mode and gestational age at delivery, timing of delivery and neonatal outcomes— neonatal birth weight, preterm birth, indicated by spontaneous birth before 37 weeks' gestation; large-for-gestational-age (LGA; defined as birth weight > 90th centile for gestational age and gender), small-for-gestational-age (SGA; defined as birth weight (SGA; defined as birth weight < 10th centile for gestational age and gender) (17), presence of shoulder dystocia, neonatal respiratory distress, neonatal hypoglycaemia, jaundice, birth injury and neonatal death. The composite outcome was a binary variable defined as 1 if at least one maternal or neonatal outcome was present, or 0 in the absence of both maternal and neonatal outcomes.

2.2.2 Secondary outcomes measure

In order to identify the secondary study aim three pharmacological interventions were grouped together. For this aim, participants were classified in two groups: 1) any pharmacological intervention, including "Metformin", "Metformin and Insulin", and "Insulin" groups and 2) "Diet".

2.2.3 Neonatal hypoglycaemia

In our institution the presence of formal BGL < 2.6 mmol/L in neonates who are less than 48 hours of age warrants immediate intervention. These neonates are admitted to the neonatal intensive care unit (NICU) for treatment. The definition of neonatal hypoglycaemia is based on the study, which demonstrated reversible disturbance in evoked potentials at BGL < 2.6mmol/l in a small cohort of asymptomatic term babies (18).

The aim of hypoglycaemia treatment is to return the neonatal BGL values to their safe range (> 3.9 mmol/L) through normal nutritional intake. For BGLs ranging from 1.5 to 2.5 mmol/L this occurs through the use of oral 40% Dextrose Gel, which is massaged into neonatal buccal mucosa, followed by refeed with either breast or formula. Severe symptomatic hypoglycaemia is corrected with an IV 10% dextrose bolus at 2 mL/kg and infusion at 60 – 80 ml/kg/day or IM glucagon. High risk neonates are monitored for at least the first 24 hours of life in NICU until the neonate's BGLs remain at safe levels (≥ 2.6mmol/L) for at least 24 hours after the last episode of hypoglycaemia.

2.3. Statistical analysis

Baseline study data are presented as mean (± SD) for normally distributed variables and median (interquartile range) for non-normally distributed variables. Analysis of variance (ANOVA) and *post-hoc* pairwise Tukey honest significance difference test, or Kruskal–Wallis test and *post-hoc* pairwise Dunn's test were used to examine the imbalance between the study groups for normally or non-normally distributed baseline data, respectively. Categorical variables are presented as number (%), and Fisher's exact test was used for the between group comparisons.

The association between pharmacological intervention for GDM and adverse perinatal outcomes was determined using unadjusted and multivariable adjusted logistic regression analyses.

An exploratory analysis examined an association between mode of birth and treatment procedures after adjustment for the differences in baseline characteristics between study groups such as fasting glucose and BMI.

The secondary outcome of the study was to identify early clinical maternal predictors for the pharmacological treatment in GDM. The analyzed study data included maternal characteristic defined as age, ethnicity, body mass index (BMI), family history of diabetes, parity, pooled number of previous miscarriages and pregnancy terminations, previous history of GDM, history of thyroid disease and thyroid stimulating hormone (TSH) values, vitamin B12 levels, 25 (OH) D levels and the timing of OGTT with BGL values on OGTT and gestational age at diagnosis of GDM. The fasting glucose was analyzed as a continuous variable to avoid misclassification error of exposure variable.

Variables were firstly screened in univariate analysis, and those with a p-value < 0.25 were included in the multivariable model. The final model was selected using stepwise regression.

Statistical analyses were conducted using R software version 4.0.4 (2021–02–15) with P value of < 0.05, which was considered statistically significant.

3. Study results

3.1. Baseline characteristics of study patients

During the time period of September 2016 to April 2018, 151 women were identified as being treated with Diet (N = 50),

Metformin (N = 35), taking Metformin and Insulin (N=46) or with Insulin alone (N=20) during singleton GDM pregnancy. The demographics of these groups are outlined in Table 1. There were differences in baseline characteristics between study groups in subjects' height, weight, timing of their OGTT, value of fasting BGL on OGTT, family history of diabetes and total vitamin B12 (Table 1).

Compared to Diet, Metformin and Insulin and Insulin groups were heavier (p = 0.009). In addition, Metformin group, although not on vitamin B12 supplementation, had higher level of total vitamin B12 (p = 0.028), Metformin and Insulin group were more likely to have family history for diabetes (p = 0.019). There were no differences in age, the number of previous pregnancies and live births, number of previous pregnancies affected by GDM, initial HbA1c level, previous thyroid disease, TSH or 25 (OH) vitamin D levels.

3.2. Treatment of gestational diabetes

Metformin and Insulin and Insulin alone groups, as having identified risk factors for the GDM at their first antenatal visit, had earlier OGTTs, an average at 21 weeks, in comparison with the Diet treated group which had an average OGTT at 28 weeks (p = 0.006). There was no difference in the history GDM in previous pregnancies between study groups or in their HbA1c with an average initial HbA1c of 5.2% (± 0.34), (33 mmol/mol). Approximately a third of these pregnant women were diagnosed with GDM in their previous pregnancies and experienced previous spontaneous miscarriages or terminations of their pregnancies.

Women that were treated with insulin or with metformin and insulin had significantly higher fasting glucose on 75 g OGTT (5.19 mmol/L or 5.01 vs. 4.6 mmol/L, respectively, p= 0.0001), in comparison with women treated with diet and lifestyle modification alone without such difference for their 1- hourly and 2- hourly BSL. Caucasian women had a higher mean fasting BGL of 4.9 mmol/L (SD = 0.55), p = 0.015 on oral GTT in comparison with a mean fasting BGL of 4.7 mmol/L (SD = 0.56) in women of Asian ethnicity.

The timing of pharmacological intervention varied between groups. Women treated with insulin were initiated on their therapy earlier at 23 ± 8.3 weeks while women treated with metformin only on average commenced on metformin at 31 ± 4.3 weeks. The mean gestational age at which insulin was added to metformin was 27 ± 6.6 weeks (Table 1).

There was no difference in the total daily dose of insulin at delivery for women in the Metformin and Insulin and Insulin alone groups. There was no difference in the foetal abdominal circumference on the antenatal scans (34-36 weeks).

3.3. Perinatal (maternal and neonatal) outcomes

Maternal and neonatal outcomes for women taking metformin (with or without additional insulin) in comparison with those managed with diet and lifestyle modification are outlined in Table 2. There was no overall difference in maternal and neonatal composite study outcomes between groups (p = 0.13), (Table 2). There was no difference in ethnicity distribution between groups (Table 1). Furthermore, there was no interaction between study procedures and the ethnicity of women with GDM in primary composite study outcome (p = 0.38). In particular, there was no overall difference between study groups in the rate of normal vaginal birth (NVB) (p = 0.19), instrumental vaginal birth (p = 0.14) or LSCS (p = 0.36) or in the gestational age of the time of birth (p = 0.17). However, the comparison of each treatment group to the dietary intervention revealed that metformin treated group had 3.1 times the odds (95% CI: 1.13 to 8.25) for the birth by LSCS with the trend for the positive association between metformin treatment and instrumental vaginal birth (Table 3). Furthermore, once the effect of the treatment procedure on mode of birth was adjusted for the value of fasting glucose on subjects' OGTT and their initial BMI this association became stronger with OR = 3.4 (95% CI: 1.04 to 8.86) for birth by LSCS for the metformin treated group and with OR = 11.12 (1.18 to 104.71) for the instrumental vaginal birth (Table 3). Once we excluded elective LSCS from the analysis, Metformin and Insulin group had lower rate of LSCS than Metformin group without difference to the Diet treated group (Table 2).

There were no differences between subjects treated with pharmacological intervention and dietary/lifestyle modifications in birth weight, numbers of shoulder dystocia, cases of respiratory distress, postpartum haemorrhage, rates of premature delivery or large-for-gestational-age neonates (Table 2). There were 19 neonates who required NICU admission: Diet with N = 7 (14%), Metformin with N=3 (9%), Metformin and Insulin with N = 7 (15%), Insulin with N = 2 (10%). The 8 newborns were separated from their mothers due to admission to NICU caused by: intrauterine growth retardation due to oligohydramnios (2 infants), significant hypoglycaemia (2 infants), respiratory distress requiring CPAP due to meconium aspiration (2 infants), foetal bradycardia (1 infant) and feeding problems due to undiagnosed cleft palate (1 infant).

One- fifth of insulin treated women delivered children who were small for their gestational age. The neonates in insulin alone treated group had the highest proportion (25%) of hypoglycaemic episodes however two of these children were affected by prematurity and by intrauterine growth retardation, respectively. The mothers of neonates with hypoglycaemia, prior to delivery, had high daily insulin requirements, which ranged between 58 units to 104 units.

3.4. Changes in vitamin B12 over time

The were 78 women who had measured total vitamin B12 level at their initial visit. The 8 of them (10%) were noted to have vitamin B12 level below the reference range (RR 150-700 pmol/L). When the cohort of these women was analyzed together, at their baseline and approximately 8 weeks later, there was a reduction in measured total vitamin B12 level from baseline vitamin B12 of 264 ± 96 pmol/L (RR 150-700pmol/L) to vitamin B12 of 242 ± 71 pmol/L (p = 0.019). Due to the limitation of small sample size, we were unable to compare differences between intervention groups.

3.5. Maternal predictors for the pharmacological treatment in pregnancy

3.5.1 Univariate analysis

In the univariate analysis the following variables were positively associated with the need for pharmacological GDM treatment: BMI

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TABLE 1 Baseline characteristics of study subjects.

	All	Diet	Metformin	Metformin And Insulin	Insulin	P -value
Number	151	50	35	46	20	
Ethnicity						
Caucasian	90 (60%)	32 (64%)	19 (54%)	29 (63%)	10 (50%)	0.23
South Asian	27 (18%)	5 (10%)	4 (11%)	10 (22%)	8 (40%)	
East Asian	17 (11%)	6 (12%)	5 (14%)	5 (11%)	1 (5%)	
South-East Asian	13 (9%)	5 (10%)	6 (17%)	2 (4%)	0 (0%)	
Middle Eastern	3 (2%)	1(2%)	1 (3%)	0	1 (5%)	
Height (cm)	162 ± 7.3	164 ± 6.2	159 ±. 6.2	163 ± 7.1	158 ± 9.4**	**0.006**
Weight (kg)	67.4 ± 13.5	64.6 ± 13.3	62.5 ± 9.9	72.2± 13.6*	69.4 ± 15.7	**0.009**
BMI (kg/m^2)	25.8 ± 4.7	24.6 ± 4.7*	24.6 ± 3.9	27.0 ± 4.3*	27.6 ± 5.6**	**0.009**
Age (years)	31.9 ± 4.9	31.4 ± 4.6	31.5 ± 5.0	32.3 ± 4.9	32.9 ± 5.8	0.61
Parity	0.8 ± 1.1	0.8 ± 1.0	0.5 ± 0.6	0.9 ± 0.9	1.3 ± 1.9	0.10
Gravidity	2.4 ± 1.6	2.4 ± 1.5	1.9 ± 1.2	2.4 ± 1.4	3.0 ± 2.3	0.12
Family History of DM	38/121 (31%)	16/42 (38%)	6/25 (24%)	6/36 (17%) *	10/18 (56%)	**0.019**
Miscarriages (N, %)	49 (33%)	19 (38%)	9 (26%)	15 (33%)	6 (30%)	0.094
History of thyroid disease	28 (19%)	8 (16%)	4 (11%)	11 (24%)	6 (30%)	0.29
TSH (mIU/L)	1.6 ± 0.88	1.5 ± 0.78	1.4 ± 0.94	1.7 ± 0.82	2.1± 1.18**	0.16
Active Vitamin B12 (pmol/L)	78 ± 36	78 ± 25	73 ± 24	91 ± 57	52 (47, 58)	0.49
Vitamin B12 (pmol/L)	264 ± 96	286 ± 99	328 ± 119^	248 ± 70	182 ± 8	**0.028**
25 (OH) D (pmol/L)	94 ± 31	96 ± 29	87 ± 36	95 ± 26	82 ± 60	0.75
Past GDM (N, %)	45 (30%)	14 (28%)	7 (20%)	17 (37%)	7 (35%)	0.49
OGTT (weeks)#	27 (17.2, 28)	28 (27, 29)	27 (20, 29)	21 (15.2, 28) *	21 (13.5, 27.5) **	**0.006**
FBGL (mmol/L) on OGTT	4.8 ± 0.6	4.6 ± 0.5	4.7 ± 0.6	5.0 ± 0.5*	5.2 ± 0.5**	**0.0001**
(+ 60 min) BGL	9.6 ± 2.0	9.9 ± 1.7	9.6 ± 1.6	9.1 ± 2.3	10 ± 2.5	0.25
(+120 min) BGL	7.8 ± 1.7	7.9 ± 1.7	8.0 ± 1.3	7.5 ± 1.7	8.2 ± 2.6	0.45
Metformin dose (mg)	971 ± 356		924 ± 383	1006 ± 334		0.32
Metformin start (weeks)	28 ± 6.3		31 ± 4.3	26 ± 6.8		**0.001**
Metformin duration (weeks)	11 ± 6.1		8 ± 4.3	12 ± 7.8		**0.011**
Insulin start (week)	26 ± 7.4			27 ± 6.6	23 ± 8.3	0.072
Insulin dose (units)#	20 (10, 31)			14.5 (9, 28)	31 (13, 39)	0.48
Initial HbA1c (%) (mmol/mol)	5.2 ± 0.4 (33)	5.2 ± 0.4 (33)	5.2 ± 0.3 (33)	5.1 ± 0.3 (32)	5.4 ± 0.3 (36)	0.45
Antenatal US (weeks)	35 ± 1.8	35 ± 1.7	35 ± 1.8	34 ± 2.0	35 ± 1.7	0.32
Abdominal Circumference (%) #	60 (40, 85)	68 (50, 85)	50 (45, 90)	53 (35, 77)	44(14, 81)	0.35
EFW (%) #	50 (42, 75)	50 (43, 71)	61 (50, 85)	56 (40, 70)	46 (16, 66)	0.22
Hypertension	12 (8%)	6 (12%)	2 (6%)	3 (7%)	1 (5%)	0.58
Abnormal Liquor	3 (2%)	1 (2%)	0	1 (2%)	1 (5%)	0.60

(Continued)

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TABLE 1 Continued

	All	Diet	Metformin	Metformin And Insulin	Insulin	P -value
Proteinuria	4 (3%)	1 (2%)	1 (3%)	0	2 (10%)	0.12
Steroid use	13 (9%)	3 (6%)	1(3%)	7 (15%)	2 (10%)	0.25

^Metformin versus Diet, * Metformin and Insulin versus Diet **Insulin versus Diet.
Values are expressed as median and interquartile range (IQR). FBGL, fasting blood glucose level; BGL, blood glucose level; OGTT, oral glucose tolerance test; BMI, body mass index.
Bolded values indicate statistical significance.

TABLE 2 Maternal and neonatal outcomes of study patients.

	Diet N=50	Metformin N=35	Metformin & Insulin N=46	Insulin N=20	Metformin vs Diet OR (95%CI)	Metformin & Insulin vs Diet OR (95%CI)	Insulin vs Diet OR (95% CI)
Primary Composite outcome (N, %)	27 (54)	26 (74)	26 (57)	16 (80)	2.3 (0.89 to 5.82)	1.2 (0.54 to 2.76)	3.1 (0.92 to 10.75)
Maternal Outcomes							
Mode of Birth							
Vaginal, (N, %)	35 (70)	15 (43)	27 (59	12 (60)	**0.4 (0.15 to 0.94)**	0.6 (0.26 to 1.52)	0.6 (0.19 to 1.67)
Instrumental, (N, %)	5 (10)	6 (17)	5 (11)	3 (15)	2.7 (0.60 to 12.16)	1.1 (0.21 to 5.71)	2.8 (0.51 to 15.04)
LSCS, (N, %)	10 (20)	**14 (40) ^**	14 (30)	5 (25)	**2.8 (1.06 to 7.41)**	1.8 (0.69 to 4.46)	1.3 (0.39 to 4.55)
Emergency LSCS, (N, %)	7 (70)	**10 (71) °**	4 (29)	4 (80)	2.9 (0.95 to 9.03)	0.5 (0.12 to 2.18)	1.8 (0.46 to 7.35)
Neonatal outcomes							
Gestational age at birth (weeks)	39 ± 1.3	39 ± 0.8	39 ± 1.4	39 ± 0.9			
Birth weight (gr)	3360 (443)	3228 (507)	3194 (452)	3124 (684)			
LGA, (N, %)	2 (4)	2 (6)	2 (4%)	2 (10)	1.5 (0.19 to 10.85)	1.1 (0.15 to 8.27)	2.8 (0.37 to 21.64)
SMA, (N, %)	2 (4)	4 (11)	3 (7)	4 (2) **	2.0 (0.42 to 9.66)	2.4 (0.55 to 10.0)	**5.6 (1.19 to 26.38)**
Premature birth, (N, %)	2 (4)	2 (6)	5 (11)	1 (5)	3.0 (0.26 to 34.48)	6.0 (0.67 to 53.49)	
Shoulder dystocia, (N, %)	2 (4)	2 (6)	3 (6)	2 (10)	1.5 (0.20 to 11.29)	1.7 (0.27 to 10.67)	1.3 (0.11 to 15.37)
Respiratory distress, (N, %)	4 (8)	2 (6)	2 (4)	2 (10)	0.7 (0.13 to 4.2)	0.8 (0.17 to 3.86)	1.3 (0.22 to 7.92)
Hypoglycemia, (N, %)	6 (12)	3 (9)	6 (13)	**5 (25) #**	0.5 (0.12 to 1.85)	0.96 (0.29 to 2.52)	2.8 (0.86 to 9.04)
Post-partum haemorrhage, (N, %)	7 (14)	5 (14)	6 (13)	3 (15)	1.2 (0.44 to 3.31)	0.3 (0.09 to 1.04)	0.8 (0.23 to 2.96)
Neonatal complications	Bilateral pyelectasis (N=1), cleft palate (N=1)		Positional talipes (N = 1)	Hypospadia-sis (N=1)			

Number (N) of participants with events and Odds Ratios with 95% Confidence intervals for the primary composite event and specific maternal and neonatal outcomes. Sample size was too small to calculate OR for Premature Birth for comparison between Insulin to Diet groups.
LGA- large for gestational age, SGA – small for gestational age.
Bolded values indicate statistical significance. ^ Metformin versus Diet, ** Insulin versus Diet, ° Metformin versus Metformin and Insulin, # P-Values are for the differences between treatment groups.

with OR = 1.1 (95% CI; 1.00 to 1.18, p=0.038), timing of the OGTT in pregnancy with OR = 0.9 (95%CI; 0.86 to 0.98, p=0.0059), fasting BGL values on OGTT with OR = 3.1 (95% CI: 1.50 to 6.47, p=0.0024) and inversely with number of previous miscarriages with OR = 0.5 (95% CI: 0.23 to 1.07, p= 0.075).

There was no association between need for pharmacological GDM treatment and following variables: ethnicity (p = 0.10), age (p = 0.47), history of previous GDM (p = 0.83), TSH level (p = 0.32), previous thyroid disease (p = 0.61), 1-hourly BSL on OGTT (p = 0.20), 2-hourly BSL on OGTT (p = 0.20), initial vitamin B12 level (p = 0.82), initial 25 (OH) D level (p = 0.40) and with positive family history for DM (p = 0.25).

3.5.2 Logistic Regression (Multivariate Analysis).

In the multivariate analysis, the timing of OGTT and personal history of miscarriages or terminations of pregnancy were inversely and significantly associated with need for pharmacological treatment while fasting BGL was a strong and positive predictor of the need for escalating treatment intervention. Maternal BMI value was no longer significantly associated with the need for pharmacological therapy (Table 4).

4. Discussion

The results from the present study support our hypothesis that metformin treatment (alone or combined with insulin) of women with GDM does not result in worse pregnancy outcomes as compared with those who were assigned to insulin. Despite no significant difference in main composite study aim between study groups and Diet group, insulin treatment alone, although prescribed for small number of GDM patients, was associated with a higher proportion of "small for gestational age" neonates and higher rates of neonatal hypoglycaemia in comparison with dietary or metformin treated groups. Such neonatal complications likely resulted from worse glycaemic control in this group of patients as indicated by their high daily maternal insulin requirements, which ranged between 58 units to 104 units.

Importantly, previous large retrospective cohort study reported that pregnancy outcomes are worse in GDM women with SGA neonates than in those without GDM with subsequent increased risks for respiratory distress syndrome, intrauterine foetal death, hypoglycaemia, jaundice and neonatal demise (19).Interestingly however, the metformin treated group in comparison with dietary intervention group had a higher risk for LSCS. Such association between mode of birth and metformin treatment is related not only to the treatment but also to the differences in our subjects basal characteristic. Previous studies have highlighted that, increased maternal BMI either in overweight or obese category without GDM, increased the risk of macrosomia and caesarean delivery when compared to normal weight women (20). In our metformin treated cohort we observed no evidence of foetal growth acceleration on third trimester ultrasound in majority of patients, likely reflective of satisfactory maternal glucose control (21). Indeed, once we excluded elective LSCS from the analysis there was no difference in number of emergency LSCS in metformin group in comparison with dietary intervention.

To our knowledge no randomised trials (RCTs) compared effects of metformin directly to dietary/lifestyle intervention in pregnancy, although several previous studies compared metformin and insulin interventions alongside dietary interventions for both trial arms. The analysis of 16 RCTs or follow-up of a RCTs revealed that metformin in comparison with insulin treatment did not increase the risk of caesarean section (RR = 0.97; 95% CI, 0.80 to 1.19) (22). Furthermore, the meta-analysis consisting of 11 trials reported that women randomised to metformin had lower risk for adverse maternal and neonatal outcomes including lower risk for the instrumental delivery compared to those randomised to insulin (23). The above data points to metformin being a useful alternative to insulin therapy with a high degree of patient acceptability.

Importantly, in comparison with insulin, metformin can significantly decrease maternal weight gain, and therefore

TABLE 3 Effect of GDM treatment procedure on mode of birth.

	LSCS vs NVB		ID VS NVB	
Study treatment groups	**OR (95% CI)**	**P - value**	**OR (95% CI)**	**P - value**
Metformin vs diet	3.06 (1.13 to 8.25)	**0.03**	4.00 (0.85 to 18.90)	0.08
Metformin and insulin vs diet	1.58 (0.62 to 4.00)	0.33	1.24 (0.23 to 6.62)	0.80
Insulin vs diet	1.36 (0.39 to 4.73)	0.62	3.00 (0.53 to 16.19)	0.21
Effect of treatment on mode of birth controlled for fasting BGL on subjects' GTT and BMI				
	LSCS vs NVB		**ID VS NVB**	
Study treatment groups	**OR (95% CI)**	**P - value**	**OR (95% CI)**	**P - value**
Metformin vs diet	3.04 (1.04 to 8.86)	**0.04**	11.12 (1.18 to 104.71)	**0.04**
Metformin and insulin vs diet	1.66 (0.59 to 4.70)	0.34	1.03 (0.06 to 18.11)	0.98
Insulin vs diet	2.22 (0.54 to 9.09)	0.27	10.32 (0.85 to 124.66)	0.07
Fasting BGL (GTT)	1.04 (0.48 to 2.25)	0.92	1.32 (0.38 to 4.51)	0.66
BMI	0.99 (0.91 to 1.08)	0.83	1.00 (0.85 to 1.17)	0.96

LSCS, Caesarean section; NVB, normal vaginal birth; ID, instrumental vaginal birth; BGL, blood glucose level; BMI, body mass index; OR, Odds Ratios.
Bolded values indicate statistical significance.

metformin is now the preferred treatment option for an increasing number of women with a BMI in obese category (24). The efficacy of metformin treatment in GDM is not without limitation, as congruent with present study, approximately 14% to 46% of pregnant women fail to achieve adequate glycaemic control with metformin alone (25).

The lack of longer-term safety studies and that metformin can cross the placenta raise potential concerns associated with metformin therapy in pregnancy. The safety and optimal metformin doses in pregnancy have not been yet defined, however most studies use metformin doses ranging from 500 mg to 2500 mg a day (22). In the present study the metformin treatment was commenced in later stages of pregnancy, on average at 28 ± 6.3 weeks of pregnancy, therefore without effect on early embryonic growth.

To date, no increased risk for non-genetic congenital anomalies has been identified following foetal exposure to metformin during the first trimester of pregnancy. A randomized, placebo-controlled trial of PCOS women who were either randomised to metformin (500 mg twice daily increasing to 1000 mg twice daily) or placebo from the first trimester gestational age between 5 and 12 weeks found no difference in the primary composite study outcome of preeclampsia, GDM and preterm delivery (26). Furthermore, no adverse safety signal was detected in randomised, placebo controlled trial of pregnant women with type 2 diabetes in pregnancy who were randomised either to metformin or placebo at 16.5 weeks of pregnancy. This study found no significant difference in congenital anomaly with 7/227 (3%) affected infants in metformin treated group in in comparison with 13/227 (6%) infants in dietary intervention group (p value of 0.16, RR 0.52 (0.22 to 1.28)) (27). Reassuringly, in previous studies, exposure *in utero* in children of GDM women to metformin (± insulin) or insulin alone led to similar total and abdominal body fat percent and metabolic measures at children at 7–9 years of life (28). Conversely, in a recent study, metformin exposure in the first trimester of pre-gestational diabetes was associated with an increased risk of birth defects and pregnancy loss; however, these adverse pregnancy outcomes were attributed to underlying disease rather than to metformin therapy (29). On-going long term follow-up studies of children born to mothers affected by GDM will help answer this current uncertainty.

In the present study, only 33% of GDM patients achieved satisfactory glycaemic control through the dietary therapy while the majority of pregnant GDM women (77%) required pharmacological treatment. The ability to predict a-priori which GDM group of patients will fail their dietary intervention would help to plan steps more effectively in their GDM management.

Past studies have identified the following predictors of the requirement to introduce pharmacological treatment in GDM. These predictors included early GDM diagnosis (e.g., at <25 weeks gestation), a family history of diabetes, non-European ethnicity, an

TABLE 4 Univariate and Multivariate analysis with predictors of pharmacological therapy in patients with gestational diabetes.

Univariate analysis			
	Odds Ratio	(95% CI)	P - value
BMI (kg/m^2)	1.1	(1.00 to 1.18)	**0.038**
OGTT (weeks)	0.9	(0.86 to 0.98)	**0.0059**
FBGL (mmol/L) (OGTT)	3.1	(1.50 to 6.47)	**0.0024**
Personal history of past miscarriage	0.5	(0.23 to 1.07)	0.075
Ethnicity (Caucasian)	0.54	(0.27 to 1.10)	0.09
Age (years)	1.02	(0.96 to 1.10)	0.47
Past GDM	1.11	(0.49 to 2.54)	0.83
(+ 60 min) BGL (mmol/L)	1.14	(0.94 to 1.38)	0.20
(+ 120 min) BGL (mmol/L)	1.03	(0.84 to 1.28)	0.76
TSH level (mIU/L)	0.78	(0.47 to 1.28)	0.32
Personal history of thyroid disease	1.21	(0.46 to 3.18)	0.61
25 (OH) D level (pmol/L)	0.90	(0.98 to 1.01)	0.40
Vitamin B12 level (pmol/L)	1.0	(1.0 to 1.01)	0.81
Family history of DM	1.59	(0.72 to 3.53)	0.25
Multivariate Analysis			
	Odds Ratio	**(95% CI)**	**P - value**
Fasting BGL (mmol/L) (OGTT)	2.77	(1.16 to 6.61)	**0.022**
Oral GTT (weeks)	0.90	(0.83 to 0.97)	**0.008**
BMI (kg/m^2)	1.05	(0.95 to 1.17)	0.38
Previous miscarriage	0.28	(0.10 to 0.74)	**0.010**

FBGL, fasting blood glucose level; OGTT, oral glucose tolerance test; BMI, body mass index; DM, diabetes mellitus.
Bolded values indicate statistical significance.

older age, elevated fasting blood glucose level, HbA1c at GDM diagnosis, and an elevated pre- pre-pregnancy BMI (20, 30). In our unique group of pregnant non-obese women, we have identified fewer predictors of the need for pharmacological GDM treatment. Those predictors included maternal characteristics such as baseline maternal BMI, value of fasting BGL on their OGTT, the number of previous miscarriages and early GDM diagnosis (e.g., at <24 weeks gestation). Although on average Caucasian women had a higher fasting glucose on their GTT than women of Asian ethnicity, their ethnicity was not a significant predictor of the need for escalating GDM therapy beyond diet alone. Maternal BMI, once controlled for the fasting BGL level on OGTT and timing of the OGTT and number of previous miscarriages, was no longer a significant indicator of the need for pharmacological GDM therapy.

In previous research, elevated pre-pregnancy maternal BMI predicted failure of dietary therapy (20) with higher maternal BMI being significantly associated with the need for medical treatment (31–33). Although obesity is associated with increasing insulin resistance and pancreatic β-cell dysfunction, it remains unclear whether weight control during pregnancy, as recommended by the Institute of Medicine, would reduce the risk of GDM or the need for insulin therapy (34). Considering that our study patients had an average BMI close to the normal range at 25.8 ± 4.7 kg/m^2, we may hypothesise that having an initial BMI in the obese category would have been more closely associated with the need for pharmacological GDM intervention.

In the present research, the value of fasting glucose level on the OGTT was the strongest indicator that women with GDM may not respond to the dietary intervention alone. This study finding is important considering that some at risk women are unable to complete OGTT in pregnancy. Interestingly we have also found the increased risk for LSCS and instrumental vaginal birth with raised fasting BGL in metformin treated group. Interestingly, once the effect of metformin treatment on mode of birth was controlled for fasting glucose on subjects' OGTT and subjects initial BMI, the risk for LSCS or instrumental vaginal birth increased significantly in metformin treated GDM women. The previous retrospective cohort study of 14,741 pregnant women found that fasting hyperglycaemia was associated with increased risk for caesarean birth (OR: 1.33, 95% CI: 1.15-1.55,P < 0.001) (35). Such strong positive association between fasting hyperglycaemia on OGTT and adverse perinatal outcomes, including caesarean birth, was noted in previous systematic review and meta-analysis of GDM women (36).

Multiple studies have highlighted the link between fasting hyperglycaemia in the first and 2nd trimester of GDM pregnancies with increased occurrence of adverse pregnancy outcomes including the need for surgical birth (4, 37, 38). In previous study only fasting plasma glucose value on the oral glucose tolerance test in pregnancy was significantly associated with pregnancy adverse outcomes, irrespectively of pharmacological intervention (39). Therefore, effective treatment of fasting BGL in women affected by GDM may potentially improve maternal and neonatal health outcomes with a great potential for the early detection of women at risk of having more adverse perinatal outcomes, irrespective of their other risk factors, such as obesity and maternal age.

Interestingly, we observed that having at least one previous miscarriage or pregnancy termination may influence the need for pharmacological treatment for GDM women. Several murine studies have reported that progesterone, which is essential to sustain pregnancy, promotes insulin resistance by multiple mechanisms during pregnancy (40–42). Interestingly, previous case control study of 1567 Korean women demonstrated that threatened miscarriage is associated with decreased risk of GDM and the severity of glucose intolerance (43). Conversely, a retrospective cohort study found that having a spontaneous miscarriage was linked to a higher risk for having subsequent gestational diabetes (44). Further research is recommended to confirm these relationships and to evaluate the pathophysiologic mechanisms that interplay between these common obstetric complications.

Several studies have shown that vitamin B12 status during pregnancy is important to the health of mother and her offspring (45). In the present study, limited by the small sample size, approximately 10% of women had total vitamin B12 level in the insufficiency range and their vitamin B12 levels declined significantly during pregnancy. As metformin treatment may reduce ileal absorption of dietary vitamin B12 (46), GDM women treated with metformin would likely benefit from monitoring of their vitamin B12 status.

Our study is not free of limitations, due to pragmatic method of data collection as part of subjects' routine clinical care, rather than at fixed short time intervals. Therefore detailed trajectories of weight gain and glycaemic control during pregnancies were not analysed in this study. However an absence of foetal growth acceleration on third trimester ultrasound in the majority of patients was likely reflective of their satisfactory maternal glucose control (21). Exclusion from the analysis of severely obese women with BMI> 35 kg/m^2 might have reduced the risk of their pregnancy complications and a rate of instrumental or caesarean birth. Due to our small number of adverse perinatal events, and in order to improve the ability to detect differences in the primary study endpoints as well as to increase study statistical power, we have designed the main composite study outcome of combined maternal and neonatal events. Additionally, we have reported detailed information on clinically important events of which the composite outcome is based on, with their measures of association (Table 2). Additional advantage of this cohort study is consistent and uniform nutritional counselling as well as consistency of care being provided by the same physician.

Our clinical cohort study was relatively small. It is possible that with a bigger cohort, the association between pharmacological interventions and adverse perinatal outcomes may reach statistical significance. However, for the second study aim, when we grouped all pharmacological interventions together, we were able to identify significant predictors for the need of pharmacological treatment in GDM.

In summary, our study addressed the paucity of existing data comparing the effect of metformin intervention in pregnancy with dietary/lifestyle intervention in women with BMI below 35 kg/m^2 and gestational diabetes. The present study has highlighted that metformin treatment of GDM may not be associated with different

pregnancy outcomes compared to the GDM managed by diet except for the increased risk for the LSCS. These study findings, however, were no longer significant once the analysis was controlled for the number of elective caesarean sections.

We have also observed that elevated fasting blood glucose on OGTT, in metformin treated GDM women, is a stronger predictor of their need for either instrumental delivery or caesarean section. Moreover, due to combined demographic, obstetric and medical data we have identified the local characteristics of women with GDM, which would help to predict their need for pharmacological therapy. This predictive model will improve streamlining of our patients' care and improve utilization of local hospital resources. Further studies are still needed to identify the most effective and safe management of gestational diabetes within the public hospital setting.

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 The Southern Eastern Sydney Local Health District Human Research Ethics Committee (Study Reference No. RESP/15/107). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Study design: MMB, AP, DB, AO'S. Study conduct: MMB. Data collection: MMB, AP. Data analysis: MMB, AP, DB, AKP. Data interpretation: MMB, AP, DB, AKP, AZ, AO'S. Drafting manuscript: MMB. Revising manuscript content: MMB, AP, DB, AKP, AZ, AO'S. Approving final version of manuscript: all authors. MB is the guarantor of this work. 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.

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Establishment and validation of a predictive nomogram for gestational diabetes mellitus during early pregnancy term: A retrospective study

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Objective: This study aims to develop and evaluate a predictive nomogram for early assessment risk factors of gestational diabetes mellitus (GDM) during early pregnancy term, so as to help early clinical management and intervention.

Methods: A total of 824 pregnant women at Zhongnan Hospital of Wuhan University and Maternal and Child Health Hospital of Hubei Province from 1 February 2020 to 30 April 2020 were enrolled in a retrospective observational study and comprised the training dataset. Routine clinical and laboratory information was collected; we applied least absolute shrinkage and selection operator (LASSO) logistic regression and multivariate ROC risk analysis to determine significant predictors and establish the nomogram, and the early pregnancy files (gestational weeks 12–16, n = 392) at the same hospital were collected as a validation dataset. We evaluated the nomogram *via* the receiver operating characteristic (ROC) curve, C-index, calibration curve, and decision curve analysis (DCA).

Results: We conducted LASSO analysis and multivariate regression to establish a GDM nomogram during the early pregnancy term; the five selected risk predictors are as follows: age, blood urea nitrogen (BUN), fibrinogen-to-albumin ratio (FAR), blood urea nitrogen-to-creatinine ratio (BUN/Cr), and blood urea nitrogen-to-albumin ratio (BUN/ALB). The calibration curve and DCA present optimal predictive power. DCA demonstrates that the nomogram could be applied clinically.

Conclusion: An effective nomogram that predicts GDM should be established in order to help clinical management and intervention at the early gestational stage.

KEYWORDS

GDM, nomogram, validation, prediction model, early pregnancy term

Introduction

Gestational diabetes mellitus (GDM) is a universal metabolic disturbance syndrome with a complicated etiology during pregnancy; insulin resistance and pancreatic β cell failure were significant factors for the pathogenesis of the disease, which gradually leads to hyperglycemia (1–4). Hyperglycemia exposure contributes to both maternal and fetal adverse complications. The degree of dysregulation of blood glucose is highly related to the risks of obstetrical and neonatal outcomes, which include cesarean section, hypertension, preeclampsia, polyhydramnios, preterm delivery, fetal growth restriction, birth injury, and respiratory distress. In the long term, there is an increased risk of developing obesity, cardiovascular disease, and type 2 diabetes mellitus in both the mother and the offspring (5). Multiple variables have been reported in previous research, such as age, gestational week, ethnicity, obesity, lifestyle, environment, and metabolism (6, 7). Since the GDM etiology is complicated, the short-term and long-term outcomes are not optimistic and have profound influences, and the demand for early prediction and intervention is increasing.

Two acceptable diagnosis methods that are acknowledged by expert professional organizations such as the International Association of the Diabetes and Pregnancy Study Group (IADPSG) are one-step screening approach (currently preferred by the American Diabetes Association) and the two-step Carpenter–Coustan screening approach (recommended by the American College of Obstetricians and Gynecologists). The one-step screening method can diagnose more patients than the two-step screening method in a large randomized trial, and there is no statistical difference regarding maternal and neonatal adverse outcomes between these two methods (8). Both methods have their own pros and cons, and each has its own cutoff threshold (9). Due to the varying diagnostic criteria, the incidence of GDM varies from 3% to 21.2% in Asia and from 0.31% to 18% globally, and the prevalence continues to rise (10–12). The WHO recommended a 75-g anhydrous glucose load screening test for diagnosis after 8–14 h overnight fasting at 24–28 gestational weeks (13). Because pregnant women undergo the oral glucose tolerance test (OGTT) at the second stage of the trimester, early warning signs for dysglycemia may be missed.

Our study aims at establishing a nomogram to predict the risk factors of GDM during early pregnancy term and to apply early intervention. Early management and intervention of GDM improves maternal and perinatal outcomes (14, 15). Prediction models can correctly identify GDM at early gestational weeks and could mostly benefit women with targeted risk factors, which helps them focus on precision lifestyle changes. These models can be used as tools to identify risk factors and stratify diseases, which can be largely applied in clinical management and treatment (16). Using statistical modeling combined with clinical variables and laboratory information, we developed prediction tools for GDM, which can be applied in early gestational weeks.

Materials and methods

Data collection

This study is a retrospective study that recruited 1,216 pregnant women at Zhongnan Hospital of Wuhan University and Maternal and Child Health Hospital of Hubei Province from 1 February to 30 April 2020. A total of 824 pregnant women in the second and third trimesters were enrolled in the training dataset, and their clinical and laboratory data during their 12th–16th gestational weeks were retrospectively collected. We also recruited 392 pregnant women during early pregnancy as a validation dataset. We collected the following maternal clinical and laboratory information: age, gestational week, gravidity and parity history, white blood cell (WBC), red blood cell (RBC), platelet (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), total protein (TP), albumin (ALB), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), fibrinogen-to-albumin ratio (FAR), blood urea nitrogen-to-creatinine ratio (BUN/Cr), and blood urea nitrogen-to-albumin (BUN/ALB). All blood samples were collected by skilled nurses, and the blood tests were taken in the laboratory of Zhongnan Hospital of Wuhan University and Maternal and Child Health Hospital of Hubei Province. The levels of these factors were measured by commercial diagnostic kits: RBC, PLT, and PLT (DXH800, UniCel automated hematology analyzer, USA); PT, APTT, and FIB (CA1500, Sysmex coagulation analyzer, USA); and TT, TP, ALP, ALB, BUN, Crea, and UA (AU5800, Beckman biochemical analyzer, USA). Inclusion criteria were as follows: (1) GDM patients with confirmed diagnosis of GDM based on the 75-g OGTT test (2010 IADPSG criteria (17); cutoff threshold values: 0 h fasting plasma glucose ≥ 5.1 mmol/L, 1 h plasma glucose ≥ 10.0 mmol/L, and 2 h plasma glucose ≥ 8.5 mmol/L) and normal pregnant women with no coexisting diseases and complications; (2) singleton pregnancy; and (3) age between 18 and 45 years. Exclusion criteria were as follows: (1) history of obstetric abnormality history, tumor, coinfection, and blood diseases; (2) presence of inflammation, cardiovascular, metabolic, immune, and endocrine diseases; and (3) type 1 diabetes mellitus or type 2 diabetes mellitus which were diagnosed before pregnancy. The details of our study process are depicted in the flowchart in Figure 1. LASSO logistic regression and multivariate ROC risk analysis were applied to establish significant factors and establish the nomogram. The early pregnancy files (gestational weeks 12–16, $n = 392$) were collected as a validation dataset. AUC, C-index, calibration curve, and DCA were used to evaluate the nomogram. The risk factor "age", which acts as a continuous variable, has a poor predictive value; according to multivariate logistic regression and clinical meaning, we select the cutoff value of "30" to divide "age" as a categorical variable.

Statistical methods

Statistical analysis was performed with SPSS 24.0 and R 4.0.0 software (R Statistical Computing Foundation, Vienna, Austria). Continuous data were expressed as mean ± standard deviation. Clinical characteristics were compared using t-test (continuous variables) and χ^2 test (categorical variables). LASSO regression was used to select the best predictive factors (18). The nomogram was established as a result of the binary logistic regression model with fivefold cross-validation. Selected factors applied in the nomogram fit the following: selected by multivariable analysis and clinically relevant. The calibration curve was applied to assess the accuracy of the predictive model (the Hosmer–Lemeshow test was used to access goodness of fit).

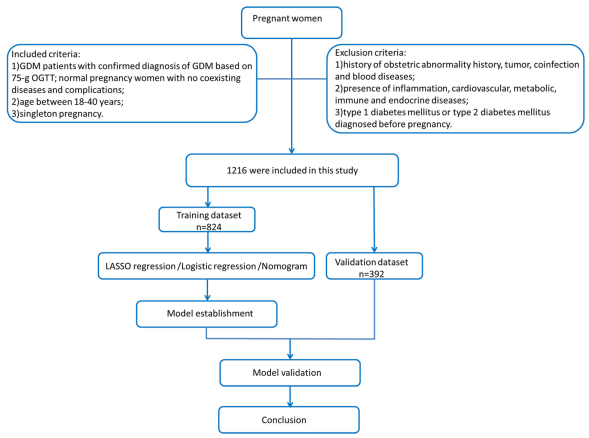

FIGURE 1
Flowchart of this study. A total of 1,216 pregnant women enrolled in our study were selected by inclusion criteria. The training dataset (n = 824) was used to estimate a GDM predictive model, and our study applied LASSO logistic regression and multivariate ROC risk analysis to determine significant predictors and establish the nomogram. A total of 392 early pregnant women were used as a validation dataset. We evaluate the nomogram by AUC, C-index, calibration curve, and decision curve analysis (DCA).

The ROC curve evaluates discriminative ability by the area under the ROC curve (AUC). The DCA curve was conducted to determine the clinical utility and benefit of the nomogram. All cutoff values were determined by the total risk scores in the training cohort. Differences with p-value < 0.05 were considered statistically significant.

Based on the 10EPP rule (19), the sample size of our predictor model should be at least 170; our study sample consists of 824 women in the training dataset and 392 women in the validation dataset, and based on the sample size of our study, the power ($1 - \beta$) calculation is equal to 1.0.

Results

Patients' clinical characteristics

We included 824 pregnant women in the training cohort and 392 pregnant women in the validation dataset. All the p-values of these factors are greater than 0.001, which indicates that there were no statistically significant differences between the training dataset and the validation dataset as shown in Table 1. The baseline characteristics of each dataset are presented in Table 2, in which data on non-GDM and GDM pregnant women from both datasets are shown separately. We selected the following predictive factors by logistic regression analysis: age, WBC, PLT, APTT, BUN, UA, FAR, BUN/Cr, and BUN/ALB. Then, we selected the statistically significant factors in multivariate logistic regression and clinical correlated factors to establish a predictive model, including the following factors: age, FAR, BUN, BUN/Cr, and BUN/ALB (shown in Table 3).

Development and validation of the nomogram

Based on the factors selected from the training cohort, LASSO regression analysis was conducted to select the predictive factors from Table 1 and establish the model with factors shown in Table 2: Five of the eighteen variables were enrolled to build the predictive model (Figure 2). These selected factors showed significant statistical differences, and they were independent of each other. The "Rms" package was used to build a nomogram to establish a GDM diagnosis model; the nomogram was constructed to predict the risk of GDM during early pregnancy (Figure 3). These five variables are given in Table 3. The AUC aimed to evaluate the discrimination of the nomogram in Figure 4; the AUC value of the training dataset is 0.808, 95% CI: 0.770–0.842 ($p < 0.05$, Figure 4A), and the AUC value of the validation dataset is 0.769, 95% CI: 0.722–0.815 ($p < 0.05$, Figure 4B). The calibration curve was used to evaluate the predictive power shown in Figure 5. The predictive model and the validation set showed the optimal predictive degree of the fitting. The DCA demonstrated the threshold probability of the prediction model nomogram in the training and validation datasets, respectively, and it was used to evaluate the clinical effects of the nomogram more visually, which indicated that the nomogram has optimal predictive power. DCA demonstrated that the nomogram could be applied clinically (Figure 6).

Discussion

GDM is defined as dysglycemia with onset or first recognition during pregnancy (20); insulin resistance and pancreatic β cell failure have been reported to be significant factors in GDM aside from the other main causes of GDM such as maternal age, obesity, inflammation, and inadequate physical exercise (21). GDM increases maternal and neonatal adverse effects in both short-term and long-term periods. In addition, it is necessary to identify and address the risk factors of GDM early and accurately. Tools that could accurately target these GDM predictors in early pregnant women will most likely benefit these women (22).

On the other hand, early warning and intervention during early pregnancy may prevent the adverse outcomes of GDM by controlling glucose level. The first-line treatment for GDM is medical nutrition therapy, weight management, and physical activities (23–25). to "70% to 85% of women diagnosed with GDM could modify their glucose condition through targeted lifestyle changes (26). In general, an early prediction model of GDM should be established, which could positively affect prevention, treatment, and prognosis.

Prior studies indicated that BUN was dose-response related with GDM during the first trimester (27). Diabetes mellitus drives the occurrence of kidney diseases (28). Meanwhile, kidney metabolites such as urea or other uremic components may increase the risk of diabetes (29). BUN was considered as a kidney function marker; a high level of urea increases insulin resistance and suppresses insulin secretion, which is associated with an increased risk of incident diabetes mellitus (30). The underlying mechanism is as follows: urea induced the production of reactive oxygen species and restrains insulin signaling by suppressing insulin receptor substrate–serine phosphorylation (31); on the other hand, uremic metabolite accumulation impaired β-cell normal function and negatively affected glucose homeostasis (32).

Meanwhile, fibrinogen is a long-acting plasma acute-phase reactant (33), and the change in albumin level has been

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TABLE 1 A summary of the variables grouped by training and validation dataset in this study.

Variable	Training dataset (n=824)	Validation dataset (n=392)	*p*
Age (years)	30±4.1	30±3.3	0.11
Gestational weeks	14±1.7	14±1.2	0.82
Laboratory results			
RBC (10^12/L)	4.0±1.2	4.0±0.4	0.96
WBC (10^9/L)	9.8±3.0	9.8±3.0	0.85
PLT (10^9/L)	217±89.7	218.2±56.9	0.89
PT (s)	10.5±3.5	10.4±0.7	0.45
APTT (s)	26.6±2.3	26.6±2.4	0.99
TT (s)	12.6±1.7	12.4±1.7	0.03
TP (g/L)	66.4±5.3	66.5±4.7	0.47
ALP (U/L)	204.5±108.1	205.2±104.2	0.39
FIB (mg/dL)	443.0±62.6	443.4±58.7	0.69
ALB (g/L)	35.4±3.5	35.4±3.5	0.87
BUN (mmol/L)	3.4±1.0	3.4±1.1	0.10
Crea (μmol/L)	49.8±9.0	50.3±9.3	0.15
UA (μmol/L)	318.0±79.0	319.9±79.2	0.29
FAR	12.6±2.2	12.7±2.2	0.83
BUN/Cr ratio	6.9±1.9	7.0±1.9	0.06
BUN/ALB ratio	9.7±3.3	10.0±3.7	0.12

Bold value means *p*-value < 0.05, which indicates statistically significant.

TABLE 2 The baseline characteristics of datasets.

Variables	Training dataset			Validation dataset		
	Non-GDM	GDM	*p*	Non-GDM	GDM	*p*
n	620 (75.2)	204 (24.8)		196	196	
Age (years)			**0.01**			**0.03**
18-30	532 (63.5)	158 (19.2)		157 (80.1)	157 (80.1)	
≥30	87 (10.6)	46 (5.6)		39 (18.9)	39 (18.9)	
Laboratory results						
RBC (10^12/L)	4.0±0.5	4.0±1.3	0.87	4.0±0.4	4.0±0.4	0.82
WBC (10^9/L)	9.4±3.0	10.0±3.0	**0.040**	10.2±2.9	9.4±3.0	**0.010**
PLT (10^9/L)	205.8±59.6	221.8±97.6	**0.031**	230.5±50.8	206.7±59.7	**<0.001**
PT (s)	10.4±0.5	10.6±4.0	0.42	10.5±0.9	10.4±0.5	0.16
APTT (s)	26.9±2.4	26.5±2.3	**0.042**	26.3±2.4	26.9±2.4	**0.037**
TT (s)	12.8±1.9	12.6±2.3	0.080	12.0±1.3	12.8±1.9	**<0.001**
TP (g/L)	66.1±5.4	66.5±5.3	0.29	67.0±3.9	66.1±5.4	0.079
ALP (U/L)	202.0±117.5	205.3±104.9	0.71	206.5±87.6	203.4±118.8	0.80
FIB (mg/dL)	439.2±68.2	449.9±59.1	0.054	438.4±58.5	448.3±58.8	0.085
ALB (g/L)	35.4±3.3	35.2±4.0	0.39	35.5±2.8	35.2±4.0	0.36

(Continued)

TABLE 2 Continued

Variables	Training dataset			Validation dataset		
	Non-GDM	GDM	*p*	Non-GDM	GDM	*p*
BUN (mmol/L)	3.3±0.9	3.7±1.2	**<0.001**	3.3±1.0	3.7±1.2	**<0.001**
Crea (μmol/L)	49.4±8.5	50.9±10.0	**0.039**	49.7±8.6	50.8±10.1	0.27
UA (μmol/L)	313.7±76.5	330.8±84.9	**0.007**	308.4±71.8	331.4±84.5	**<0.001**
FAR	12.5±2.3	12.9±2.3	**0.025**	12.4±2.1	12.9±2.3	**0.025**
BUN/Cr ratio	6.7±1.8	7.4±2.0	**<0.001**	6.6±1.7	7.4±2.0	**<0.001**
BUN/ALB ratio	9.3±3.1	10.7±3.9	**<0.001**	9.4±3.5	10.7±3.8	**<0.001**

Bold value means *p*-value < 0.05, which indicates statistically significant.

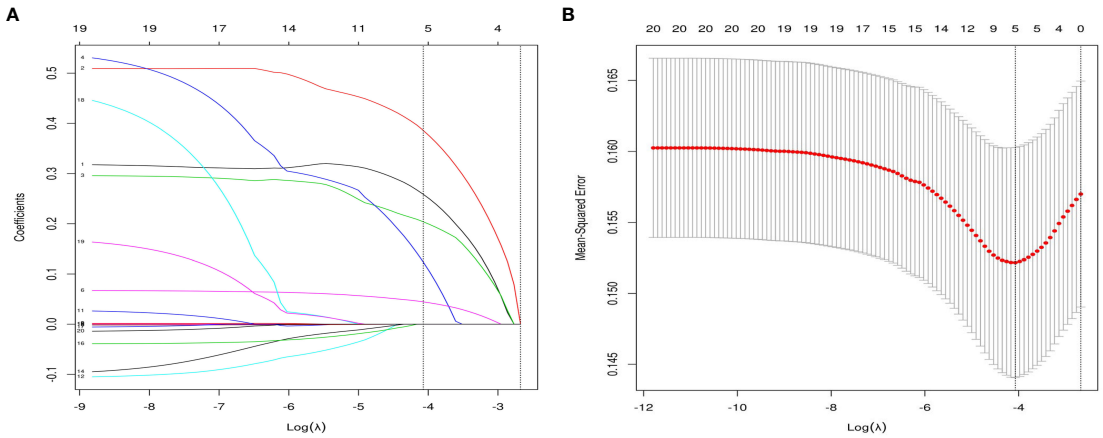

FIGURE 2
Variable selection by the LASSO binary logistic regression model. **(A)** eighteen variables with nonzero coefficients were selected by deriving the optimal lambda. **(B)** Following verification of the optimal parameter (λ) in the LASSO model, the mean squared error changes with respect to the Log (λ) value, and the vertical dotted line near Log (λ) = −4 is drawn based on 1 standard error criteria.

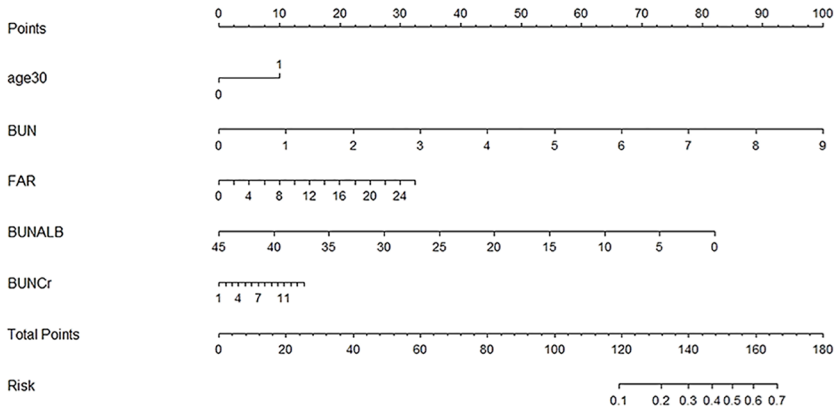

FIGURE 3
Nomogram to estimate the probability of GDM. A nomogram used basic pregnancy file information to predict GDM. Find the predictor points on the uppermost point scale that correspond to each variable of the pregnant woman and add them up; the total points projected to the bottom scale indicate the probability of GDM.

TABLE 3 Multivariable logistic model of probability of GDM in training dataset.

Variables	OR	B	*p*	95%CI	
Age (years)	1.93	0.66	**<0.001**	1.34	2.79
BUN (mmol/L)	1.59	0.46	**<0.001**	1.33	1.91
FAR	1.61	0.47	**0.017**	1.09	2.37
BUN/Cr ratio	2.38	0.87	**<0.001**	1.66	3.40
BUN/ALB ratio	2.31	0.84	**<0.001**	1.61	3.33

Bold value means *p*-value < 0.05, which indicates statistically significant.

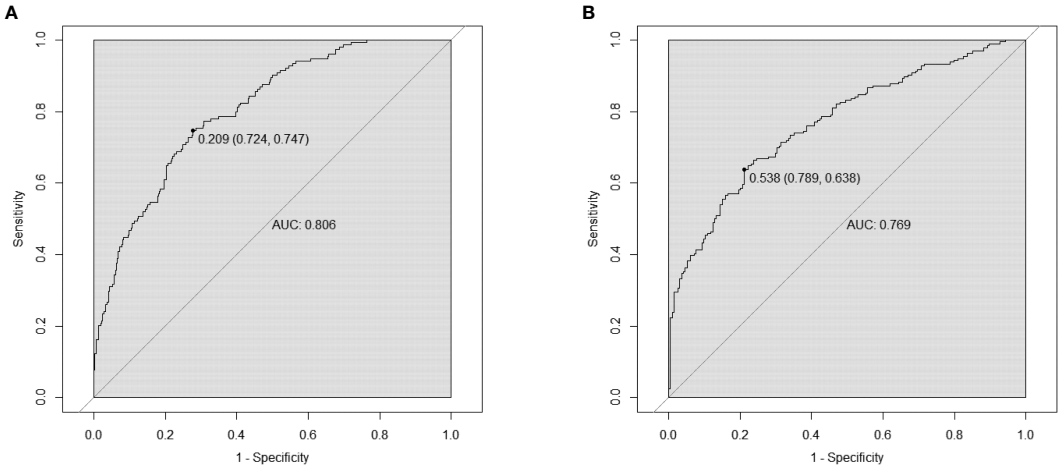

FIGURE 4
Receiver operating characteristic (ROC) curves of nomograms in the training dataset and validation dataset, respectively. **(A)** The AUC value of the training dataset is 0.808, 95% CI: 0.770–0.842 ($p < 0.05$). **(B)** The AUC value of the validation dataset is 0.769, 95% CI: 0.722–0.815 ($p < 0.05$).

attributed to the changes in nutritional status; furthermore, hypoalbuminemia represents a chronic inflammatory state caused by malnutrition (33, 34). Likewise, FAR has been proven to be a more powerful inflammatory-based prognostic predictor of overall survival than other single prognostic markers (35–37); compared with healthy pregnancies, FAR was considered to be an independent risk factor for predicting spontaneous abortion, and increased FAR levels were considered to be related to the thrombotic process in recurrent abortion (38, 39). BUN/Cr is an important indicator to evaluate acute renal injury and gastrointestinal hemorrhage, and a low BUN/Cr level is associated with higher risks of total and ischemic stroke (40–42).

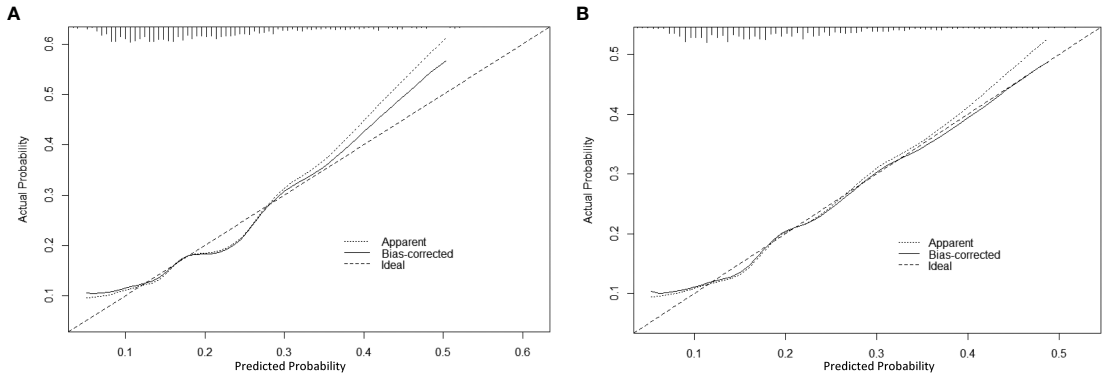

FIGURE 5
The calibration curve of the nomogram for predicting GDM in the training dataset and validation dataset, respectively. Calibration focused on the accuracy of the probability between the predictive model and the actually observed value. The *y*-axis represents the actual diagnosed cases of GDM, the *x*-axis represents the predicted risk of GDM, and the solid line represents the prediction of the training dataset **(A)** and the validation dataset **(B)**.

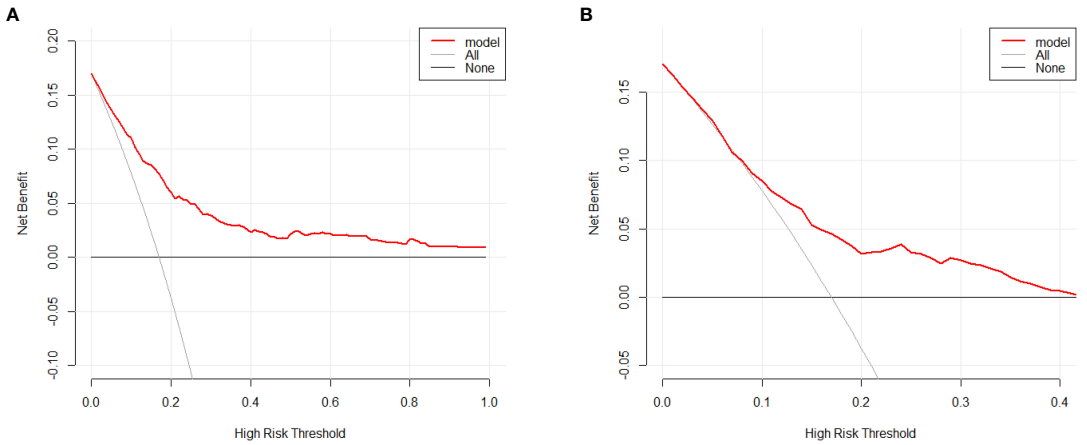

FIGURE 6
Decision curve analysis for the GDM risk nomogram. The *y*-axis estimates the net benefit, the transverse solid line represents the probability of risk that pregnant Asian women have no GDM, and the oblique solid line represents the probability of risk that pregnant Asian women have GDM. **(A)** Training dataset. **(B)** Validation dataset.

BUN/ALB is a novel prognostic marker that has a higher predictive ability than single urea nitrogen and albumin in pneumonia and acute pulmonary embolism (43–46). Given the low cost and the abundance of laboratory offerings, and the fact that these markers provided poor clinical outcomes in previous studies, we generated a predictive nomogram of GDM through serial measures.

From an economics perspective, our study takes advantage of early pregnancy files and validates the nomogram that was set up for 824 enrolled pregnant women. In this multicenter study, we have identified five predictors, namely, age, BUN, FAR, BUN/ALB, and BUN/Cr, which were significantly associated with GDM. These five predictors are independent of each other, and research about their relationship has rarely been reported. We also developed a nomogram that could predict the incidence of GDM during early pregnancy.

Our study has strengths and limitations; this is a multicenter retrospective study with a large sample size of pregnant women, and we used an early pregnant stage dataset verified by the nomogram. The GDM predictive nomogram focused on several clinical factors which could be readily available at low cost via routine blood tests in clinical practice, and the nomogram can be performed with optimal predictive power with better combined clinical characteristics with laboratory results. This model can be widely used in less-developed and developing countries where the incidence of GDM is rapidly increasing. It provides risk assessment based on first pregnancy profiles for early detection and intervention and to control glucose level. Thus, it should be widely carried out in more basic-level hospitals. However, many factors should be considered first. We should expand the sample size *via* dynamic monitoring of different gestational weeks and detect more variables and risk factors during pregnancy before the model can be widely used in clinical practice.

In summary, by analyzing basic information from pregnancy files, we found five independent risk factors of GDM: age, BUN, FAR, BUN/Cr, and BUN/ALB. According to the GDM nomogram predictive model validated by the early pregnancy dataset, we could help patients' clinical management at the early gestational stage.

Data availability statement

The datasets presented in this article are not readily available due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available. Requests to access the datasets should be directed to zhangyuanzhen@whu.edu.cn.

Ethics statement

The study was approved by the Institutional Ethics Committee of the Zhongnan Hospital of Wuhan University and the Maternal and Child Health Hospital of Hubei Province, the informed consent number was No. 2020072K.

Author contributions

LL wrote the first draft of the manuscript. LL, S-ML, and YZ contributed to the conception and design of the study. YZ is the first corresponding author. QZ, ZW, and FT collected the data. LL, QZ, and HL performed the data processing and analysis. YT contributed to the critical revision of the manuscript. All authors

contributed to manuscript revision, and read 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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Prediction model for gestational diabetes mellitus using the XG Boost machine learning algorithm

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Objective: To develop the extreme gradient boosting (XG Boost) machine learning (ML) model for predicting gestational diabetes mellitus (GDM) compared with a model using the traditional logistic regression (LR) method.

Methods: A case–control study was carried out among pregnant women, who were assigned to either the training set (these women were recruited from August 2019 to November 2019) or the testing set (these women were recruited in August 2020). We applied the XG Boost ML model approach to identify the best set of predictors out of a set of 33 variables. The performance of the prediction model was determined by using the area under the receiver operating characteristic (ROC) curve (AUC) to assess discrimination, and the Hosmer–Lemeshow (HL) test and calibration plots to assess calibration. Decision curve analysis (DCA) was introduced to evaluate the clinical use of each of the models.

Results: A total of 735 and 190 pregnant women were included in the training and testing sets, respectively. The XG Boost ML model, which included 20 predictors, resulted in an AUC of 0.946 and yielded a predictive accuracy of 0.875, whereas the model using a traditional LR included four predictors and presented an AUC of 0.752 and yielded a predictive accuracy of 0.786. The HL test and calibration plots show that the two models have good calibration. DCA indicated that treating only those women whom the XG Boost ML model predicts are at risk of GDM confers a net benefit compared with treating all women or treating none.

Conclusions: The established model using XG Boost ML showed better predictive ability than the traditional LR model in terms of discrimination. The calibration performance of both models was good.

KEYWORDS

gestational diabetes mellitus, machine learning, prediction model, extreme gradient boosting, logistic regression

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic complication to occur during pregnancy and is classed as a mild form of diabetes. It is normally diagnosed at 24–28 weeks' gestation, and is characterized by hyperglycemia (1). The global prevalence of hyperglycemia during pregnancy is approximately 15.8%, and over 80% of cases are due to GDM (2). With the growth of the economy and the transition to a more sedentary lifestyle, the prevalence of GDM in Chinese women continues to increase, and ranges from 14.8% to 24.24% (3–5). Over time, China has loosened its fertility restrictions, most recently with the replacement of the two-child policy with the three-child policy. Thus, this increase in GDM prevalence can be attributed mainly to the rising rates of pregnant women who are of advanced maternal age.

Hyperglycemia brings about both short- and long-term outcomes, resulting in a significant impact on the health of both pregnant women and their offspring. Several studies in mothers have reported that GDM is associated with adverse pregnancy complications, including pre-eclampsia, the need for delivery by cesarean section, as well as type 2 diabetes and cardiovascular disease after delivery (6). GDM can also affect their offspring, being associated with a higher prevalence of macrosomia, shoulder dystocia, birth trauma, stillbirth, and, in later life, obesity and metabolic syndrome (7). According to the Developmental Origins of Health and Disease framework for GDM, exposure to intrauterine hyperglycemia before GDM screening at 24–28 weeks' gestation is associated with the abnormal growth and development of the fetus (8). which includes smaller fetuses at 24 weeks' gestation increased abdominal circumference growth rates (9), and hyperinsulinemia (6). Lifestyle interventions during early pregnancy can reduce the risk of GDM by 18%–62% (10, 11), but are not effective if initiated at a later stage (12). Thus, we concluded that a hysteretic diagnosis of GDM in the second or third trimester of pregnancy might lead to a narrow time frame for sufficient intervention. Therefore, it is imperative to establish a prediction model for women at risk of GDM to provide early intervention prior to the diagnosis of the condition at 24–28 weeks' gestation.

There is accumulating evidence indicating that models based on multiple risk factors can improve predictive abilities (9). Machine learning (ML) algorithms, as an artificial intelligence technology, have the advantage of presenting high-dimensional predictors constructed to model relatively small datasets with reduced overfit, and demonstrate a powerful selflearning ability to find complex relationships between predictors (9, 13). As major predictors of GDM, demographic characteristics and clinical features contribute to improving the predictive ability of models combined with biomarkers (14, 15). Consequently, we aim to present the results of prediction models for GDM based on demographic characteristics, clinical features, and laboratory parameters to make full use of the available variables. In addition, we compare and evaluate the performance of ML and logistic regression (LR) models to show the advantages of each.

Materials and methods

Participants

This case–control study of pregnant women was conducted at the Shenzhen Hospital of the Southern Medical University, Shenzhen, China. Pregnant women were eligible to participate in the study if they met all of the following inclusion criteria: (1) they were aged ≥ 18 years; (2) they had undergone all routine antenatal assessments; (3) they had taken a 75-g oral glucose tolerance test (OGTT) at 24–28 weeks' gestation; and (4) they were willing to participate in this study and to sign the informed consent form. The exclusion criteria were as follows: (1) pre-existing type 1 or type 2 diabetes; (2) a history of severe diseases, such as hypertension or heart disease; and (3) taking medications affecting insulin and blood glucose levels.

Data collection

Information on participants' demographic characteristics was collected by using a structured questionnaire. Clinical features and laboratory parameters in the first trimester were collected from the hospital's electronic medical record system (EMRS).

Diagnosis of GDM

GDM was diagnosed at 24–28 weeks' gestation when any one of the 75-g OGTT values met or exceeded 5.1 mmol/L at 0 h, 10.0 mmol/L at 1 h, and 8.5 mmol/L at 2 h, in accordance with the recommendations set out at the International Association of Diabetes and Pregnancy Study Groups Consensus Panel 2010 (IADPSG).

Statistical analysis

All analyses were performed using IBM® SPSS® Statistics version 26.0 software (IBM Corporation, Armonk, NY, USA). Continuous variables of two groups were expressed as means and standard deviations, and analyzed by Student's *t*-test for normally distributed variables. Categorical variables were described as frequencies (percentages), and evaluated by a chi-squared test. Test results with a *p*-value of less than 0.05 were considered statistically significant. Results from these tests, clinically relevant findings, and previous literature were used to preliminarily screen the set of variables for potentially meaningful predictors of GDM. Multiple imputations were used to deal with missing data, to avoid selection bias. The prediction model using LR was carried out in R (The R Foundation, Vienna, Austria) using the rms package, and XG Boost ML was carried out by R package (XG Boost, XG Boost Explainer, and MLR).

Prediction models

In this study, we included variables with a *p*-value of < 0.05 in the univariate analysis, whereas variables indicated in previous literature and clinically meaningful variables were included in the LR analysis (stepwise). ML can present novel or complex combinations of multidomain variables, and also has features that weigh variable importance and reduce overfit (16). Therefore, we incorporated all variables of the univariate analysis into the model using XG Boost ML.

The model for GDM, trained on the training set, was validated in the testing set with the optimal hyperparameters using 10-fold cross-validation.

Model evaluation

The discrimination of the models was assessed using the receiver operating characteristic (ROC) curves and the area under the ROC curve (AUC). The calibration plots and the Hosmer–Lemeshow (HL) test were used to evaluate the calibration of each model. Decision curve analysis (DCA) was introduced to evaluate the clinical use of the models.

Results

Participant characteristics

In total, 925 pregnant women were included in this study (735 in the training set; 190 in the testing set). The alternative 33 variables were collected for each pregnant woman. Table 1 shows the univariate analysis of the demographic characteristics, clinical features, and laboratory parameters of participants with GDM (cases) and participants without GDM (controls) in the training set. Participants with GDM were significantly older and had higher pre-pregnancy body mass index (BMI) and mean arterial pressure (MAP) than participants without GDM. The average time since the last pregnancy was also longer in this group than in the control group. The percentage of women who had previously GDM and the number with a family history of diabetes mellitus were also significantly higher in the GDM group, but participants in this group were also markedly younger at menarche than those in the non-GDM group (all p-values were < 0.05). Laboratory parameters, including platelet count, white blood cell count, and the levels of glucose in urine, ketone in urine,

TABLE 1 Demographic characteristics, clinical features, and laboratory parameters of participants with GDM and non-GDM control participants in the training set.

Variable	GDM (*N* = 147)	Non-GDM (*N* = 588)	*p*-value
Demographic characteristics			
Age (years)	32.068 ± 4.208	30.005 ± 4.027	0.000*
Occupation, *n* (%)			0.254
None/homemaker	43 (29.25%)	145 (24.66%)	
Working	104 (70.75%)	443 (75.34%)	
Time spent in education (years), *n* (%)			0.705
< 12	18 (12.24%)	83 (14.12%)	
12–16	117 (79.59%)	466 (79.25%)	
> 16	12 (8.16%)	39 (6.63%)	
Smoking, *n* (%)	4 (2.72%)	11 (1.87%)	0.514
Alcohol consumption, *n* (%)	33 (22.45%)	179 (30.44%)	0.056
Clinical features, *n* (%)			
Gravidity			0.109
1	54 (36.73%)	259 (44.05%)	
≥ 2	93 (63.27%)	329 (55.95%)	
Parity, *n* (%)			0.193
0	76 (51.70%)	339 (57.65%)	
≥ 1	71 (48.30%)	249 (42.35%)	
Menarche age (years)	13.381 ± 1.411	13.536 ± 1.471	0.000*
Time since last pregnancy (years)	2.8027 ± 3.309	1.9354 ± 2.637	0.001*
Pre-pregnancy BMI (kg/m^2)	21.681 ± 3.024	20.630 ± 2.582	0.000*
MAP (mmHg)	80.896 ± 8.822	78.641 ± 7.735	0.002*
Previous GDM, *n* (%)	36 (24.49%)	18 (3.06%)	0.000*
Previous macrosomia, *n* (%)	2 (1.36%)	8 (1.36%)	1.000
Polycystic ovary syndrome, *n* (%)	9 (6.12%)	21 (3.57%)	0.162
Family history of diabetes mellitus, *n* (%)	21 (14.29%)	51 (8.67%)	0.041*
Laboratory parameters			
Routine blood tests			

(Continued)

TABLE 1 Continued

Variable	GDM (*N* = 147)	Non-GDM (*N* = 588)	*p*-value
Hemoglobin (g/L)	123.232 ± 12.314	122.238 ± 11.076	0.086
Red blood cell count (× 10^{12}/L)	4.147 ± 0.452	4.123 ± 0.452	0.061
Platelet count (× 10^9/L)	244.612 ± 59.113	231.952 ± 54.730	0.014*
White blood cell count (×10^9/L)	8.815 ± 2.240	8.408 ± 2.044	0.031*
Routine urine and renal function tests			
Urine specific gravity	1.019 ± 0.007	1.020 ± 0.008	0.075
Urine pH	6.643 ± 0.685	6.643 ± 0.690	0.417
Glucose in urine, *n* (%)	12(8.16%)	22(3.74%)	0.022*
Ketones in urine, *n* (%)	36(24.49%)	99(16.84%)	0.032*
Uric acid	64.295 ± 5.339	60.752 ± 2.518	0.086
Hepatic function tests			
Total bilirubin (μmol/L)	7.159 ± 3.255	7.072 ± 3.043	0.714
ALT (U/L)	14.256 ± 12.050	12.063 ± 7.540	0.008*
AST (U/L)	16.489 ± 7.023	15.721 ± 5.097	0.131
Total protein (g/L)	69.842 ± 5.304	69.445 ± 5.104	0.450
Thyroid function tests			
Thyroid-stimulating hormone (mIU/L)	1.598 ± 1.364	1.750 ± 1.415	0.677
Thyroid hormone T_3 (nmol/L)	3.196 ± 1.784	3.010 ± 0.647	0.017*
Thyroid hormone T_4 (nmol/L)	1.383 ± 0.586	1.396 ± 0.869	0.456
Glycemic test			
Fasting plasma glucose (mmol/L)	4.659 ± 0.426	4.562 ± 0.377	0.000*
HbA_{1c} (%)	5.225 ± 0.354	5.045 ± 0.315	0.004*

*$p < 0.05$.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin; MAP, mean arterial pressure.

alanine aminotransferase, thyroid hormone T_3, fasting plasma glucose, and glycated hemoglobin (HbA_{1c}), were also higher in women with GDM than in control participants. The demographic characteristics, clinical features, and laboratory parameters of participants in the training and testing sets are compared in Table 2. Good consistency in the data between the training data set and the testing data set is shown for the majority of the variables.

Predictors of models

Four predictors, previous GDM, age, HbA_{1c} level, and MAP, were used to construct the predictive model using LR (Table 3). Twenty predictors were finally included to build the model using XG Boost ML. Figure 1 shows the relative importance of the 20 variables included in the predictive model for GDM using XG Boost ML.

TABLE 2 Demographic characteristics, clinical features, and laboratory parameters of the training and testing sets.

Variables	Training set (*N* = 735)	Testing set (*N* = 190)	*p*-value
Demographic characteristics			
Age (years)	30.418 ± 4.144	29.474 ± 3.590	0.004*
Occupation, *n* (%)			0.255
None/homemaker	188 (25.578%)	41 (5.578%)	
Working	547 (74.422%)	149 (20.272%)	
Time spent in education (years), *n* (%)			0.125

(Continued)

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TABLE 2 Continued

Variables	Training set (*N* = 735)	Testing set (*N* = 190)	*p*-value
< 12	101 (13.741%)	19 (2.585%)	
12–16	583 (79.320%)	151 (20.544%)	
> 16	51 (6.939%)	20 (2.721%)	
Smoking), *n* (%)	15 (2.041%)	4 (0.544%)	0.955
Alcohol consumption	212 (28.844%)	63 (8.571%)	0.246
Clinical features), *n* (%)			
Gravidity			0.117
1	313 (42.585%)	92 (12.517%)	
≥ 2	422 (57.415%)	96 (13.061%)	
Parity			0.032*
0	415 (56.463%)	123 (16.735%)	
≥ 1	320 (43.537%)	66 (8.980%)	
Menarche age (years)	13.505 ± 1.460	13.405 ± 1.724	0.421
Time since last pregnancy (years)	2.109 ± 2.803	1.739 ± 2.640	0.102
Pre-pregnancy BMI (kg/m^2)	20.841 ± 2.707	20.966 ± 2.971	0.579
MAP (mmHg)	79.092 ± 8.009	81.422 ± 8.656	0.001*
Previous GDM, *n* (%)	54 (7.347%)	11 (1.497%)	0.454
Previous macrosomia, *n* (%)	10 (1.361%)	0 (0.000%)	0.106
Polycystic ovary syndrome, *n* (%)	30 (4.082%)	12 (1.633%)	0.187
Family history of diabetes mellitus, *n* (%)	72 (9.796%)	16 (2.177%)	0.565
Laboratory parameters			
Routine blood tests			
Hemoglobin (g/L)	122.437 ± 11.333	123.284 ± 10.072	0.348
Red blood cell count (× 10^{12}/L)	4.128 ± 0.452	4.105 ± 0.444	0.528
Platelet count (× 10^9/L)	234.489 ± 55.823	243.351 ± 54.367	0.050
White blood cell count (× 10^9/L)	8.489 ± 2.090	8.795 ± 2.023	0.071
Routine urine and renal function tests			
Urine specific gravity	1.020 ± 0.008	1.017 ± 0.009	0.000*
Urine pH	6.643 ± 0.689	6.589 ± 0.679	0.333
Glucose in urine	1.112 ± 0.585	1.048 ± 0.317	0.155
Ketone in urine	1.457 ± 1.104	1.462 ± 1.106	0.954
Uric acid level	234.818 ± 61.470	215.842 ± 52.786	
Hepatic function tests			
Total bilirubin (μmol/L)	7.089 ± 61.470	7.309 ± 4.158	0.417
ALT (U/L)	12.502 ± 8.667	12.336 ± 6.579	0.806
AST (U/L)	15.874 ± 5.539	16.666 ± 3.611	0.062
Total protein (g/L)	69.524 ± 5.143	70.079 ± 5.133	0.185
Thyroid function tests			
Thyroid-stimulating hormone(mIU/L)	1.720 ± 1.405	1.847 ± 1.902	0.305

(Continued)

TABLE 2 Continued

Variables	Training set (*N* = 735)	Testing set (*N* = 190)	*p*-value
Thyroid hormone T_3 (mmol/L)	3.047 ± 0.987	3.199 ± 0.898	0.054
Thyroid hormone T_4 (mmol/L)	1.393 ± 0.820	1.354 ± 0.774	0.554
Glycemic test			
Fasting plasma glucose (mmol/L)	4.582 ± 0.389	4.369 ± 0.665	0.000*
HbA_{1c} (%)	5.081 ± 0.331	5.284 ± 0.318	0.000*

*$p < 0.05$.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin; MAP, mean arterial pressure.

Accuracy of prediction models

For the data from the training set, the AUC of the prediction model for GDM using stepwise LR is 0.752, whereas the AUC of the model using XG Boost ML is 0.946; these are shown in Figures 2, 3, respectively. The accuracy of the two models for the data from the training set is 0.786 and 0.875, respectively. The specificity of the model using XG Boost ML was higher than that of the model using traditional LR for the data from both the training and testing sets. However, the sensitivity of the model using XG Boost ML was lower than that of the model using traditional LR, as shown clearly in Table 4.

Calibration of different models

The calibration plots demonstrate the consistency between the predicted values and the real outcomes, which are shown in Figures 4–7. The Hosmer–Lemeshow (HL) test *p*-values were 0.288 and 0.402 for the training set and testing sets, respectively, in the model using LR, and 0.831 and 0.556 for the training set and testing sets, respectively, in the model using XG Boost ML.

Clinical use

The DCA results for the two models are presented in Figures 8, 9. Compared with treating all women and none of the women, the prediction models using LR provide a net benefit between a threshold probability of 6%–63% and 87%–90%. The DCA plot indicated good positive net benefits in the model using XG Boost ML with a threshold probability of between 5% and 92%.

Discussion

Early screening and prediction of the likelihood of pregnant women developing GDM are imperative to the prevention and treatment of this condition (17). We compared two models and found that XG Boost ML models had better performance in terms of discrimination and achieved a larger AUC, which was as high as 0.946. Our results are concordant with a previous study showing that ML algorithms can be more accurate than traditional LR methods (18). The HL test shows that the observed probability is largely consistent with the predicted probability, which implies that both models had good calibration.

Given evidence indicates that, in the situation of no overfitting, a prediction model with a greater number of predictors has an improved prediction ability compared with a model with fewer predictors (19). Similarly, in our study, the XG Boost ML model presents 20 predictors with a higher predictive accuracy than the LR model with four predictors. Furthermore, linear models, such as LR models, highlight a clear linear contribution of each variable for GDM models, making them available for clinical implementation, whereas XG Boost ML models can weight the importance of factors and assess their complex non-linear relationships by boosting, integrating multiple factors, assess their complex non-linear relationships by boosting, and clearly demonstrate the relative contribution of each variable to GDM (18).

A recent relative study has indicated that hematologic and biochemical parameters measured during routine antenatal examination can be used in ML models to predict GDM (20). However, it has not until now been possible to weigh the relative importance of each variable. In this study we have shown that it is possible quantify the likelihood of individual independent risk factors leading to GDM. Another related study (18) developed a ML prediction model based on a large population and weighed the

TABLE 3 Four predictors included in the model using stepwise LR in the training set.

Variable	β	SE	*p*-value	OR	95% CI
Age (years)	0.096	0.024	0.000	1.101	1.052 to 1.154
Previous GDM	2.057	0.321	0.000	7.822	4.172 to 14.666
MAP (mmHg)	0.029	0.012	0.020	1.029	1.005 to 1.054
HbA_{1c} (%)	1.301	0.335	0.000	3.672	1.903 to 7.083
Constant	−13.542	2.045	0.000	0.000	0.000 to 0.000

LR, logistic regression; OR, odds ratio.

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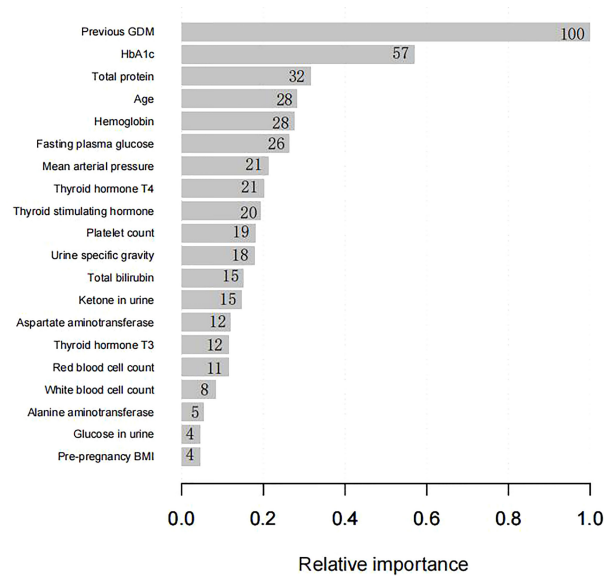

FIGURE 1
The relative importance of the 20 variables included in the XG Boost ML model for GDM in the training set. BMI, body mass index; GDM, gestational diabetes mellitus; HbA_{1c}, glycated hemoglobin; XG Boost ML, extreme gradient boosting (XG) machine learning (ML).

importance of risk factors, but there was no exploration of biomarkers in early pregnancy in this study; by contrast, this was explored in our study.

In the two models, previous GDM was the most classical predictor, and LR analysis showed that pregnant women with previous GDM are 7.8 times more likely to develop GDM (OR = 7.822; $p < 0.05$). Furthermore, other model studies have shown (9, 21) that previous GDM increases the risk of GDM in a current pregnancy 13.7- to 21.1-fold ($p < 0.05$). One review also found that having GDM in a previous pregnancy is the strongest risk factor for GDM, with reported recurrence rates of up to 84% (22). In addition to previous GDM, age, HbA_{1c} level, and MAP were considered independent factors for GDM in the LR analysis. Previously, age and HbA_{1c} level have been strongly associated with an elevated risk of GDM (17, 21). With increasing age, the fertility and organ function of pregnant women are reduced, and insulin sensitivity and pancreatic β-cell function are decreased, which in turn lead to insulin resistance (IR) and an increased risk of hyperglycemia. HbA_{1c} level, an identified risk factor, can diagnose the severity of GDM and reflects the average blood glucose level in the past 2 to 3 months, which is significantly related to the degree of IR (23). A previous study revealed that HbA_{1c} level is a reliable predictor of GDM(OR = 3.11; $p < 0.05$)and that HbA_{1c} levels are elevated in women with GDM, although still within the normal range (24), which is consistent with our results. MAP was calculated from one-third systolic blood pressure (SBP) and two-thirds diastolic blood pressure (DBP), both of which are considered to be predictors of GDM (18, 25, 26). MAP can probably predict GDM because IR is the involved in the pathogenesis of both gestational hypertension (GH) and GDM, and the level of MAP, which can reflect the severity of GH, also stimulates a certain degree of GDM (27).

Another 16 predictors, comprising pre-pregnancy BMI and 15 laboratory parameters routinely measured during antenatal assessment, were confirmed as risk factors by XG Boost ML. Pre-pregnancy BMI, despite being considered an established predictor of GDM (28), has the lowest predictive ability, probably because of the low frequency of overweight and obesity (among our sample affecting approximately 11.700% and 14.700% of women in the training and testing sets, respectively). Another explanation is that the relationship between BMI and GDM is complex, with women with GDM and a

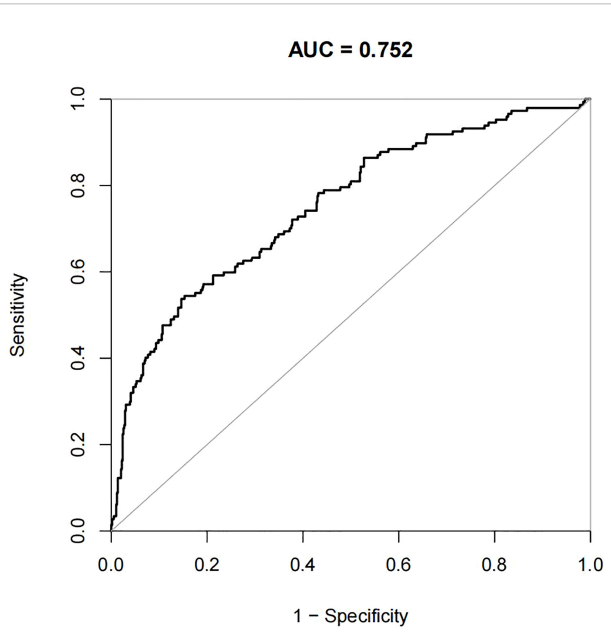

FIGURE 2
The AUC of the prediction model for GDM by stepwise LR. AUC, area under the receiver operating characteristic curve; GDM, gestational diabetes mellitus; LR, logistic regression.

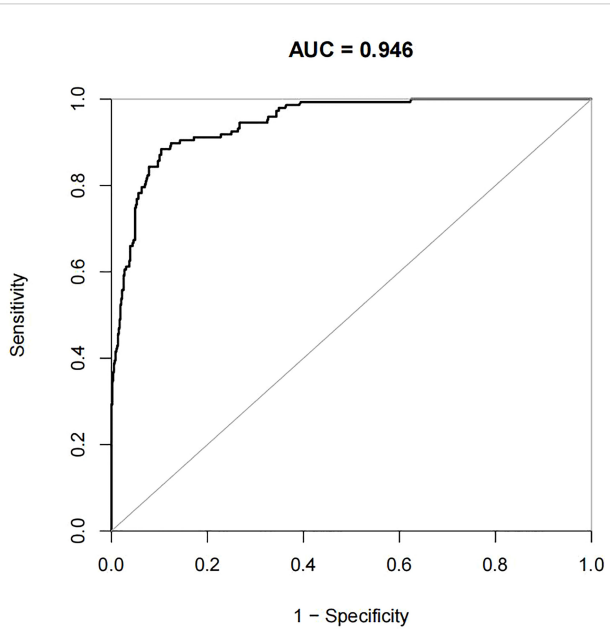

FIGURE 3
The AUC of the prediction model for GDM by XG Boost ML. AUC, area under the receiver operating characteristic curve; GDM, gestational diabetes mellitus; XG Boost ML, extreme gradient boosting (XG) machine learning (ML).

TABLE 4 Accuracy of the four prediction models.

		Accuracy (95% CI)	AUC (95% CI)	Cut-off point	Youden's index	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Training set (*N* = 735)	Model using stepwise logistic regression	0.786	0.752 (0.706 to 0.797)	0.240	0.391	0.544	0.847	0.471	0.881
	Model using XG Boost ML	0.875 (0.849 to 0.898)	0.946	0.500	0.783	0.408	0.992	0.923	0.870
Testing set (*N* = 190)	Model using stepwise logistic regression	0.842	0.745 (0.648 to 0.842)	0.310	0.433	0.500	0.922	0.600	0.888
	Model using XG Boost ML	0.837 (0.777 to 0.886)	0.750	0.518	0.697	0.250	0.974	0.692	0.848

AUC, area under the receiver operating characteristic curve; XG Boost ML, extreme gradient boosting (XG) machine learning (ML).

high BMI having IR and women with GDM and a low BMI having defective insulin secretion (29).

Existing studies have identified that several laboratory parameters are independent predictors of GDM, such as glycemic markers (e.g., fasting glucose and HBA_{1c} levels), alanine aminotransferase (ALT) levels, and thyroid function (levels of the thyroid hormones T_3 and T_4) (9, 18, 20); all of these are available clinically in the first trimester of pregnancy. The possible link between these variables and GDM could be explained by the fact that hyperglycemia can change the hemodynamics of the body, and that these variables can reflect the inflammation and immune responses that are highly associated with IR (30). Prior research has identified several blood potential biomarkers, such as platelet count, white blood cell count, and red blood cell count, which were positively correlated with the development of GDM (30). Consistent with a previous study (9), high T_3 and low T_4 levels were identified as being predictors of GDM in our study, strongly confirming the existence of a close relationship between thyroid function and GDM. ALT and AST (aspartate aminotransferase), as markers of hepatocellular damage, were also examined as predictors of GDM in our study. The pathogenesis of GDM is linked with IR, which may in turn be caused by mild ALT and AST elevations (15, 31). In summary, the laboratory parameters support the hypothesis that pregnancy blood routine examination is conducive to GDM screening.

Limitations

This study has several limitations. Firstly, this study has limited sample size. Secondly, the fact is that a time external verification was used to verify the extrapolation in a single center. Lastly, there is a lack of complete data for all laboratory parameters and a comparison of multiple ML models. Variables such as clinical features and laboratory parameters are based on retrospective data from the EMRS that may have inevitable selection biases. Further multicenter prospective studies should be carried out to update and validate the models based on a large, population-based sample. Models

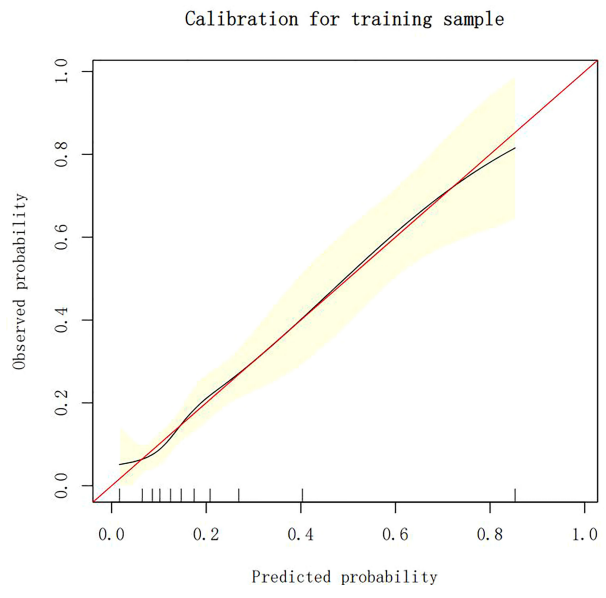

FIGURE 4
The calibration plots of the training set by LR. LR, logistic regression.

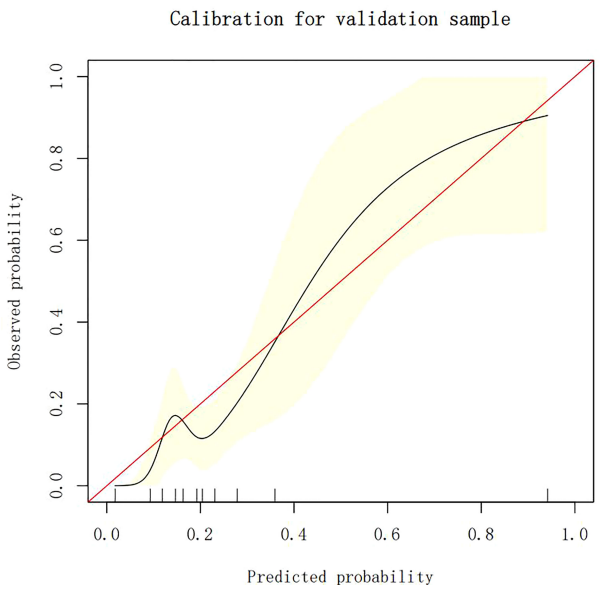

FIGURE 5
The calibration plots of the testing set by LR. LR, logistic regression.

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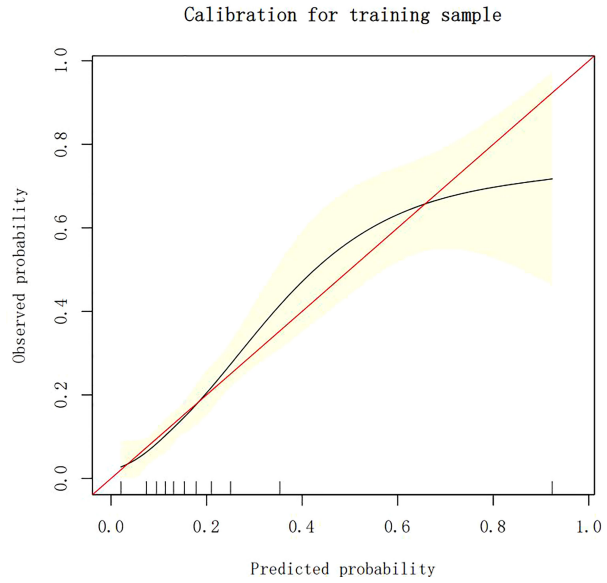

FIGURE 6
The calibration plots of the training set by XG Boost ML. XG Boost ML, extreme gradient boosting (XG) machine learning (ML).

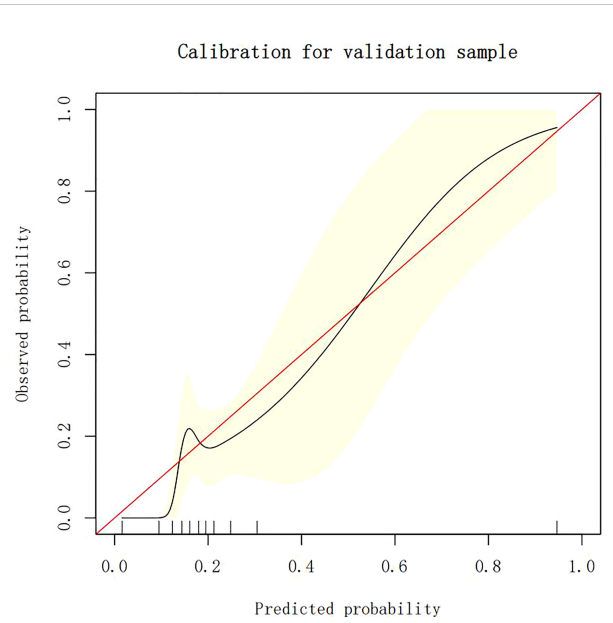

FIGURE 7
The calibration plots of the testing set by XG Boost ML. XG Boost ML, extreme gradient boosting (XG) machine learning (ML).

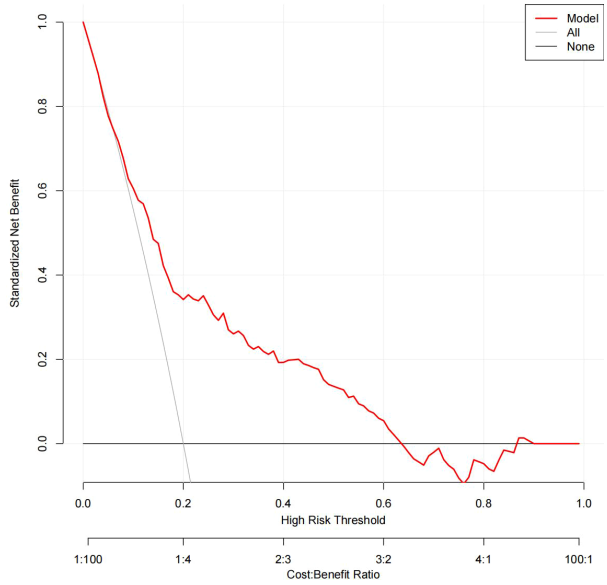

FIGURE 8
The DCA of the model using LR. DCA, decision curve analysis; LR, logistic regression.

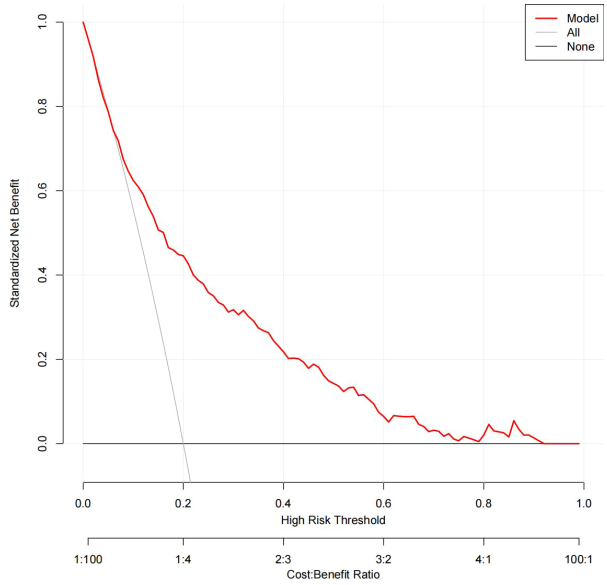

FIGURE 9
The DCA of the model using XG Boost ML. DCA, decision curve analysis; XG Boost ML, extreme gradient boosting (XG) machine learning (ML).

constructed from more variables that are available from EMRS are often the most feasible option.

Conclusion

In conclusion, a model with four predictors and using traditional LR and a model with 20 predictors and using XG Boost ML were successfully built and used to predict GDM. Compared with traditional LR, the XG Boost ML model can improve the discrimination of a prediction model for GDM and make full use of more predictors. The common laboratory parameters from pregnant women's antenatal assessments can be used to predict the likelihood of their developing GDM.

Data availability statement

The datasets presented in this article are not readily available because the generated datasets belong to hospital. Requests to access the datasets should be directed to XH, 731538045@qq.com.

Ethics statement

This study was approved by the corresponding Hospital Ethics Committee (No.: NYSZYYEC20200032). 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

XH and XiaolH contributed to the conception and design of the study. XH organized the database. XH and YY performed the statistical analysis. XH wrote the first draft of the manuscript. XH, XiaolH, YY, and JW wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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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The association between maternal HbA1c and adverse outcomes in gestational diabetes

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Background: The role of HbA1c in women with gestational diabetes mellitus (GDM) is still unclear, particularly in the Asian population.

Aim: To investigate the association between HbA1c levels and adverse outcomes considering maternal age, pre-pregnancy body mass index (BMI), and gestational weight gain (GWG) in women with GDM.

Method: A retrospective study included 2048 women with GDM and singleton live births. Using logistic regression, the associations between HbA1c and adverse pregnancy outcomes were assessed.

Result: Compared to women with HbA1c ≤ 5.0%, HbA1c was significantly associated with macrosomia (aOR 2.63,95%CI1.61,4.31), pregnancy-induced hypertension (PIH, aOR 2.56,95%CI1.57,4.19), preterm birth (aOR 1.64,95%CI 1.05,2.55), and primary Cesarean section (primary C-section, aOR1.49,95% CI1.09,2.03) in GDM women with HbA1c ≥5.5% while significantly associated with PIH (aOR 1.91,95%CI1.24,2.94) in women with HbA1c 5.1-5.4%. The associations between HbA1c and adverse outcomes varied with maternal age, pre-pregnancy BMI, and GWG. In women aged ≤29 years, there's significant association between HbA1c and primary C-section when HbA1c was 5.1-5.4% and ≥5.5%. In women aged 29-34 years and HbA1c ≥5.5%, HbA1c was significantly associated with macrosomia. In women aged ≥35 years, there's significant association between HbA1c and preterm birth when HbA1c was 5.1-5.4% and macrosomia and PIH when HbA1c ≥5.5%. In pre-pregnant normal-weight women, HbA1c was significantly associated with macrosomia, preterm birth, primary C-section, and PIH when HbA1c ≥5.5% while HbA1c was significantly associated with PIH when HbA1c was 5.1-5.4% . In pre-pregnant underweight women with HbA1c 5.1-5.4%, HbA1c was significantly associated with primary C-section. HbA1c was significantly associated with macrosomia among women with inadequate GWG or excess GWG and HbA1c≥5.5%. In women with adequate GWG, there's significant association between HbA1c and PIH when HbA1c was 5.1-5.4% and ≥5.5% .

Conclusion: Conclusively, HbA1c at the time of diagnosis is significantly associated with macrosomia, preterm birth, PIH, and primary C-section in Chinese women with GDM.

KEYWORDS

gestational diabetes mellitus, obesity, gestational weight gain, pre-pregnancy body mass index, glycated hemoglobin A1c, adverse outcomes

1 Introduction

Gestational diabetes mellitus (GDM) is carbohydrate intolerance resulting in hyperglycemia during pregnancy without prior history of diabetes (Type 1 or Type 2) (1). It is screened using fasting plasma glucose (FPG), 1-h postprandial glucose (PG), 2-h PG of 75g oral glucose tolerance test (OGTT) during 24-28 weeks, according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (2). The availability of screening for gestational diabetes in the past years has increased the detection rate of GDM (3). The incidence of GDM in China is 14.8%, caused by increasing weight gain, maternal age, family history, and many other factors linked with the pregnancy period of women (4). The increase in gestational diabetes incidence and its association with Type 2 diabetes remains crucial (5). GDM is associated with both short and long-term pregnancy adverse outcomes, including macrosomia, large for gestational age (LGA), preeclampsia, primary Cesarean section (C-section), shoulder dystocia, preterm birth, postpartum diabetes mellitus and risk of Type 2 diabetes in offspring (6–8).

HbA1c is used in diagnosing, treatment, preventing, and detecting progress of diabetes (9). In women with hyperglycemia, glycated hemoglobin A1c (HbA1c) level has been associated with birthweight, primary C-section, hypoglycemia, cord-serum C-peptide, pre-eclampsia, preterm birth, the sum of skin folds, percent body fat >90th percentile (10). It has been reported that adverse outcomes in early pregnancy can be predicted by HbA1c (11–13) as well as in GDM pregnant women (14, 15). But different HbA1c cut-offs have been used in past studies to predict adverse outcomes in GDM pregnancy. HbA1c level ≥5.0% was used to predict neonatal complications and ≥6.2% to predict postpartum diabetes mellitus (14, 16). HbA1c might be useful in predicting adverse outcomes in GDM and studies indicating the association between HbA1c and adverse outcomes have been conducted in Caucasian women with GDM (17). However, there is a lack of enough evidence in the Asian population.

This retrospective study aims to investigate the relationship between HbA1c levels and adverse pregnancy outcomes considering maternal age, pre-pregnancy body mass index (BMI), and gestational weight gain (GWG) among GDM women, which might provide evidence for the prevention of adverse outcomes in GDM pregnant women.

2 Methods

2.1 Study design and population

A retrospective study was conducted among women with gestational diabetes who received regular prenatal care and delivered at the Women's Hospital, School of Medicine, Zhejiang University from 1-July-2017 to 30-June-2018. Women who were diagnosed with GDM by OGTT in the second trimester of pregnancy, delivered a live singleton more than 28 gestational weeks, and had complete medical records were included. Women who had a prior history of diabetes mellitus, chronic diseases (hypertension, liver, kidney, heart, lung, and other major organ diseases), autoimmune diseases (Sjogren's syndrome, anticardiolipin syndrome, myasthenia gravis), or tumors were excluded. Finally, 2048 GDM women were included in this study.

Relevant information about pregnant women, including age, height, weight before pregnancy (within one month before pregnancy), weight gain during pregnancy, gravidity, parity, OGTT value (FPG, 1-h PG, 2-h PG), HbA1c, mode of delivery, gestational week of delivery, neonatal birth weight, pregnancy complications such as macrosomia, pregnancy-induced hypertension (PIH, including gestational hypertension, preeclampsia, eclampsia) was obtained.

2.2 Diagnostic criteria

2.2.1 GDM diagnostic criteria

GDM was diagnosed according to IADPSG criteria by 75g OGTT in the second trimester of pregnancy by measurement of FPG, 1-h PG, and 2-h PG. OGTT and HbA1c tests were performed in the morning after overnight fasting of at least 8 hours at 24-28 weeks of gestation. G lucose level was measured using a clinical chemistry system (Beckman Coulter AU5800) automatic analyzer. HbA1c was measured by high-performance liquid chromatography

Abbreviations: AOR, Adjusted Odds Ratio; BMI, Body Mass Index; CI, Confidence Interval; DBP, Diastolic Blood Pressure; FPG, Fasting Plasma Glucose; GDM, Gestational Diabetes Mellitus; GWG, Gestational Weight Gain; HbA1c, Glycated Hemoglobin A1c; LGA, Large for Gestational Age; OGTT, Oral Glucose Tolerance Test; PIH, Pregnancy Induced Hypertension; PPG, Postprandial Glucose; SBP, Systolic Blood Pressure; SD, Standard Deviation.

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(HPLC) on an automated glycosylated hemoglobin analyzer (HLC-723G8), which has been certified by the National Glycohemoglobin Standardization Program (NGSP) to conform to the results of the Diabetes Complications and Control Trial and standardized according to International Federation of Clinical Chemistry (IFCC) reference system.

2.2.2 BMI

BMI was calculated as pre-pregnancy weight in kilograms(kg) divided by the square of height in meters(m). Pre-pregnancy BMI was categorized into underweight (<18.5 kg/m^2), normal weight (18.5 kg/m^2-23.9 kg/m^2), overweight (24.0 kg/m^2-27.9 kg/m^2), and obese (≥28.0 kg/m^2) groups according to Chinese criteria. (National Health Commission of the People's Republic of China: Criteria of Weight for Adults. [(accessed on 10 August 2021)];2013 Available online: http://www.nhc.gov.cn/ewebeditor/uploadfile/2013/08/20130808135715967).

2.2.3 GWG

GWG was the difference between pre-delivery and pre-pregnancy weight. According to the standard definition of the Institute of Medicine (IOM) guidelines in 2009 (18), appropriate GWG was 12.5-18.0 kg for underweight, 11.5-16.0 kg for normal weight, 7.0-11.5 kg for overweight and 5.0-9.0 kg for obesity respectively. Additionally, falling below the thresholds was defined as inadequate GWG, while exceeding the thresholds was defined as excessive GWG.

2.2.4 Adverse pregnancy outcomes

Neonates were defined as LGA if their birth weight was >90th percentile based on national population references for age and sex. Neonates with gestational age ≥ 28 weeks and < 37 weeks were considered as preterm neonates. Neonates with birth weight ≥4000g were defined as macrosomia. PIH was diagnosed in women with no previous history of hypertension with systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg on two occasions at least 4 hours apart after 20 gestational weeks with or without proteinuria (19).

2.3 Statistical analysis

Maternal and neonatal demographic and clinical features were reported as frequency (%) or means (± SD). Categorical variables, including maternal age groups, parity, gravidity, pre-pregnancy BMI group, GWG groups, and difference in the incidence of adverse pregnancy outcomes among HbA1c groups, were evaluated by chi-squared test. Continuous data, including birthweight, FPG, 1h-PG, 2h-PG, and maternal age, were evaluated using one-way ANOVA. HbA1c level was divided into three different categories by quartiles, which included ≤25th (5.0%, 31mmol/mol), 25th-75th (5.1-5.4%, 32-36mmol/mol) and ≥75th (5.5%, 37mmol/mol). Logistic regression was used to explore the association between HbA1c level and adverse outcomes in different maternal age groups, pre-pregnancy BMI groups, and GWG groups. Two-sided *p-values* less than 0.05 were considered significant. All statistical analyses were done with SPSS 26.0 software.

3 Results

3.1 General clinical characteristics and pregnancy outcomes of three HAb1c groups

Our study enrolled 2048 women with GDM of live singleton births without missing data (Figure 1). There were significant differences in maternal age (p<0.001), pre-pregnancy BMI (p<0.001), GWG (p<0.001), parity (p=0.001), and gravidity (p=0.001) among three HbA1c groups (Table 1). There were also significant differences in the incidence of macrosomia (p<0.001), preterm birth (p=0.020), primary C-section (p<0.007), and PIH (p<0.001) among HbA1c groups. Additionally, higher incidences of adverse outcomes (macrosomia, preterm birth, primary C-section, and PIH) were observed in GDM women with HbA1c ≥5.5% at the time of GDM diagnosis compared to other HbA1c groups. There was no significant difference in the incidence of LGA among HbA1c groups (Table 1).

3.2 Association between HbA1c and adverse outcomes

In GDM women with HbA1c ≥5.5%, HbA1c was significantly associated with preterm birth (aOR 1.64,95%CI1.05,2.55), macrosomia (aOR 2.63,95%CI1.61,4.31), and primary C-section

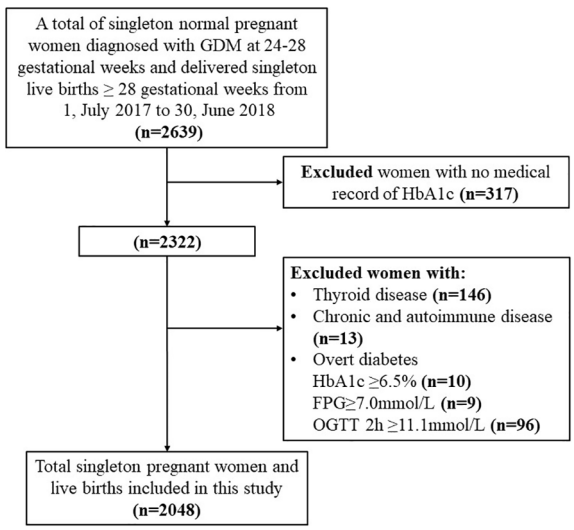

FIGURE 1
Flow chart of the study population. Demonstrates the inclusion and exclusion criteria of our study population; glycated hemoglobin A1c (HbA1c); gestational diabetes mellitus (GDM); fasting plasma glucose (FPG); 2hPG (2-hour plasma glucose); Oral glucose tolerance test (OGTT); chronic diseases (hypertension, liver, kidney, heart, lung and other major organ diseases, or tumors); autoimmune diseases (Sjogren's syndrome, anticardiolipin syndrome, myasthenia gravis).

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TABLE 1 Obstetrical characteristics by HbA1c groups in GDM[1].

Characteristic	HbA1c% (mmol/mol)			
	≤5.0 (31mmol/mol) (n=755)	5.1≤HbA1c≤ 5.4 (32– 36 mmol/mol) (n=942)	≥5.5 (37 mmol/mol) (n=351)	p[2]
Birth weight	3248.2 ± 451.0	3291.9± 491.1	3403.0 ± 593.5	<0.001
Maternal Age	31.7 ± 4.2	32.6 ± 4.4	33.7 ± 4.8	<0.001
<29	35.4%	28.0%	19.7%	
30-34	37.5%	38.0%	36.2%	
≥35	27.2%	34.0%	44.2%	
Gravidity				0.001
0	34.7%	29.1%	26.5%	
1 to 2	53.2%	54.1%	52.7%	
≥3	12.1%	16.8%	20.8%	
Parity				0.001
Nullipara	418 (55.4%)	437(46.4%)	155 (44.2%)	
Multipara	337(44.6%)	505(53.6%)	196 (55.8%)	
Pre-pregnancy BMI				<0.001
Normal	70.7%	68.9%	53.6%	
underweight	18.5%	10.0%	4.6%	
Overweight	9.5%	17.7%	30.5%	
Obese	1.2%	3.4%	11.4%	
OGTT				
FPG	4.5 ± 0.4	4.7 ± 0.5	5.0± 0.6	<0.001
1h-PG	9.8± 1.3	10.0 ± 1.1	10.3 ± 1.4	<0.001
2h-PG	8.7 ± 1.1	8.7 ± 1.2	8.8 ± 1.2	0.031
GWG				<0.001
Adequate	40.9%	43.4%	35.0%	
Inadequate	43.4%	35.5%	34.5%	
Excess	15.6%	21.1%	30.5%	
Macrosomia	4.4%	6.2%	13.4%	<0.001
Preterm birth	7.4%	10.0%	12.5%	0.020
Primary C-section	24.0%	27.2%	33.0%	0.007
PIH	4.2%	8.8%	15.1%	<0.001
LGA	0.9%	1.1%	1.4%	0.756

[1]BMI in kg/m$^{2;}$ values were expressed as mean ± standard deviation (SD) or n (%) unless indicated otherwise. Glycated hemoglobin A1c, HbA1c; gestational diabetes mellitus, GDM; oral glucose tolerance test, OGTT; fasting plasma glucose, FPG; postprandial glucose, PPG; pregnancy induced hypertension, PIH; gestational weight gain, GWG.
[2]Based on chi-square test.

(aOR 1.49,1.09,2.03) compared to their counterparts with HbA1c ≤5.0%. Interestingly, both GDM women with HbA1c 5.1%-5.4% and HbA1c ≥5.5% had significantly increased risk of PIH (aOR 1.91, 95%CI 1.24,2.94; aOR 2.56, 95%CI 1.57,4.19), respectively compared to their counterparts with HbA1c ≤5.0% (Table 2).

3.3 Association between HbA1c and adverse outcomes in different maternal age groups

There w ere significantly positive associations between HbA1c level and primary C-section in women aged ≤29 years with HbA1c

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TABLE 2 Association between HbA1c and adverse outcomes.

Adverse outcomes	HbA1c% (mmol/mol)		
	≤5.0 (31mmol/mol) (n=755)	5.1≤HbA1c≤ 5.4 (32–36mmol/mol) (n=942)	≥5.5 (37mmol/mol) (n=351)
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Preterm birth (n=194)	Ref	1.39 (0.97,1.97)	1.64 (1.05,2.55)*
Macrosomia (n=138)	Ref	1.26 (0.80,1.97)	2.63 (1.61,4.31)*
PIH (n=168)	Ref	1.91 (1.24,2.94)*	2.56 (1.57,4.19)*
Primary C-section (n= 553)	Ref	1.23 (0.97,1.56)	1.49 (1.09,2.03)*

[1]Glycated hemoglobin A1c (HbA1c) adjusted odds ratio (aOR), confidence interval (CI), pregnancy induced hypertension (PIH), and Ref represents the reference.
[2]Multiple logistic regression model was adopted and adjusted for gravidity, parity, maternal age, gestational weight gain (GWG), and pre-pregnancy BMI. *p < 0.05.

5.1 - 5.4% (aOR 1.51,95%CI1.00,2.29) or HbA1c ≥5.5% (aOR 2.35, 95%CI 1.22,4.53) compared to their counterparts with HbA1c ≤5.0%. Interestingly, young women aged ≤29 years showed an increased risk of PIH when their HbA1c was≥5.5% (aOR 3.53,95%CI1.34,9.30). Additionally, women aged ≥35 years with HbA1c ≥5.5% also showed an increased risk of PIH (aOR 2.56,95% CI1.13,5.78) compared to women ≥35 years with HbA1c ≤5.0%. HbA1c ≥5.5% was significantly associated with macrosomia among

TABLE 3 Association between HbA1c and adverse outcomes in different maternal age groups.

Maternal age	HbA1c% (mmol/mol)		
	≤5.0 (31mmol/mol) (n=755)	5.1≤HbA1c≤ 5.4 (32–36mmol/mol) (n=942)	≥5.5 (37mmol/mol) (n=351)
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
≤29 years (n=600)			
Preterm birth	Ref	1.02 (0.52,2.02)	2.26 (0.93,5.45)
Macrosomia	Ref	1.32 (0.62,2.78)	1.12 (0.38,3.31)
PIH	Ref	2.09 (0.95,4.60)	3.53 (1.34,9.30)*
Primary C-section	Ref	1.51 (1.00,2.29)*	2.35 (1.22,4.53)*
30-34 years (n=768)			
Preterm birth	Ref	1.07 (0.59,1.94)	1.48 (0.71,3.07)
Macrosomia	Ref	0.87 (0.42,1.78)	2.48 (1.16,5.31)*
PIH	Ref	1.89 (0.91,3.91)	2.04 (0.88,4.69)
Primary C-section	Ref	0.98 (0.67,1.44)	1.18 (0.72,1.96)
≥ 35 years (n=680)			
Preterm birth	Ref	2.11 (1.14,3.90)*	1.43 (0.67,3.03)
Macrosomia	Ref	2.46 (0.89,6.79)	5.52 (2.00,15.24)*
PIH	Ref	1.73 (0.81,3.69)	2.56 (1.13,5.78)*
Primary C-section	Ref	1.23 (0.78,1.94)	1.44 (0.85,2.43)

[1]Glycated hemoglobin A1c, HbA1c; adjusted odds ratio, aOR; confidence interval, CI; pregnancy induced hypertension, PIH; reference, Ref.
[2]Multiple logistic regression model was adopted and adjusted for gravidity, parity, gestational weight gain (GWG) and pre-pregnancy BMI. *p < 0.05.

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TABLE 4 Association between HbA1c and adverse outcomes in different pre-pregnancy BMI groups.

Pre-pregnancy BMI	HbA1c% (mmol/mol)		
	≤5.0 (31mmol/mol) (n=755)	5.1≤HbA1c≤ 5.4 (32–36mmol/mol) (n=942)	≥5.5 (37mmol/mol) (n=351)
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Normal (n=1371)			
Preterm birth	Ref	1.31 (0.85,2.01)	2.21 (1.29,3.78)*
Macrosomia	Ref	1.26 (0.72,2.20)	2.92 (1.52,5.61)*
PIH	Ref	1.87 (1.07,3.26)*	2.72 (1.36,5.45)*
Primary C-section	Ref	1.00 (0.75,1.33)	1.51 (1.01,2.25)*
Underweight (n=250)			
Preterm birth	Ref	1.03 (0.33,3.22)	-
Macrosomia	Ref	1.55 (0.22,10.72)	-
PIH	Ref	-	-
Primary C-section		2.58 (1.26,5.26)*	1.24 (0.27,5.60)
Overweight and Obese (n=427)			
Preterm birth	Ref	1.87 (0.75,4.66)	1.34 (0.51,3.52)
Macrosomia	Ref	0.80 (0.33,1.94)	1.75 (0.75,4.07)
PIH	Ref	1.69 (0.78,3.66)	2.12 (0.97,4.62)
Primary C-section	Ref	1.65 (0.88,3.07)	1.51 (0.80,2.86)

[1]Glycated hemoglobin A1c, HbA1c; adjusted odds ratio, aOR; confidence interval, CI; pregnancy induced hypertension; reference, Ref.
[2]Multiple logistic regression model was adopted and adjusted for gravidity, parity, gestational weight gain (GWG) and maternal age. *p < 0.05.

women aged 30 -34 years old (aOR2.48,95%CI1.16,5.31) and those aged ≥35 years (aOR 5.52, 95%CI 2.00,15.24) compared to HbA1c ≤5.0% (Table 3).

3.4 Association between HbA1c and adverse outcomes in different pre-pregnancy BMI groups

Pre-pregnant normal-weight women with HbA1c ≥5.5% had significantly increased risk of preterm birth (aOR 2.21, 95%CI 1.29,3.78), macrosomia (aOR2.92,95%CI1.52,5.61), PIH (aOR 2.72,95%CI1.36,5.45) and primary C-section (aOR 1.51,95% CI1.01,2.25) compared to pre-pregnant normal weight women with HbA1c ≤5.0%. Interestingly, pre-pregnant underweight women with HbA1c 5.1 - 5.4% at the time of GDM diagnosis were significantly associated with a higher risk of primary C-section compared to their counterparts with HbA1c ≤5.0% (aOR 2.58,1.26,5.26. (Table 4).

3.5 Association between HbA1c and adverse outcomes in different GWG groups

Interestingly, women with adequate GWG with HbA1c ≥5.5% at the time of GDM diagnosis were significantly associated with risk of PIH (aOR 3.42,95%CI1.48,7.88) compared to their counterparts with HbA1c ≤5.0%. On the other hand, women with inadequate GWG or excess GWG with HbA1c ≥5.5% also showed an increased risk of macrosomia compared to women with inadequate GWG or excess GWG who had HbA1c ≤5.0% (aOR 4.71, 95%CI 1.52,14.58; aOR 3.27,95%CI 1.39,7.71) (Table 5).

4 Discussion

This retrospective study demonstrated a strong relationship between HbA1c at the time of GDM diagnosis (24–28 weeks) and adverse pregnancy outcomes (preterm birth, macrosomia, PIH, and primary C-section) in Chinese women with GDM. Chinese women below recommended HbA1c (6.0%) by ADA might be at high risk of adverse outcomes. In our study, women with HbA1c ≥5.5% had a higher rate of adverse outcomes compared to women with HbA1c 5.1%-5.4% and ≤5.0%. Compared to HbA1c ≤5.0%, HbA1c ≥ 5.5% was significantly associated with an increased risk of macrosomia, preterm birth, PIH, and primary C-section. Our results support the existing evidence that HbA1c might be a biomarker for predicting adverse pregnancy outcomes in GDM women; however, we innovatively demostrated that maternal age, pre-pregnancy BMI, and GWG should be considered when determining the relationship between HbA1c and adverse outcomes. Therefore, our findings may help initiate focused individual prenatal care, health education, and

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TABLE 5 Association between HbA1c and adverse outcomes in different GWG groups.

GWG	HbA1c% (mmol/mol)		
	≤5.0 (31mmol/mol) (n=755)	5.1≤HbA1c≤ 5.4 (32–36mmol/mol) (n=942)	≥5.5 (37mmol/mol) (n=351)
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Adequate (n=933)			
Preterm birth	Ref	1.81 (0.96,3.41)	1.42 (0.59,3.38)
Macrosomia	Ref	0.84 (0.44,1.60)	1.59 (0.72,3.51)
PIH	Ref	2.33 (1.11,4.86)*	3.42 (1.48,7.88)*
C-section	Ref	1.38 (0.95,1.99)	1.13 (0.66,1.92)
Inadequate (n=752)			
Preterm birth	Ref	1.19 (0.73,1.95)	1.70 (0.92,3.14)
Macrosomia	Ref	2.44 (0.85,7.00)	4.71 (1.52,14.58)*
PIH	Ref	1.84 (0.86,3.92)	2.27 (0.91,5.69)
Primary C-section	Ref	1.06 (0.72,1.55)	1.59 (0.96,2.63)
Excess (n=363)			
Preterm birth	Ref	1.18 (0.45,3.08)	1.64 (0.58,4.67)
Macrosomia	Ref	1.51 (0.66,3.43)	3.27 (1.39,7.71)*
PIH	Ref	1.64 (0.74,3.62)	2.28 (0.97,5.37)
Primary C-section	Ref	1.22 (0.71,2.12)	1.76 (0.93,3.33)

[1]Glycated hemoglobin A1c, HbA1c; adjusted odds ratio, aOR; confidence interval, CI; pregnancy induced hypertension, PIH; reference, Ref.
[2]Multiple logistic regression model was adopted and adjusted for gravidity, parity, maternal age and pre-pregnancy BMI. *p < 0.05.

strict counselling to prevent adverse outcomes in high-risk GDM women.

HbA1c during mid-pregnancy have been reported to have the risk of adverse outcomes; however, findings are still controversial. This is due to the measurement of HbA1c in different gestational age, different population involved in the study, and different GDM diagnostic criteria. Given this background, there is still lack of optimum HbA1c for identifying adverse outcomes for GDM women. Surprisingly, HbA1c <5.0% (31mmol/mol) in Asian Indian women with GDM was associated with an increased risk of adverse outcomes (20). A study conducted in Taiwan that included 1989 GDM high-risk women reported that women with mid-pregnancy HbA1c levels lower than 4.5% (26mmol/mol) and higher or equal to 6% (42mmol/mol) were both at increased risk of gestational hypertension, preterm birth, admission to the neonatal intensive care unit, low birth weight, and macrosomia compared to women with HbA1c 4.5%–4.9% (26mmol/mol–30mmol/mol) (21). A study showed that Chinese women above the HbA1c cutoff of 6.0% (42mmol/mol) recommended by the American Diabetes Association (ADA) at the time of GDM diagnosis were at increased risk of primary cesarean section, high birth weight, hypertension during pregnancy, placenta abruption, macrosomia, and neonatal asphyxia compared to women with HbA1c<6.0% (42mmol/mol) (22). In our study, we found that women with HbA1c ≥5.5%might be at increased risk of adverse outcomes, similar to previous studies (17, 23, 24). Zhang Q et al. divided women into two groups including below and above recommended HbA1c cutoff by ADA; however, the sample size of women with HbA1c ≥6.0%(42mmol/mol) was relatively small (49 women), and the risk of adverse outcomes in women with HbA1c<6.0%(42mmol/mol) was not evaluated (22). Therefore, this may explain the differences in our findings. The present study evaluated the association between HbA1c at the time of GDM diagnosis with adverse outcomes in the Asian Chinese population, regardless of recommended HbA1c cutoff <6.0%(42mmol/mol) by ADA. It has been suggested that HbA1c <6.0%(42mmol/mol) cutoff might be higher for Asian women with GDM, thus predisposing them to a higher risk of adverse outcomes (25). It is imperative to note that studies on the association between HbA1c at the time of GDM diagnosis and adverse outcomes were conducted within the Caucasian population, and there is a lack of evidence for the Asian population (17). Therefore, further studies are needed to evaluate the role of HbA1c at the time of GDM diagnosis and determine optimum cutoff of HbA1c for adverse outcomes in Asian women, particularly Chinese women.

Studies have indicated a strong relationship between HbA1c lower than recommended cutoff <6.0%(42mmol/mol) and macrosomia in Asian women with GDM, similar to our findings (20, 21, 25). Although the mechanism is still unknown, according to Hughes et al., relatively higher HbA1c within the normal range at 24

-28 weeks is associated with adverse pregnancy outcomes due to poor glycemic control in the past 12 weeks before GDM diagnosis (26). Additionally, both high HbA1c and excess GWG have been strongly related to the risk of macrosomia offspring in accordance with our findings (27, 28). Pregnant women with excessive GWG have higher levels of amino acids, free fatty acids, and glucose, thus, increasing the risk of high birth weight (29). On the other hand, hyperglycemia leads to macrosomia by glucose crossing the placenta, increasing the utilization of glucose by the fetus and thus increasing fetal adipose tissue (30). Zhang, Q et al. found there's no significant difference of adverse outcomes in women with inadequate GWG between those with HbA1c ≥6.0%(42mmol/mol) and HbA1c<6.0%(42mmol/mol) (22), contrary to our findings. We noted that women with inadequate GWG with HbA1c levels ≥5.5% (37mmol/mol) had an increased risk of macrosomia compared to women with inadequate GWG women who had HbA1c ≤ 5.0% (31mmol/mol) in accordance with the previous study (31). In the present research, higher HbA1c levels (≥5.5%,37mmol/mol) may contribute to macrosomia in women with insufficient GWG, while a combination of high HbA1c levels and excess GWG might contribute to macrosomia in women with excess GWG. Therefore, strict counselling on lowering HbA1c in women with inadequate GWG and excess GWG might help prevent macrosomia in Chinese women with GDM.

Preterm birth is the leading cause of neonatal mortality and morbidity (32). Contrary to our findings, studies have shown no association between HbA1c and preterm birth (23). We noted that pre-pregnant normal-weight women with HbA1c ≥5.5% (37mmol/mol) and those aged ≥35 years had a significantly higher risk of preterm birth compared to normal-weight women with HbA1c ≤5.0%. Women with inappropriate weight during pregnancy are at increased risk of delivering preterm offspring and severe neonatal morbidity (33, 34). Although the mechanism between weight and preterm birth is still unclear, malnutrition during pregnancy may lead to a lack of essential nutrients, increasing the risk of chronic diseases and inflammation, leading to preterm birth (35). Malnutrition is less likely to be the cause of preterm birth in Zhejiang province; thus, we assume that higher HbA1c in women with normal pre-pregnant BMI might be the leading cause of preterm birth. There are many risk factors for preterm birth; our findings imply that higher HbA1c levels below the ADA-recommended HbA1c cutoff were also likely to lead to preterm birth in normal-weight Chinese women with GDM. Therefore, it is essential to consider the impact of HbA1c on preterm birth, particularly in women with HbA1c≥5.5%(37mmol/mol). Lowering HbA1c by strict blood glucose monitoring and appropriate GWG can help prevent preterm birth, particularly in normal-weight women. However, research may be required to evaluate the relationship between HbA1c and preterm birth, considering all relevant preterm birth-related factors. Solid conclusions on the relationship between HbA1c and preterm birth may help women with GDM prevent preterm birth.

Asian women have lower HbA1c levels compared to other women; thus, the ADA HbA1c cutoff of <6.0%(42mmol/mol) used based on studies that involved only Caucasian women might be higher for Chinese GDM women. An increase in HbA1c is related to the occurrence of microvascular disease, which may play a certain role in the pathogenesis of PIH (36). Moreover, hyperglycemia promotes increased insulin production leading to vascular stenosis, increased vascular resistance, and high blood pressure. Hyperinsulinemia can stimulate the sympathetic nerve, strengthen its excitability, and thus lead to high blood pressure. In the present study, HbA1c was significantly associated with the risk of PIH in women with HbA1c 5.1%-5.4% (32mmol/mol-36mmol/mol) and HbA1c ≥5.5% (37mmol/mol), particularly among women with adequate GWG when compared to women with HbA1c ≤5.0% (31mmol/mol). It is still debatable whether GWG using IOM guidelines is suitable for Chinese GDM women. However, studies show that IOM guidelines may not be appropriate for Chinese women based on the fact that the GWG cutoff by IOM guidelines is based on Caucasian women's characteristics (37), which might not be suitable for Chinese women. Multiple studies found that GDM women who acquired too much weight during pregnancy had a higher risk of PIH, whereas minimal gestational weight gain was related to a lower risk of hypertensive diseases (14). The possible mechanism is that fat accumulation leads to high estrogen in the body, thus mediating aldosterone secretion, sodium retention caused by the renin-angiotensin system, or directly increasing the recollection of the renal tubules, resulting in hypertension. Another mechanism might be that increased fat accumulation leads to abnormal blood lipid metabolism, which may lead to hypertension. Therefore, using GWG cutoffs based on Chinese women's characteristics may help Chinese women gain appropriate weight. It is also imperative to note that GWG cutoffs specifically for women with GDM are still lacking. Therefore, more studies on GWG cutoffs in Chinese pregnant women with GDM are warranted. It is imperative to note that gestational weight has been reported as a predictor of glycemic control and adverse pregnancy outcomes in women with GDM (38). Thus, strict GWG monitoring and lowering HbA1c levels may help reduce the risk of PIH in Chinese women with GDM, particularly those with HbA1c 5.1%-5.4% (32mmol/mol-36mmol/mol) and HbA1c ≥5.5% (37mmol/mol).

In the present study, the association between HbA1c and the risk of primary C-section varied in different pre-pregnancy BMI groups and maternal age groups. Studies have revealed the utility of HbA1c as a biomarker for predicting C-sections (39). Meanwhile, our results also indicated that normal-weight women with HbA1c levels≥5.5% (37mmol/mol) and underweight women with HbA1c 5.1%-5.4% (32mmol/mol – 36mmol/mol) had an increased risk of primary C-section. Antoniou et al. showed that women with pre-pregnancy BMI ≤ 25 kg/m^2 and HbA1c ≤5.5% (37mmol/mol) had a lower risk of C-section (31). However, women with ≤ 25 kg/m^2 and HbA1c ≥5.5%(37mmol/mol) were not evaluated in Antoniou et al.'s study. Our findings are in accordance with the HAPO study that showed HbA1c ≥5.8% (at 24 -32 gestational weeks) was significantly associated with an increased risk of primary C-section compared to lower HbA1c levels in pregnant women with hyperglycemia (10). On the other hand, HbA1c in the early trimester at a mean gestational week of 9.25 was significantly associated with primary C-section in non-diabetic Indian women

(40). Researchers hypothesize that abnormal glycemia in early pregnancy, which may be indicated by comparatively high HbA1c at the time of GDM diagnosis, is the mechanism underlying the relationship between primary C-section and higher mid-pregnancy HbA1c levels (40). HbA1c reflects glycemia status in the past several weeks; thus, relatively high HbA1c at the time of GDM diagnosis might be associated with poor glycemic control during early pregnancy. It is also important to note that HbA1c at GDM diagnosis that is quite high but still falls within the normal range indicates poor glucose control and is associated with higher odds of adverse outcomes (24, 25); thus, women with relatively high HbA1c within the normal range should not be ignored instead they should be strictly monitored. HbA1c is an independent risk factor of primary C- section (41); however, optimum HbA1c and optimum gestational age at which HbA1c might predict primary C-section remain unknown. While HbA1c at term might provide clinical care information for women at high risk of labor induction or a failed induction (41), HbA1c at term does not offer information on earlier primary and preventive care for women at high risk of adverse outcomes. Our findings on the association between HbA1c at 24 -28 weeks with the risk of primary C-section might have an advantage over findings of HbA1c at term and primary C-section (41), as our findings provided information that can lead to preventive care for GDM women at high risk of primary C-section earlier on, in pregnancy. Studies showed that women who receive strict counselling and follow-up during pregnancy have better glycemic control, a lowered HbA1c level, improved health, and better pregnancy outcomes (42, 43). Therefore, we recommend strict counselling and close follow-up for women with HbA1c 5.1% -5.4%(32mmol/mol-36mmol/mol) and ≥5.5%(37mmol/mol) at 24-28 weeks, particularly those with pre-pregnancy normal weight and underweight BMI for prevention of primary C-section.

While prevention care for pregnant women with diabetes with HbA1c ≥ 6.0%(42mmol/mol) is well established, there is still a lack of specific guidelines on HbA1c to prevent adverse outcomes in GDM. Our findings indicated that even though the recommended HbA1c cutoff for pregnant women with diabetes is <6.0%(42mmol/mol), it is still crucial to consider HbA1c cutoffs specific for women with GDM in consideration of race. Disregarding relatively higher HbA1c within the normal range in Chinese women with GDM can lead to severe adverse pregnancy outcomes (25); thus, earlier counselling and follow-up of women with relatively higher HbA1c(below the recommended ADA HbA1c cutoffs) at the time of GDM diagnosis may reduce the risk of adverse pregnancy outcomes. Nevertheless, further studies are needed to determine an optimum HbA1c cutoff based on Chinese women's characteristics to prevent adverse outcomes.

To the best of our knowledge, this study is the first to explore the association between HbA1c levels and adverse outcomes considering maternal age, pre-pregnancy BMI, and GWG. Our findings may help healthcare providers to manage GDM pregnant women personally and reduce the risk of adverse outcomes using HbA1c level, pre-pregnancy weight, maternal age, and GWG.

There are several limitations to our study. Firstly, we included a relatively small-size sample. Secondly, there was no further exploration of demographic characteristics, nutrition, and lifestyle, which may influence the results of our study despite the adjustment of confounders. Finally, this was a single-center and retrospective study; further multi-center and future research is required to investigate the utility of HbA1c in predicting adverse outcomes in different ethnicities and gestational age in consideration of pre-pregnant BMI, maternal age, and GWG.

Conclusively, HbA1c is significantly associated with macrosomia, preterm birth, PIH, and primary C-section in GDM women, particularly in women with HbA1c≥5.5%. Our findings may help healthcare providers identify women at high risk of adverse outcomes and manage pregnant women with GDM through counselling and health education by their HbA1c, thereby reducing the incidence of adverse outcomes in GDM. Nonetheless, Chinese women with HbA1c below the recommended HbA1c cut-off are also at high risk of adverse outcomes, which should not be disregarded. Thus, further advanced studies are needed to determine optimal HbA1c cut-offs for predicting adverse outcomes in consideration of Chinese population characteristics. Most importantly, maternal age, pre-pregnancy BMI, and GWG should be considered while evaluating the association between HbA1c and adverse outcomes.

Data availability statement

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

Ethics statement

This study was approved by the Human Ethics committee at Women's Hospital, School of Medicine, Zhejiang University (IRB-20210269-R). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design: ZL, DC, and LQ; Analysis and interpretation of the data: All authors; Drafting of the paper: MM and LZ; Paper revision and editing: ZL; Revising paper critically for intellectual content: All authors; Data collection: QW and LZ; Final approval of the version to be published: All authors. All authors agreed to the final content of the manuscript for submission and accountability for all aspects of this 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.

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Dynamic changes of serum taurine and the association with gestational diabetes mellitus: A nested case-control study

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Objective: There is a lack of risk factors that can effectively identify gestational diabetes mellitus (GDM) in early pregnancy. It is unclear whether serum taurine in the first trimester and dynamic changes have different characteristics in GDM women. Whether these features are associated with the occurrence of GDM has not yet been elucidated. The main objective of this study was to observe the dynamic changes of serum taurine during pregnancy and investigate the relationship between serum taurine levels and GDM in the first and second trimesters.

Methods: This was a nested case-control study in 47 women with GDM and 47 age-matched normoglycemic women. We examined serum taurine at 8-12 weeks' gestation and 24-28 weeks' gestation. The serum taurine of the two groups was compared. Multivariable logistic regression analysis was performed to investigate how serum taurine was associated with GDM.

Results: The serum taurine concentration of GDM women was significantly lower than that of normoglycemic women in the first trimester(2.29 vs 3.94 μmol/L, P<0.001). As the pregnancy progressed, serum taurine concentration in normoglycaemic women decreased significantly(3.94 vs 2.47 μmol/L, P<0.001), but not in the GDM group(2.29 vs 2.37 μmol/L, P=0.249), resulting in the disappearance of differences between the two groups(2.47 vs 2.37 μmol/L, P=0.160). After adjustment for pre-pregnancy body mass index(BMI), fasting plasma glucose(FPG), and lipid profiles in the first trimester, the serum taurine concentration in the first trimester was negatively correlated with the risk of GDM (OR=0.017, 95% CI=0.003-0.107, P<0.001). Furthermore, dynamic change of serum taurine showed a significantly positive correlation with the risk of GDM (OR=9.909, 95% CI=3.556-27.610, P<0.001).

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Conclusion: Low serum taurine concentration in the first trimester was significantly associated with the development of GDM. As the pregnancy progressed, the association between serum taurine and GDM disappeared in the second trimester, which might be related to the inhibition of taurine transporter(TauT) activity by high glucose.

KEYWORDS

biomarker, gestational diabetes mellitus, taurine, taurine transporter, dynamic change

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disease in pregnancy, with an incidence of 9%-25% globally according to the International Diabetes Federation (IDF) (1). Women with GDM are at an increased risk of gestational hypertension, pre-eclampsia, and cesarean section, as well as long-term risk of type 2 diabetes (T2DM) and cardiovascular disease (2). Maternal hyperglycemia will increase the risk of large for gestational age (LGA), shoulder dystocia or birth injury, and neonatal hypoglycemia (3). The offspring of GDM women are at increased long-term risk of obesity, abnormal glucose metabolism, and cardiovascular disease (4). With the continuous progress in knowledge of GDM, the oral glucose tolerance test (OGTT) at 24-28 gestational weeks was the diagnostic criteria for GDM (2). Recent studies evaluating maternal glycemia in relation to fetal growth trajectory have confirmed the early impact of maternal glycemia on fetal overgrowth and obesity prior to the diagnosis of standard GDM (5, 6). Lifestyle interventions such as dietary counseling or physical activity in the first trimester were demonstrated to effectively reduce the incidence of GDM and its associated adverse pregnancy outcomes (7, 8). As a result, it is of great clinical value to identify risk factors for GDM, especially in the first trimester.

Taurine which is the most abundant free amino acid in the human body and the key component of bile acid has many biological effects such as antioxidant, anti-inflammatory, improvement of insulin resistance(IR), neuroprotection, and anti-neurotoxicity (9, 10). Taurine can be made endogenous from cysteine or methionine, provided extrinsic from the diet, or affected by gut microbiota (11, 12). There was a significant negative correlation between taurine and non-gestational blood glucose, and taurine supplementation was effective in improving diabetes and other chronic metabolic diseases and preventing related complications (10). A recent study suggested a lower plasma taurine level in the first trimester seemed to be a fair marker of inadequate insulin secretion and to be more closely associated with a higher risk of GDM development in multiparas (13). However, the dynamic changes in serum taurine from the first to second trimester were unknown.

The main objective of this study was to observe the dynamic changes of serum taurine during pregnancy and investigate the relationship between serum taurine levels and GDM in the first and second trimesters.

Materials and methods

Patient cohorts

The participants in this nested case-control study were from a prospective cohort study in the Beijing Obstetrics and Gynecology Hospital, Capital Medical University. All pregnant women who intended to give birth in this hospital were enrolled in the cohort study at 8-12 gestational weeks and followed up until delivery. To evaluate the relationship between serum taurine and GDM, we selected eligible subjects from the recruited pregnant women above. Singleton pregnant women aged 18 to 44 years were recruited and only participants with complete clinical information were included in the analysis. Women with hypertension, diabetes, hyperlipidemia, liver or kidney dysfunction, and infectious diseases (hepatitis, pulmonary tuberculosis, etc.) before pregnancy were excluded. A 75-g OGTT was carried out at 24-28 gestational weeks. The diagnosis of GDM was made when any one of the following values was met or exceeded in the 75-g OGTT: 0 h (fasting), 5.1 mmol/L; 1 h, 10.0 mmol/L; and 2 h, 8.5 mmol/L according to ADA criteria (14). Normoglycaemic women were matched for age (± 3 years) to each case of GDM women in the same cohort (Figure 1).

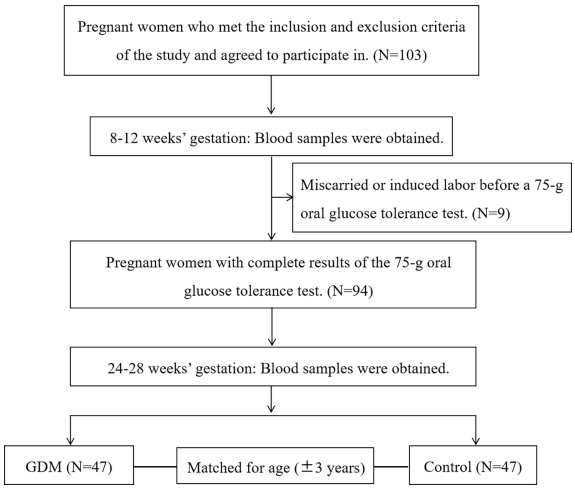

FIGURE 1
Flowchart of the included participants in this study.

Clinical measurements and covariates

Anthropometric measurements of participants were completed by trained medical staff at recruitment using a standardized protocol. Clinical data were collected by medical record review. Pre-pregnancy body weight was self-reported. A family history of diabetes was defined as a first-degree relative with T2DM. The fasting plasma glucose(FPG) and lipid profiles, including cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were determined as described in a previous study (15).

Taurine examination

Blood samples were collected from participants following an overnight fast at 8-12 weeks and 24-28 weeks, and serum specimens were isolated and stored at -80°C for further examination. The serum taurine levels were examined by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS, Thermo Scientific, USA). First, 100 μL of human serum was briefly added to a 0.5 mL glass centrifuge tube. After centrifugation at 14000 r/min for 5 min, the serum sample was dried under nitrogen at 50°C. Then, 60 μL of N-butyl alcohol and 12 mol/L HCI (95:5, v/v) were added and vortexed for 30 seconds in a seal. After incubation at 65° C for 15 min for derivatization, the derivatized solution was centrifuged, and dried under nitrogen at 50°C again. The residue was reconstituted by adding 100 μL of acetonitrile and water (4:1, v/v), vortexed for 30 seconds, centrifuged at 14000 r/min for 5 min, and injected at 20 μL for LC-MS/MS analysis.

Sample size calculation

The sample size was calculated using the mean and standard deviation of serum taurine in two groups. The test level (α) was 0.05, and the power (1-β) was 0.8. Serum taurine concentrations are 0.6 ± 0.1 mmol/L in diabetic patients and 0.8 ± 0.2 mmol/L in healthy adults (16). The minimum sample size was 48, and the sample size of this study was 94, which was sufficient according to the sample size calculation.

Statistics

Data were analyzed using the SPSS 26.0 software. Data with normal distributions were shown as the mean ± standard deviation, and nonnormal distributed data were shown as the median (interquartile range), respectively. T-tests and Wilcoxon tests were used to analyze the differences in continuous variables between the GDM group and the control group. Serum taurine concentrations were also compared by t-test. Categorical variables, including serum taurine levels (categorized into quartiles), were evaluated using the Cochran-Armitage. As pre-pregnancy body mass index(BMI) remained higher in the GDM group, we adjusted for pre-pregnancy BMI when comparing serum taurine levels in the two groups. Binary logistic regression for the association between GDM and serum taurine was carried out with adjustment for potentially confounding variables. The results are represented by the odds ratio (OR) and 95% confidence interval (CI). The differences were considered statistically significant when $P<0.05$.

Results

Clinical and laboratory characteristics

The study included 47 GDM women and 47 normoglycemic women. There was no history of GDM, macrosomia, or low birth weight delivery in both two groups. Pre-pregnancy BMI was significantly higher in the GDM women(22.32 vs 20.67, p=0.001), and other clinical indicators were similar, including gravidity, primipara, and history of polycystic ovary syndrome. However, FPG and lipid profiles including TC, TG, and LDL, were significantly higher among GDM women in the first trimester (FPG: 4.86 vs 4.64mmol, P=0.017; TC: 4.46 vs 4.12, P=0.021; TG: 1.26 vs 1.02, P=0.023; LDL: 2.33 vs 2.08, P=0.025)(Table 1). At OGTT, the blood glucose value of the GDM group was significantly higher, but there was no difference in lipid profiles

TABLE 1 Baseline characteristics and glycolipids metabolism in the first trimester between two groups.

	GDM (n=47)	Control (n=47)	P-value
Age (year)	33.0 ± 3.61	32.1 ± 2.91	0.170
Gravidity (first pregnancy)	21(44.68%)	24(51.06%)	0.536
Primipara	30(63.83%)	32(68.09%)	0.663
Smoking	2(4.55%)	1(2.13%)	0.608
Alcohol consumption	5(11.36%)	4(8.51%)	0.734
History of adverse pregnancy outcomes	8(17.02%)	3(6.38%)	0.156
History of PCOS	3(6.38%)	0(0.00%)	0.242
Family history of hypertension	13(29.55%)	11(23.40%)	0.506
Family history of diabetes	11(23.40%)	6(12.77%)	0.180
Pre-pregnancy BMI (kg/m^2)	22.32 ± 2.72	20.67 ± 2.03	0.001
FPG (mmol/L)	4.86 ± 0.49	4.64 ± 0.36	0.017
TC (mmol/L)	4.46 ± 0.74	4.12 ± 0.65	0.021
TG(mmol/L)	1.26(0.73)	1.02(0.42)	0.023
HDL(mmol/L)	1.48 ± 0.30	1.48 ± 0.29	0.922
LDL(mmol/L)	2.33 ± 0.61	2.08 ± 0.48	0.025

History of adverse pregnancy outcomes included spontaneous abortion, preterm, stillbirth, delivery of deformities, and early neonatal death. PCOS, polycystic ovary syndrome; FPG, fasting plasma glucose; TC, cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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between the two groups in the second trimester (Table S1 in the supplemental material).

Serum taurine levels between or within GDM and normoglycemic women

We compared serum taurine concentrations of GDM women and normoglycemic women at different stages of pregnancy, as well as the dynamic changes of serum taurine in the two groups (Table 2). The serum taurine concentration of GDM women was significantly lower than that of normoglycemic women in the first trimester(2.29 vs 3.94 μmol/L, P<0.001). When stratified by quartile, there were 23 controls and no GDM women with a taurine concentration less than 2.22 and there were 2 controls and 21 GDM women with a taurine concentration greater than 3.74 (P<0.001). The serum taurine concentration was similar between the two groups in the second trimester(2.37 vs 2.47 μmol/L, P=0.147), and there was no significant difference in quartile stratification(P=0.064). With the progress of pregnancy, serum taurine concentration decreased significantly in the control group (3.94 vs 2.47 μmol/L, P<0.001), but not in the GDM group(2.29 vs 2.37 μmol/L, P=0.249) (Figure 2).

TABLE 2 Serum taurine concentration and quartile stratification comparison between two groups.

	GDM (n=47)	Control (n=47)	T/R	P-value
Taurine in the first trimester (μmol/L)	2.29 ± 0.31	3.94 ± 1.32	-8.327	<0.001
Quartile Stratification			-0.749	<0.001
<2.22	21 (44.68%)	2(4.26%)		
2.22-2.67	21 (44.68%)	4(8.51%)		
2.68-3.74	5 (10.64%)	18(38.30)		
>3.74	0(0.00%)	23 (48.94%)		
Taurine in the first trimester (μmol/L)	2.37 ± 0.33	2.47 ± 0.34	-1.462	0.147
Quartile Stratification			-0.192	0.064
<2.19	14 (29.79%)	9 (19.15%)		
2.19-2.39	14 (29.79%)	11 (23.40%)		
2.40-2.62	11 (23.40%)	12 (25.53%)		
>2.62	8 (17.02%)	15 (31.91%)		
△Taurine	0.08 ± 0.49	-1.47 ± 1.44	6.983	<0.001

△Taurine, changes in taurine from the first to second trimester.

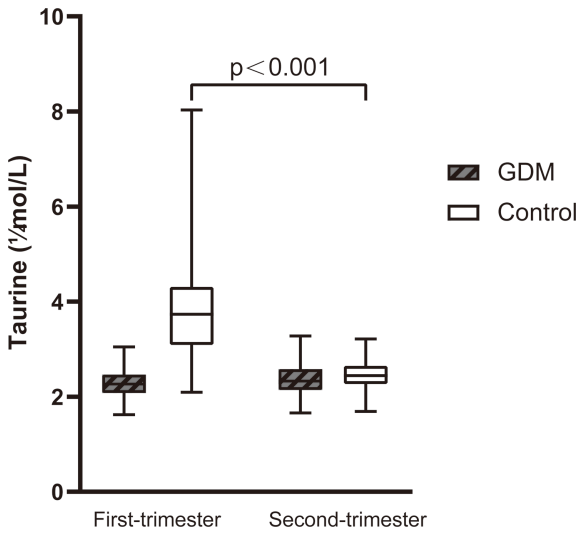

FIGURE 2
The dynamic changes of serum taurine between the first and second trimester of women with GDM and controls. Serum taurine concentration in control decreased significantly (P<0.001).

The association between serum taurine and GDM

Univariate logistic regression analysis showed that there was a significant negative correlation between serum taurine concentration in the first trimester and the risk of GDM (OR=0.013, 95% CI=0.002-0.082, P<0.001, Table 3). Furthermore, dynamic change of serum taurine showed a significantly positive correlation with GDM(OR=11.098, 95% CI=4.085-30.155, P<0.001, P<0.001, Table 3). Results did not change after adjustment for pre-pregnancy BMI, FPG, and lipid profiles in the first trimester (Taurine in the first trimester: OR=0.017, 95% CI=0.003-0.107, P<0.001; ΔTaurine: OR=9.909, 95% CI=3.556-27.610, P<0.001; Table 3). However, serum taurine concentration in the second trimester was not correlated with GDM in any case.

Discussion

Our study showed that serum taurine concentration in the first trimester was significantly lower in women who were later diagnosed with GDM. As the pregnancy progressed, serum taurine concentration in normoglycaemic women decreased significantly, resulting in the disappearance of differences between the two groups. Low serum taurine concentration in the the first trimester was significantly associated with the occurrence of GDM, and this correlation also no longer existed in the second trimester.

A significant negative association between taurine and T2DM has been demonstrated (16). Previous RCT studies have shown that taurine supplementation could effectively improve metabolic indicators of T2DM, including glycemic indexes, lipid profiles, and inflammatory biomarkers, and prevent related complications (17–19). The T2DM patients in these studies were all detected with

TABLE 3 The relationship between Taurine and GDM.

	OR(95% CI)	P-value	Adjusted OR (95% CI)	P-value
Taurine in the first trimester	0.013(0.002-0.082)	<0.001	0.017(0.003-0.107)	<0.001
Taurine in the second trimester	0.400(0.115-1.387)	0.149	0.248(0.056-1.089)	0.065
△Taurine	11.098 (4.085-30.155)	<0.001	9.909(3.556-27.610)	<0.001

△Taurine, changes in taurine from the first to second trimester. OR odds ratio, CI confdence interval. Adjusted OR, adjusted for pre-pregnancy BMI, FPG, TC, TG, LDL.

improvement in clinical metabolic markers after supplementing with 3000mg/day of taurine for 8 weeks. In addition, animal experiments showed that taurine had a protective effect on liver damage in GDM offspring (20). A study conducted the dietary survey at 24-28 gestational weeks and found that taurine intakes were lower in GDM than non-GDM in normal-weight women (21). However, there were few studies establishing a link between serum taurine levels and the risk of GDM. A recent study suggested a lower plasma taurine level in the first trimester seemed to be a fair marker of inadequate insulin secretion and to be more closely associated with a higher risk of GDM development in multiparas (13). This was consistent with our findings regarding the relationship between low serum taurine concentration in the first trimester and GDM.

Our study further compared the serum taurine concentrations in the second trimester and analyzed its dynamic changes. We found that as the pregnancy progressed, serum taurine concentration decreased significantly in normoglycaemic women but not in GDM women, resulting in the disappearance of differences between the two groups. The taurine decline trend from the first to second trimester was significantly negatively associated with the occurrence of GDM. Taurine is an amino acid that links the mother with the offspring during pregnancy, and fetuses depend on the taurine supplied by mothers *via* the placenta (22). The concentration of taurine in the placental tissue is 100-150 times higher than that of the fetus and mother (23). The placental tissues concentrate taurine efficiently and transfer taurine to fetal circulation based on the taurine transporter(TauT) activity (22). Animal studies have demonstrated that taurine concentration correlated with the peak of neurogenesis (24), which explained the decrease in serum taurine concentration in normoglycaemic women as the pregnancy progressed. However, high glucose levels could acutely inhibit taurine's transport by TauT (25), which might be the reason why there was no difference in serum taurine concentration between the first and second trimester of GDM women in our study. The offspring of GDM have a long-term risk of neurodevelopmental disorder (26), and the role of taurine transport inhibition is worth further study.

The beneficial effects of taurine on T2DM and its related complications have been widely reviewed in human clinical practice (27). Taurine played a hypoglycemic role by improving insulin sensitivity, stimulating insulin secretion, and reducing inflammation and oxidative stress (27). Previous studies have reported the role of taurine in maintaining glucose homeostasis involving several possible mechanisms, such as modulating several pancreatic cells (28) and inhibiting inflammatory factor and nuclear factor kappa-B(NF-κB) activity to reduce inflammatory-mediated destruction of pancreatic β cells (29). It is not clear whether the pathogenesis of GDM induced by taurine deficiency in the first trimester is identical to that in non-pregnant women. In our former study, we reported gut microbiota changes in the first trimester were potentially associated with the development of GDM (30). The gut microbiota could trigger inflammatory processes by increasing gut permeability by exposing tight gap junction proteins to bacterial lipopolysaccharides (31, 32). Taurine is a microbiota-related metabolite derived from bile acids by certain microorganisms (33), and animal studies have shown that taurine has a protective effect on intestinal barrier function (34). Taurine deficiency might play a critical role in the pathogenesis of GDM, resulting in the loss of intestinal barrier protection and chronic inflammation. Although a direct causal relationship between taurine and its pathological state has not been established, it might be a potential marker for GDM. We hope to develop a sensitive and reliable GDM prediction model with serum taurine in the first trimester to help identify high-risk individuals at an early stage. In addition, the clinical intervention can be stratified according to the high-risk degree to avoid the waste of medical resources.

Strengths and limitations

This was the first study to compare the dynamic changes of serum taurine concentrations from the first to second trimester. Our results demonstrated that small molecule metabolites varied during pregnancy and should be combined with dynamic changes to analyze their relationship with disease. Unfortunately, we were unable to collect umbilical cord blood to test their serum taurine levels to verify the relationship between taurine transport and the dynamic change of serum taurine concentration during pregnancy. In the future, the serum taurine levels of mothers and newborns could be detected simultaneously to reveal this correlation and its role in offspring nervous system development. In addition, this study was a single-center study, limited by the sample size and limited geographical area.

Conclusion

Our study revealed that GDM women had a reduced serum taurine level in the first trimester. Elevated serum taurine concentration from the first to second trimester was significantly associated with the development of GDM. The relationship between taurine deficiency and GDM may be related to increased intestinal permeability and systemic inflammation, and the specific mechanism needs to be further explored.

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 Beijing Obstetrics and Gynecology Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All the authors contributed significantly to the manuscript. GL and XM contributed to the study design and interpretation of the data. JW and YW contributed to the drafting and revision of the manuscript. JW and WZ coordinated and executed the statistical analysis. CL, XY, and YZ contributed to the collection of data. WS, XW, and SL contributed to the enrollment and follow-up in clinic. All authors reviewed and approved the final 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.

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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.2023.1116044/full#supplementary-material

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Maternal and fetal predictors of anthropometry in the first year of life in offspring of women with GDM

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Introduction: Gestational Diabetes Mellitus (GDM) carries an increased risk for adverse perinatal and longer-term cardiometabolic consequences in offspring. This study evaluated the utility of maternal anthropometric, metabolic and fetal (cord blood) parameters to predict offspring anthropometry up to 1 year in pregnancies with GDM.

Materials and methods: In this prospective analysis of the *MySweetheart* study, we included 193/211 women with GDM that were followed up to 1 year postpartum. Maternal predictors included anthropometric (pre-pregnancy BMI, gestational weight gain (GWG), weight and fat mass at the 1st GDM visit), and metabolic parameters (fasting insulin and glucose, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), Quantitative insulin-sensitivity check index (QUICKI), HbA1c, triglycerides, and high-density lipoprotein (HDL) at the 1st visit and HbA1c at the end of pregnancy). Fetal predictors (N=46) comprised cord blood glucose and insulin, C-Peptide, HOMA-IR, triglycerides and HDL. Offspring outcomes were anthropometry at birth (weight/weight z-score, BMI, small and large for gestational age (SGA,LGA)), 6-8 weeks and 1 year (weight z-score, BMI/BMI z-score, and the sum of 4 skinfolds).

Results: In multivariate analyses, birth anthropometry (weight, weight z-score, BMI and/or LGA), was positively associated with cord blood HDL and HbA1c at the 1st GDM visit, and negatively with maternal QUICKI and HDL at the 1st GDM visit (all $p \leq 0.045$). At 6-8 weeks, offspring BMI was positively associated with GWG and cord blood insulin, whereas the sum of skinfolds was negatively associated with HDL at the 1st GDM visit (all $p \leq 0.023$). At 1 year, weight z-score, BMI, BMI z-score, and/or the sum of skinfolds were positively associated with pre-pregnancy BMI, maternal weight, and fat mass at the 1st GDM visit and 3rd trimester HbA1c (all $p \leq 0.043$). BMI z-score and/or the sum of skinfolds were

negatively associated with cord blood C-peptide, insulin and HOMA-IR (all p ≤0.041).

Discussion: Maternal anthropometric, metabolic, and fetal metabolic parameters independently affected offspring anthropometry during the 1st year of life in an age-dependent manner. These results show the complexity of pathophysiological mechanism for the developing offspring and could represent a base for future personalized follow-up of women with GDM and their offspring.

KEYWORDS

gestational diabetes, cord blood, offspring anthropometry, fetal metabolism, maternal metabolism

1 Introduction

Gestational Diabetes Mellitus (GDM) is defined as diabetes first diagnosed during the second or third trimester of pregnancy, not fulfilling the criteria of pre-existing diabetes (1). The prevalence of GDM varies significantly worldwide, ranging from 1% to > 30% and is ~ 11% in Switzerland (2). It has been suggested that the intrauterine environment of GDM may affect fetal programming and future health in offspring of mothers with GDM (3–5). GDM carries an increased risk for adverse perinatal outcomes, such as large for gestational age (LGA) and increased adiposity, birth trauma, respiratory distress syndrome, jaundice, hypoglycemia, and admission to the neonatal intensive care unit (6–8). The impact of GDM on offspring anthropometry is present at birth and in later childhood (4, 8, 9), but data during the 1st year of life in this population are lacking. A higher body mass index (BMI) as well as an increased risk for overweight and obesity during childhood has been found in GDM-exposed offspring in most studies (4, 10, 11). In the HAPO study, GDM was positively associated with childhood overweight or obesity at a mean age of 11.4 years and this was mediated by the maternal BMI during pregnancy (9). These findings are in agreement with the KiGGS study (12). Data on cardiometabolic consequences of GDM in the offspring have been in part inconsistent. They might include elevated blood pressure (13) and a higher risk for dyslipidemia (14). They have a higher risk of impaired glucose metabolism (15, 16) during childhood and adolescence and an increased risk for obesity, insulin resistance, metabolic syndrome, prediabetes, and type 2 diabetes during early adulthood (17, 18).

In women with GDM, maternal anthropometric (pre-pregnancy BMI, GWG) and metabolic parameters (glucose values during oGTT, HbA1c, C-peptide and lipids) during the 2nd and 3rd trimester of pregnancy, have been associated with neonatal anthropometry including birth weight, BMI, macrosomia, large and small for gestational age (LGA, SGA) (19–23). Although data on the impact of cord blood metabolic parameters on neonatal anthropometry and adiposity are available in the general population (24, 25), they are limited in the GDM population. In pregnancies with GDM, cord blood insulin, C-peptide, and glucose values have been associated with weight, BMI, the sum of skinfolds and fat mass at birth, whereas the impact of fetal lipid metabolism remains controversial (26–29). Previous studies have assessed these associations only in older offspring, i.e., during childhood and adolescence (9, 11, 12, 30). The impact of maternal and fetal metabolism on infant anthropometry at different time points during the 1st year of life has not been studied in the GDM population and data in the general population are scarce. This might shed light on different pathophysiological processes regarding developmental aspects of metabolic health.

The aim of this study was to evaluate the utility of maternal anthropometric and metabolic, as well as fetal (cord blood) parameters as predictors of infant anthropometric and adiposity outcomes at different time points during the 1st year of life in pregnancies with GDM.

Abbreviations: *AGA*, Appropriate for Gestational Age; *BIA*, Bioelectrical impedance analysis; *BMI*, body mass index; *CI*, confidence interval; *DS*, standard deviation, *GA*, Gestational age; *GDM*, gestational diabetes mellitus; *GWG*, gestational weight gain; *HAPO FUS*, Hyperglycemia and Adverse Pregnancy Outcome Follow-Up Study; HbA1c, glycated hemoglobin; *HOMA-IR*, Homeostatic Model Assessment for Insulin Resistance; *IADPSG*, International Association of Diabetes and Pregnancy Study Group; *IDL*, intermediate density lipoprotein; *IOM*, institute of medicine; *LDL*, low density lipoprotein; *LGA*, Large for gestational age; *N*, Number; *oGTT*, oral glucose tolerance test; *QUICKI*, quantitative insulin-sensitivity check index; *OR*, odds ratio; *SGA*, Small for gestational age.

2 Materials and methods

2.1 Study design and follow-up

This study is a secondary analysis of the *MySweetheart trial*, a randomized-controlled intervention trial of 211 women with GDM and their offspring (Clinicaltrials.gov NCT02890693) (31). They were followed during pregnancy up to one year postpartum between 2016 and 2021, in the Diabetes and Pregnancy Unit in the Lausanne University Hospital, Switzerland. The intervention

consisted of a multidimensional interdisciplinary lifestyle and psychosocial intervention in women with GDM and their offspring compared with an active lifestyle and guidelines-based usual care. The allocation ratio was 1:1 using a block randomization method (blocks of 4) after stratification. Details of the study protocol have been described elsewhere (31).

2.1.1 Participant recruitment and consent

Women ≥18 years diagnosed with GDM between 24 and 32 weeks of gestational age (GA), who understood French or English, and consented to participate were included in *MySweetheart trial*. Women on strict bed rest, with severe mental disorder and pre-existing diabetes were excluded from the study. Signed informed consent was obtained from all participating women. The study was conducted in accordance with the guidelines of the declaration of Helsinki, and good clinical practice. The Human Research Ethics Committee of the Canton de Vaud approved the study protocol (study number 2016-00745).

2.1.2 Diagnosis of gestational diabetes

GDM was diagnosed according to the International Association of Diabetes and Pregnancy Study Group (IADPSG Criteria). GDM was confirmed if fasting blood glucose was ≥5.1 mmol/l and/or 1-h blood glucose was ≥10.0 mmol/l and/or 2-h blood glucose was ≥8.5 mmol/l, following a 75 g oGTT (32). Included women were randomized to the control or intervention group after the baseline visit and signing of an informed consent.

2.1.3 Follow-up

2.1.3.1 Control group

Women randomized to usual care (N=106 women with GDM) received a very active guideline-based treatment-as-usual clinical follow-up based on the American Diabetes Association and on the Endocrine Society guidelines for the management of GDM (33, 34). They had regular appointments every 1-3 weeks with a medical doctor, a diabetes-specialist nurse and/or a dietician after the GDM diagnosis. During the 1st visit, women were counselled on GDM and taught how to perform self-monitoring of blood glucose control 4 times during the day (fasting and 2 hours post-prandial). They were also advised on gestational weight gain (GWG) based on the Institute of Medicine (IOM) 2009 recommendations (35, 36). Patients had one appointment with a dietician for a personalized dietary counselling, and were encouraged to increase physical activity according to the Endocrine Society Guidelines (33). If glucose values remained above targets two or more times during a 1 to 2-week period (fasting glucose >5.3 mmol/l, 1-h postprandial glucose >8 mmol/l and/or 2-h postprandial glucose >7 mmol/l) despite lifestyle changes, insulin treatment (or very rarely metformin) was introduced depending on patient's glucose values and preference. After delivery, capillary glucose measures and glucose-lowering treatments were stopped and women saw a physician and a dietician at the 6-8 weeks postpartum after an oGTT test to discuss further management and receive lifestyle counselling.

2.1.3.2 Intervention group

Women randomized to the intervention group (N=105 women) received a multidimensional, interdisciplinary lifestyle and psychosocial intervention on top of the usual care. The focus was on eating behavior and a balanced food intake as well as physical activity and breastfeeding. The intervention also included a psychosocial component including the assessment of depression during and after pregnancy. Throughout the period of pregnancy and up to 1 year postpartum, patients were supported by a lifestyle coach (see (31) for more details).

2.1.3.3 Visits

Women were evaluated at different moments during the study, i.e., at the 1st GDM visit at 24-32 weeks (baseline; visit 1), at birth (visit 2), at 6-8 weeks postpartum (visit 3), and at 1 year postpartum (visit 4). Offspring were evaluated at birth, 6-8 weeks and at 1 year. At each visit, several measures were assessed. In the following section, we only mention measures that were analyzed in this present study.

Visit 1-1st GDM visit: At 24-32 weeks of GA information on maternal socio-demographic characteristics were collected and maternal anthropometric parameters and fasting metabolic biomarkers were measured.

Visit 2- Birth: Immediately after childbirth, blood was drawn from the umbilical cord to measure laboratory biomarkers. Offspring anthropometric parameters were obtained from the hospital birth record.

Visit 3- 6-8 Weeks: At 6-8 weeks of life, offspring's anthropometric measures including weight, length, BMI and skinfold measures were obtained.

Visit 4- 1 year: At this visit, offspring's anthropometric measures including weight, BMI, skinfold measures were collected.

2.2 Maternal and offspring parameters

2.2.1 Maternal sociodemographic and anthropometric parameters

Maternal socio-demographic parameters, including age, ethnicity, and parity were collected during a structured face-to-face interview at the 1st GDM clinical visit. Ethnicity was classified in Low (Europe, North America) and High Risk (Asia, Central and South America, Africa, Oceania) ethnic groups (37). Pre-pregnancy BMI was calculated based on self-reported pre-pregnancy weight or retrieved from medical charts and measured height on the 1st visit at the GDM clinic1. Weight was measured at the 1st GDM visit to the nearest 0.1 kg in women wearing light clothes and no shoes with an electronic Seca ® scale. Height was measured at the 1st GDM visit to the nearest 0.1 cm with a regularly calibrated Seca ® height scale. GWG was determined as the difference between the weight at the end of pregnancy and pre-pregnancy weight. At the 1st GDM visit, Bioelectrical Impedance Analysis (BIA) was performed (Akern BIA 101) to estimate fat free mass (FFM) using the Kyle equation (38), and fat mass was calculated using the formula: **Fat Mass = Weight – FFM**. Maternal medical treatment for GDM was classified in 2

categories (no treatment, treatment with insulin and/or very rarely metformin).

2.2.2 Offspring anthropometric parameters

Birth growth parameters such as weight (g) and length (cm) were documented at birth; percentiles and z-scores for each of the above-mentioned parameters were calculated using the Intergrowth 21st newborn size application tool (39) and BMI was calculated. LGA was defined as birth weight >90th percentile and SGA as birth weight <10th percentile for sex and gestational age. Gestational age was calculated according to the date of the last menstruation, or as assessed by the fetal ultrasound in the cases where gestational age was corrected during the early *in-utero* ultrasound evaluation. Neonatal data were obtained from patient medical chart for all newborns born in the Lausanne University Hospital. In the cases where delivery took place in another hospital or clinic, anthropometric parameters at birth were provided by the respective hospital.

At the 6-8 weeks and 1 year visits, offspring weight (kg) and length (cm) were measured. Weight was measured to the closest 0.1 kg, with a calibrated scale (Seca ® model 336). Babies were weighed without any clothes or in nappy. If the weight was measured with the nappy, the respective weight of the nappy was subtracted. Length was measured to the closest 0.1 cm with the same scale (Seca ® model 336) and BMI was calculated. Z-scores for weight, length and BMI were calculated using the using the WHO Anthro Survey Analyser tool -Offline version (40).

Skinfold thickness was measured to the nearest 0.1mm at 4 anatomical sites (biceps, triceps, subscapular, and iliac) using a Harpenden Skinfold Caliper. Skinfolds were measured three times at each anatomical site and mean value of each skinfold measure was used to calculate the sum of the 4 skinfolds.

2.2.3 Maternal and fetal (cord blood) metabolic parameters

At the 1st GDM visit, maternal metabolic health parameters, including fasting glucose, insulin, HbA1c, high-density lipoprotein (HDL), and triglycerides were measured. Maternal HbA1c also were measured at the end of pregnancy (last visit before delivery). At birth, glucose, insulin, C-peptide, high-density lipoprotein (HDL), and triglycerides were measured in the cord blood. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated using the formula (Fasting insulin in mIU/L x Fasting glucose in mmol/l)/22.5 (41). The Quantitative insulin-sensitivity check index (QUICKI) was calculated using the formula QUICKI = 1/[log(Fasting insulin in mIU/L) + log(Fasting glucose in mg/dl)] (42).

2.2.4 Laboratory methods

Plasma glucose was measured using a Hexokinase/Glucose-6-Phosphat-Dehydrogenase (HK/G6P-DH) assay. Insulin and C-peptide were measured with an electrochemiluminescence Immunoassay. HbA1c was measured using a chemical photometric method (conjugation with boronate; Afinion®). HDL cholesterol and triglycerides were measured with an enzymatic colorimetric method (CHOD-PAP and GPO-PAP respectively).

2.2.5 Predictors and outcomes

Maternal *anthropometric* parameters comprised of pre-pregnancy BMI, 1st GDM visit weight and fat mass (BIA) and GWG. Maternal *metabolic* parameters included fasting glucose, insulin, HOMA-IR, QUICKI, HDL, triglycerides as well as HbA1c at the 1st and last GDM visit. Cord blood *metabolic* parameters included glucose, insulin, C-peptide, HOMA-IR, HDL, and triglycerides. Outcomes comprised offspring anthropometric parameters at birth, 6-8 weeks and 1 year. More precisely, birth outcomes included weight z-score, BMI, LGA, and SGA, and outcomes at 6-8 weeks and 1 year, weight z-score, BMI, BMI z-score, and the sum of 4 skinfolds.

2.3 Statistical analysis

All data were analysed using Stata/SE 16.0 (StataCorp LLC, TX, USA). The normality of continuous variables was assessed using histograms and Q-Q plots. Outcomes variables were normally distributed. For consistency all continuous variables were described as mean and standard deviation. Binary outcomes were described as N (percentages) (Table 1). Comparisons between the intervention and control group and between the two ethnicity group categories (low/high-risk) were done using the unpaired t-test for normally distributed continuous variables, the Mann-

TABLE 1 Maternal and offspring characteristics.

Maternal Characteristics	Mean ± SD	Infant characteristics	Mean ± SD
Number of patients	193	**Birth anthropometric parameters**	
Age (years)	33.6 ± 4.8	Number of patients (N, %)	190 (Male:52)
High risk ethnicity (yes; N(%))	39 (22.7)	Gestational age (weeks)	39.7 ± 1.1
Personal history of GDM (yes; N(%))	24 (21.4)	Weight (kg)	3.4 ± 0.46
Pre-pregnancy BMI (kg/m^2)	25.9 ± 5.1	Length z-score (SD) [1]	0.10 ± 1.4
Gestational weight gain (kg)	12.6 ± 6.5	Weight z-score (SD) [1]	0.18 ± 1.1
Gestational age at the 1st GDM visit (weeks)	29.0 ± 2.4	BMI (kg/m2)	13.7 ± 1.7

(Continued)

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TABLE 1 Continued

Maternal Characteristics	Mean ± SD	Infant characteristics	Mean ± SD
Weight at the 1st GDM visit (kg)	79.6 ± 14.7	LGA [1,2]	22 (11.8%)
Fat mass by BIA at the 1st GDM visit (kg)	31.9 ± 9.5	SGA [1,3]	20 (10.8%)
Maternal metabolic parameters			
Glucose at the 1st GDM visit (mmol/L)	4.9 ± 0.49	**6-8 weeks anthropometric parameters**	
Insulin levels at the 1st GDM visit (mIU/L)	16.1 ± 8.2	Number of patients (N, %)	185 (Male:51)
HOMA-IR at the 1st GDM visit	3.6 ± 2.1	Age (days)	44.7 ± 9.3
QUICKI at the 1st GDM visit	0.24 ± 0.03	Weight z-score (SD) [4]	-0.12 ± 1.0
HbA1c at the 1st GDM visit (%)	5.1 ± 0.31	Length z-score (SD) [4]	0.06 ± 1.3
HbA1c at the 1st GDM visit (mmol/mol)	32.2 ± 2.0	BMI (kg/m2)	15.2 ± 2.0
Triglycerides at the 1st GDM visit (mmol/L)	2.4 ± 0.77	BMI z-score (SD) [4]	-0.2 ± 1.3
HDL at the 1st GDM visit (mmol/L)	1.8 ± 0.38	BMI z-score >1SD	20 (11.1%)
Gestational age at the last GDM visit (weeks)	36.9 ± 1.2	Sum of 4 skinfolds (mm)	34.5 ± 7.5
HbA1c at the last GDM visit (%)	5.3 ± 0.28		
HbA1c at the last visit (mmol/mol)	34.4 ± 1.8	**1 year anthropometric parameters**	
Fetal parameters		Number of patients (N, %)	170 (Male:52)
Number of patients	46	Age (months)	12.4 ± 1.0
Cord blood glucose (mmol/L)	4.0 ± 1.1	Weight z-score (SD) [4]	0.32 ± 0.91
Cord blood insulin (mIU/L)	11.6 ± 9.4	Length z-score (SD) [4]	0.27 ± 1.2
Cord blood C-Peptide (μg/L)	1.6 ± 0.76	BMI (kg/m2)	16.9 ± 1.6
Cord blood HOMA-IR	2.1 ± 0.16	BMI z-score (SD) [4]	0.23 ± 1.1
Cord blood triglycerides (mmol/L)	0.53 ± 0.38	BMI z-score >1SD [4]	39 (24.4%)
Cord blood HDL (mmol/L)	0.76 ± 0.22	Sum of 4 skinfolds (mm)	38.2 ± 10.6

GDM gestational diabetes mellitus, BMI body mass index, BIA Bioelectrical impedance analysis, HOMA-IR Homeostatic Model Assessment for Insulin Resistance, QUICKI quantitative insulin-sensitivity check index, HbA1c glycated hemoglobin, HDL high density lipoprotein, SD standard deviation, LGA large for gestational age, SGA small for gestational age.
[1] according to the Intergrowth 21st newborn size application tool (39).
[2] LGA: birth weight >90th percentile for sex and gestational age using the Intergrowth 21st newborn size application tool (39).
[3] SGA: birth weight <10th percentile for sex and gestational age using the Intergrowth newborn size application tool (39).
[4] according to the WHO Anthro Survey Analyser tool (40).

Whitney test for continuous variables with non-normal distribution and the Fisher's exact test for binary variables. In all analyses, predictors and outcomes did not differ in the groups (intervention *vs* control group, low *vs* high ethnicity group category) and the effect sizes were similar. Therefore, women from intervention and control groups and of low- and high-risk ethnicity were pooled together and adjusted for group allocation in all analyses. All analyses were also adjusted for infant age and sex, where appropriate.

We initially performed univariate linear and logistic regression analyses with infant anthropometric parameters as the dependent variables (Supplementary Tables 1–3).

Maternal and fetal (cord blood) predictors with a p-value < 0.05 in univariate analysis were included in stepwise multiple regression analyses models. We performed three different multivariate models, a first one including both maternal and fetal predictors, and a second and third one including only maternal or only fetal predictors, respectively. Fetal predictors were available for N = 46 participants. These analyses were adjusted for group allocation, infant age and sex where appropriate, as well as maternal ethnicity group category, parity and maternal age. These analyses were performed in order to identify the most significant maternal and fetal predictors of infant anthropometric parameters at birth, 6-8 weeks and 1 year (Table 2). We tested for collinearity for all predictors and separate models were performed for predictors with a collinearity index ≥ 0.6. More specifically, as the collinearity index was ≥ 0.6 between HbA1c at the 1st and last GDM visit, between pre-pregnancy BMI, weight and fat mass by BIA at the 1st GDM visit, between insulin, HOMA-IR and QUICKI, as well as between cord blood insulin, C-peptide and HOMA-IR, separate multivariate models were performed for these predictors if more than one of them were significantly related to the respective outcome variable in univariate analyses (see Supplementary Tables 1–3). For all analyses, β-coefficients (for continuous outcomes) and adjusted odds ratios (aORs-for binary outcomes)

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are reported along with their 95% confidence intervals (CIs), and statistical significance was set at 0.05.

3 Results

The initial population included 211 women with GDM participating in the randomized-controlled intervention, and their offspring. One woman was excluded because the diagnosis of GDM was done before 13 weeks of gestation, and 17 were excluded due to multiple gestation (N=4), and/or because their offspring were born premature (< 37 weeks of gestational age, N=16). Thus, 193 women (93 intervention group/100 control group) were included in the final analysis.

3.1 Maternal, fetal and infant characteristics

Detailed information on the maternal characteristics, cord blood metabolic parameters, and offspring anthropometric outcomes at birth, 6-8 weeks, and 1 year are shown in Table 1. Briefly, mean maternal age was 33.6 ± 4.8 years, pre-pregnancy BMI was 25.9 ± 5.1 kg/m^2 and GWG 12.6 ± 6.5 kg. GA at birth was 39.7

TABLE 2 Maternal and fetal predictors of infant anthropometry in multivariate regression analysis.

Offspring anthropometry	Predictors	OR [4]/β-coefficient	95% CI		p-value
Birth					
	Maternal and Fetal (BF)				
Weight z-score (SD) [1]	QUICKI at the 1st GDM visit	-20.87	-38.40	-3.34	0.023
	Cord blood HDL (mmol/l)	3.77	1.33	6.21	0.005
	Maternal				
BMI (kg/m2)	HDL at the 1st GDM visit (mmol/l)	-1.55	-2.52	-0.58	0.002
LGA[1,2]	HbA1c at the 1st GDM visit (%) [4]	5.45	1.04	28.66	0.045
	Fetal				
Weight z-score (SD) [1]	Cord blood HDL (mmol/l)	1.61	0.25	0.30	0.022
6-8 weeks					
	Maternal and Fetal (BF)				
BMI (kg/m2)	Gestational weight gain (kg)	0.09	0.03	0.15	0.006
	Maternal				
BMI (kg/m2)	Gestational weight gain (kg)	0.06	0.01	0.12	0.023
Sum of 4 Skinfolds (mm)	HDL at the 1st GDM visit (mmol/l)	-3.86	-7.17	-0.55	0.023
	Fetal				
BMI (kg/m2)	Cord blood insulin (mIU/L)	0.07	0.01	0.12	0.022
1 year					
	Maternal and Fetal (BF)				
BMI z-score (SD) [3]	Cord blood HOMA-IR	-0.37	-0.07	-0.05	0.026
Sum of 4 Skinfolds (mm)	HbA1c at the 1st GDM visit (%)	11.64	0.527	22.4	0.041
	Cord blood insulin (mIU/L)	-0.62	-1.04	-0.21	0.005
	Cord blood C-peptide (μg/L)	-8.65	-13.86	-3.45	0.002
	Cord blood HOMA-IR	-3.72	-6.45	-1.00	0.009
	Maternal				
Weight z-score (SD) [3]	Weight at the 1st GDM visit (kg)	0.01	0.00	0.02	0.017
	HbA1c at the 1st GDM visit (%)	0.54	0.03	1.05	0.038
BMI (kg/m^2)	Weight at the 1st GDM visit (kg)	0.02	0.00	0.04	0.022
	HbA1c at the last GDM visit (%) [5]	1.26	0.15	2.36	0.027

(Continued)

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TABLE 2 Continued

Offspring anthropometry	Predictors	OR [4]/β-coefficient	95% CI		p-value
	HbA1c at the 1st GDM visit (%) [5]	0.93	0.03	0.82	0.043
BMI z-score (SD) [3]	Pre-pregnancy BMI (kg/m^2) [5]	0.03	0.00	0.07	0.037
	Weight at the 1st GDM visit (kg) [5]	0.02	0.00	0.03	0.010
	Fat mass by BIA at the 1st GDM visit (kg) [5]	0.02	0.00	0.04	0.033
	Fetal				
BMI z-score (SD) [3]	Cord blood HOMA-IR	-0.37	-0.70	-0.05	0.026
Sum of 4 Skinfolds (mm)	Cord blood insulin (mIU/L) [5]	-0.68	-1.11	-0.25	0.003
	Cord blood C-peptide (μg/L) [5]	-8.65	-13.86	-3.45	0.002
	Cord blood HOMA-IR [5]	-3.72	-6.45	-1.00	0.009

OR Odds Ratio, CI Confidence Interval, BMI body mass index, GDM gestational diabetes mellitus, BIA Bioelectrical impedance analysis, HOMA-IR Homeostatic Model Assessment for Insulin Resistance, QUICKI quantitative insulin-sensitivity check index, HbA1c glycated hemoglobin, HDL high density lipoprotein, SD standard deviation, LGA large for gestational age, SGA small for gestational age.
[1] according to the Intergrowth 21st newborn size application tool (39).
[2] LGA: birth weight >90th percentile for sex and gestational age using the Intergrowth 21st newborn size application tool (39).
[3] according to the WHO Anthro Survey Analyser tool (40).
[4] this value corresponds to an OR.
[5] separate models were performed due to high collinearity (collinearity index ≥ 0.6) between predictors.
Stepwise multiple logistic regression analyses, adjusted for maternal age, ethnicity (high/low risk), parity, allocation group (intervention/control), infant sex and age (where appropriate). Outcomes are only shown if at least one predictor is found. Only significant results are displayed (defined significance, p-value <0.05, see text). Three distinct models were performed (combined model, including maternal and fetal predictors, model including only maternal or only fetal predictors), and results are displayed separately.

± 1.1 weeks, mean weight z-score at birth was +0.18 ± 1.1 standard deviations (SD) and 11.8% of newborns were LGA. At 6-8 weeks and 1 year, mean offspring BMI z-score was -0.2 ± 1.3 and +0.23 ± 1.1 SD respectively.

3.2 Associations between maternal and fetal predictors and offspring anthropometry at birth, 6-8 weeks, and 1 year in univariate analyses

Different maternal metabolic and fetal predictors were associated with offspring outcomes at birth, while maternal anthropometric and metabolic as well as fetal predictors were associated with offspring outcomes at 6-8 weeks and 1 year in univariate analyses (Supplementary Tables 1–3).

3.3 Associations between maternal and fetal predictors and offspring anthropometry at birth, 6-8 weeks and 1 year in multivariate analyses

The significant results of all multivariate univariate analyses are shown in Table 2.

3.3.1 Birth

In the models including only maternal predictors, HDL at the 1st GDM visit was negatively associated with offspring BMI, and HbA1c at the 1st GDM visit was positively associated with LGA (p ≤0.045). In the models including only fetal predictors, cord blood HDL was positively associated with the weight z-score (p ≤0.022). In the combined maternal and fetal model, maternal QUICKI at the 1st GDM visit was negatively associated and cord blood HDL was positively associated with the weight z-score (p ≤0.023).

3.3.2 6-8 weeks

In the models including only maternal predictors, HDL at the 1st GDM visit was negatively associated with the sum of skinfolds, whereas GWG showed a positive association with BMI (both p =0.023). In the model including only fetal predictors, cord blood insulin presented a positive association with offspring BMI (p =0.022). Lastly, in the combined model, GWG was positively associated with BMI (p =0.006).

3.3.3 1 year

In the models including only maternal predictors, pre-pregnancy BMI, as well as weight and fat mass at the 1st GDM visit showed a positive association with the offspring BMI z-score (all p ≤0.037). Weight at the 1st GDM visit and HbA1c at the 1st and last GDM visit presented a positive association with BMI (both p ≤0.043). Moreover, weight and HbA1c at the 1st GDM visit were positively correlated the weight z-score (both p ≤0.038). In models including only fetal predictors, cord blood HOMA-IR, C-peptide and insulin showed a negative association with the sum of 4 skinfolds (all p ≤0.009). Cord blood HOMA-IR presented a negative association with the BMI z-score (p =0.026). In the combined maternal and fetal models, HbA1c at the 1st GDM visit showed a positive, whereas cord blood insulin, C-peptide and HOMA-IR a negative association with the sum of 4 skinfolds (all p ≤0.041). Finally, cord blood HOMA-IR was negatively associated with the BMI z-score (p =0.026).

4 Discussion

This prospective, observational study of women with GDM and their offspring found that maternal anthropometric, metabolic and fetal metabolic parameters distinctively predicted offspring anthropometry during the 1st year of life. Maternal metabolic parameters during the 3rd trimester including QUICKI and HDL were negatively associated with offspring anthropometry at birth; HDL was negatively associated with offspring anthropometry at 6-8 weeks,whereas HbA1c was positively associated with offspring anthropometry at 1 year. Maternal anthropometric parameters, such as pre-pregnancy BMI, weight and fat mass during the 3rd trimester, and GWG predicted higher offspring anthropometry, but only after birth. Cord blood HDL correlated positively with weight z-score at birth, while cord blood insulin, C-peptide and HOMA-IR were associated with anthropometry during the 1st year of life in an age dependent pattern, showing positive associations at birth and 6-8 weeks and negative associations at 1 year.

4.1 Impact of maternal and fetal metabolism on birth anthropometry

Maternal HDL and QUICKI at the 1st GDM visit, both observed in situations of increased insulin sensitivity, were negatively associated with weight z-score and BMI respectively. In contrast, no associations were found between maternal HDL levels and birth anthropometry in another population with GDM (19). However, they found that maternal triglyceride levels were positively associated with adjusted birth weight centiles and LGA in their insulin-treated subpopulation; similar results have been documented in studies in the general pregnant population (19, 22, 23). In insulin-resistant states, when triglycerides are elevated, HDL is often decreased and may be a more stable marker than triglycerides (43). An adverse maternal lipid profile programs offspring regarding obesity in human and animal studies at and beyond birth, by multiple mechanisms including the offspring's eating behavior and energy expenditure, adipocyte development, genetics, epigenetics and shared post-natal environment and the inverse could be true for markers of favorable lipid profiles such as higher HDL (44, 45). HbA1c reflects overall maternal and thus subsequent fetal glucose exposure and was positively associated with LGA. This is in agreement with previous data in women with GDM (19), but has not been found in all studies (20, 21). As increased adiposity at birth represents a risk factor for obesity and the metabolic syndrome later in life (46), higher HbA1c levels, but also lower HDL levels in pregnancy may be used for risk stratification in these pregnancies with the aim to reduce the metabolic risk of the offspring (21). In contrast to previous studies in GDM populations, maternal anthropometric parameters had no impact on birth anthropometry (19–21). This may be explained by the smaller variability of maternal anthropometric parameters in our cohort and the fact that the impact of maternal anthropometry may be reduced by the strict monitoring, which is represented by the low % of LGA in our sample.

In terms of fetal metabolism, cord blood HDL showed a positive association with birth weight z-score, in agreement with a study in the general population (25), but on contrast to other studies (19, 23). Interestingly, cord blood HDL influenced birth anthropometry independently from maternal parameters in our study, highlighting the importance of fetal lipid metabolism for fetal growth, that might be distinct from, albeit also dependent of, the impact of maternal parameters. The findings of two previous studies in GDM showing inverse correlations between cord blood triglyceride and birth anthropometry further underline our results (19, 28). Large molecules such as HDL cannot cross the placenta directly, but they could affect the metabolism of other lipids, depending on the concentration and presence (47, 48). As proposed by Ye et al. (48), this potential interaction between lipid particles in the fetus could be critical for the fetal and neonatal metabolism, and may have a lasting impact on the metabolic health of the offspring. Cord blood markers including insulin, C-peptide and HOMA-IR were related to birth anthropometry in univariate, but not in multivariate analyses. Studies in healthy pregnancies, with mild untreated hyperglycemia (HAPO) or GDM have found a positive association between cord blood insulin and/or C-peptide and birth anthropometry, but they did not adjust for cord blood HDL (19, 24, 25, 27, 28). In agreement with previous studies, cord blood glucose was not related to birth anthropometry (26, 28).

4.2 Impact of maternal and fetal metabolism on infant anthropometry at 6-8 weeks of life

GWG was positively associated with infant BMI and maternal HDL negatively associated with the sum of skinfolds at 6-8 weeks in multivariate analyses (maternal and combined model). Maternal metabolic parameters related to insulin resistance were only correlated to higher anthropometric parameters in univariate analyses. Similarly, another study also found no relationship between maternal 3rd trimester C-peptide levels and the offspring's adipose tissue at 6 weeks and 4 months of age in adjusted models (49). Lastly, our study found a positive association between cord blood insulin and infant BMI.

4.3 Impact of maternal and fetal metabolism on infant anthropometry at 1 year

Regarding maternal metabolic parameters, HbA1c at the 1st GDM visit was positively associated with weight z-score, BMI, and the sum of skinfolds and HbA1c at the last GDM visit was positively associated with BMI at 1 year. Similarly, the HAPO-FUS study found a positive association between 3rd trimester HbA1c and offspring anthropometry, including BMI, body fat and the presence of overweight/obesity later in childhood, at 10-14 years (16).

Maternal anthropometric parameters, including pre-pregnancy BMI, 1st GDM visit weight and fat mass were also positively associated with weight z-score, BMI and BMI z-score at 1 year. This is in accordance with data in the general population where higher pre-pregnancy BMI was associated with higher offspring BMI and adiposity at 4-7 years (16, 44, 50). These findings may be explained by fetal programming and/or lifestyle and genetic characteristics (50, 51).

In terms of fetal metabolism, cord blood insulin, C-Peptide, and HOMA-IR were inversely associated with infant BMI z-score and the sum of skinfolds at 1 year, in agreement with a study in the general population which found a negative association between cord blood insulin and the sum of 4 skinfolds and % body fat at 3 years of age, but not in older children (52). Similarly, another study showed an inverse association between cord blood C-peptide and weight at 1 year in girls (53). In contrast, other studies in the general population have found a positive or no correlation between cord blood insulin and infant anthropometry or adiposity at 1-2 years (54, 55). Lastly, cord blood C-peptide was positively associated with offspring adiposity parameters at a mean age of 11.4 years in the HAPO Study and FUS (56).

The switch in the effect of cord blood insulin, C-peptide and HOMA-IR on offspring anthropometry during the 1st years of life (positive association at birth and 1st months of life, negative association at 1 year and the positive association in later childhood and adolescence) is intriguing and needs more research. A hypothesis for our findings is that at birth and the 1st months of life cord blood insulin, C-peptide and HOMA-IR may be markers of metabolic (glucose) overload in these babies and thus the impact of the maternal metabolism and fuel overload is significant. This may lead to fat accretion and body fat accumulation (mostly maternally-driven and not a clear marker of initial fetal or infant insulin resistance). However, as infants of mothers with GDM are insulin resistant and get even more insulin-resistant with increasing fat accretion, the insulin resistance at the adipose tissue level, could then prevent further fat accumulation in the subcutaneous adipose tissue, and might foster fat deposition in ectopic tissues (57). Thereby, fat cell lipolysis may also play a role (57). Further investigation is necessary to unravel these pathophysiological mechanisms. In later childhood, mechanisms related to excess energy intake and insulin resistance could again become more dominant for fat accretion.

4.4 Strengths and limitations

This is one of the rare studies assessing the impact of maternal and fetal parameters on infant anthropometric and adiposity parameters at different time points during the 1st year of life in pregnancies with GDM. Its prospective nature allowed us to include detailed information on various maternal and fetal parameters and to assess complex associations between maternal and fetal metabolism and growth during the 1st year of life. However, some limitations can also be noted. Cord blood parameters were available for a small proportion of our population (46 patients), which may have under or overestimated some of our correlations. Moreover, due to the small sample size, particularly regarding cord blood parameters, we were not able to perform separate analyses for the intervention and control group or according to low and high-risk ethnicity. However, maternal and fetal predictors and infant anthropometric parameters were not different between groups. Moreover, we did not assess the correlation between fetal anthropometry and birth and infancy anthropometry as the majority of fetal ultrasounds were not performed at our center. Lastly, collinearity was present between multiple maternal and fetal predictors. Therefore, in multivariate analyses, multiple testing models were necessary, which may have under- or overestimated some of our results.

5 Conclusions

Maternal anthropometric, metabolic and fetal metabolic parameters distinctively influenced offspring anthropometry during the 1st year of life and this in an age-dependent manner. Distinct age-dependent associations were particularly present for cord blood metabolic parameters. These observations show the complexity of the pathophysiological mechanism for the developing offspring and need further investigation. In the future, these predictors could be used for a more personalized follow-up of women with GDM and their offspring, to reduce the risks associated with an unfavorable *in-utero* environment and to foster a favorable fetal programming.

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 Human Research Ethics Committee of the Canton de Vaud (study number 2016-00745). The study was conducted in accordance with the guidelines of the declaration of Helsinki, and good clinical practice. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JP and AH conceived the study, designed the trial, obtained grant funding, and oversaw management of the trial. LG and DQ helped in designing parts of the study and participated in the implementation of the study. M-CA performed the data analysis, and interpretation and wrote the draft manuscript, under the supervision of JP. AL and BS participated in data analysis. DQ, LG, AH and JP revised the manuscript for important intellectual content and gave final approval for the version to be published. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1144195/full#supplementary-material

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Birth weight and large for gestational age trends in offspring of pregnant women with gestational diabetes mellitus in southern China, 2012-2021

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Background: With increasing prevalence of gestational diabetes mellitus (GDM) and changing management of GDM in pregnancy, it is imperative to understand the evolution of its current outcomes. The present study aimed to explore whether birth weight and large for gestational age (LGA) trends in women with GDM have changed over time in southern China.

Methods: In this hospital-based retrospective study, all singleton live births for the period 2012 to 2021 were collected from the Guangdong Women and Children Hospital, China. GDM was diagnosed following the criteria of the International Association of Diabetes and Pregnancy Study Group. The cutoff points for defining LGA (>90th centile) at birth based on INTERGROWTH-21st gender-specific standards. Linear regression was used to evaluate trends for birth weight over the years. Logistic regression analysis was used to determine the odds ratios (ORs) of LGA between women with GDM and those without GDM.

Results: Data from 115097 women with singleton live births were included. The total prevalence of GDM was 16.8%. GDM prevalence varied across different years, with the lowest prevalence in 2014 (15.0%) and the highest prevalence in 2021 (19.2%). The mean birth weight displayed decrease in women with GDM from 3.224kg in 2012 to 3.134kg in 2021, and the z score for mean birth weight decreased from 0.230 to -0.037 (P for trend < 0.001). Among women with GDM, the prevalence of macrosomia and LGA reduced significantly during the study period (from 5.1% to 3.0% in macrosomia and from 11.8% to 7.7% in LGA, respectively). Compared to women without GDM, women with GDM had 1.30 (95% CI: 1.23 - 1.38) times odds for LGA, and the ORs remained stable over the study period.

Conclusions: Among offspring of women with GDM, there are decreased trends of birth weight in parallel with reductions in LGA prevalence between 2012 and 2021. However, the risk of LGA in women with GDM remains stable at relatively

high level over the 10-year period, and efforts are still needed to address regarding causes and effective intervention strategies.

KEYWORDS

birth weight, gestational diabetes mellitus (GDM), large for gestational age (LGA), trends, pregnancy

Introduction

Birth weight is an important predictor of neonatal morbidity and mortality, reflecting both maternal health and neonatal health (1, 2). In the recent past, a number of researchers have demonstrated the trends in birth weight. Data from the United States and the United Kingdom showed an increasing trend in mean birth weight (3, 4). Increased birth weight is associated with early neonatal complications, as well as cardiovascular and metabolic disease later in adulthood (5). Around 50% of pregnancy women with pre-existing diabetes mellitus are delivering large for gestational age (LGA) neonates (6, 7). The emergence of new technologies for managing diabetes mellitus is revolutionizing the management of adverse conditions in pregnancy. However, several studies have observed a paradoxical trend that infant born to women with type 1 diabetes increasingly show overgrowth despite apparent good maternal glycemic control (8). Pregnancy women with diabetes are receiving increased intervention in Scotland, but a continuous increase in birth weight and the proportion of LGA were found from 1998 to 2013 (9). Fetal macrosomia and LGA infants born to women with diabetes were increased between 1991 and 2003 in Sweden (10) and between 1987 and 2016 in Australia (11). Gestational diabetes mellitus (GDM), which is the most common complication during pregnancy, is a definitive risk factor for fetal overgrowth and long-term offspring complications (12–14). The prevalence of GDM is increasing worldwide during the past few decades (15). In 2011, after the new diagnostic criteria of the International Association of Diabetes and Pregnancy Study Group (IADPSG) was gradually carried out, the prevalence of GDM increased almost 3-5 times, up to 14.8% in mainland China (16). Despite marked improvement in managing blood glucose levels, women with GDM still carries risks for the growing fetus. It is not clear whether birth weight and the proportion of LGA in offspring of women, who are diagnosed as GDM by the IADPSG criteria, have changed over time in China. Understanding the past and current trends of the birth weight and LGA is imperative to improving the health outcomes for women with GDM. The present study aimed to examine the 10-year trends in birth weight and prevalence of LGA between women with and without GDM, using hospital-based databases (2012–2021) in southern China.

Methods

Study population

This was a hospital-based retrospective study, which was conducted in Guangdong Women and Children Hospital, the provincial health center for maternal and child health surveillance of Guangdong, southern China. All singleton pregnancies with live birth between January 2012 and December 2021 were retrospectively selected from the hospital information system. Live births with gestational age between 24 and 42 weeks were included. For mothers who had GDM screening and delivered in Guangdong Women and Children Hospital were included. The data (maternal age, parity, mode of delivery, date of newborn's birth, gestational week at birth, and birth weight) was collected from the electronic medical records of Guangdong Women and Children Hospital. We excluded women with hypertensive disorders, pre-pregnancy diabetes, multiple pregnancies or fetal anomalies or missing data on gestational age.

Ethical statement

Ethical approval was obtained from the Ethics Committee of the Guangdong Women and Children Hospital. In accordance with national legislation and institutional regulations, written informed consent for participation was not necessary for this study. The accessed patient data adhered to applicable data protection and privacy regulations.

Screening and diagnoses of GDM

During the study period, pregnant women were screened for GDM using IADPSG criteria at 24-28 weeks of gestation. GDM was diagnosed if any of the blood glucose values equals to or exceeds: fasting blood glucose 5.1 mmol/L, 1-h blood glucose 10.0 mmol/L, and 2-h blood glucose 8.5 mmol/L (17).

Statistical analysis

We defined low birth weight as a birth weight of <2.5 kg, and macrosomia as a birth weight ≥ 4.0 kg. Birth weight was also calculated as birth weight z-scores using the INTERGROWTH-21st standards (18). The cutoff points for defining small for gestational age (<10th centile) and LGA (>90th centile) at birth based on INTERGROWTH-21st gender-specific standards.

Continuous variables were reported as the mean ± standard deviation, and categorical variables were reported as numbers and percentages. To compare differences between women with GDM

and those without GDM, the t-test was used for continuous variables and the chi-square test was used for categorical variables. Linear regression was used to evaluate trends for birth weight over the years. The annual percentage change (APC) of trends were determined based on logarithmically transformed percentages and their standard errors. Logistic regression analysis was used to determine the odds ratios (ORs) of the macrosomia and LGA between women with GDM and those without GDM, adjusting for maternal age and parity. Data analysis was performed using the SPSS statistical software package (V26, IBM Statistics, Chicago, IL, USA). P <0.05 was considered to be the threshold for statistical significance in analyses.

Results

A total of 115097 women with singleton live births were included in the study. The prevalence of GDM was 16.8%, which varied across different years, with the lowest prevalence in 2014 (15.0%) and the highest prevalence in 2021 (19.2%) (Figure 1). There were four significant trend periods for prevalence of GDM during this period: decreased from 2012 to 2014 with an APC of -6.9, increased from 2014 to 2017 with an APC of 4.7, decreased from 2017 to 2019 with an APC of -4.1, increased from 2019 to 2021 with an APC of 9.8. Table 1 shows the characteristics of the participants. Compared to the women without GDM, the women with GDM had higher maternal age, higher proportions of multiparous and cesarean. The prevalence of macrosomia and LGA were significantly higher in women with GDM than those without GDM.

Figure 2 shows the trends of mean birthweight in women with and without GDM between 2012 and 2021. The mean birth weight appeared almost flat trend for the 10-year period in women without GDM, but displayed decrease in women with GDM from 3.224kg in 2012 to 3.134kg in 2021. Decreased changes of mean birth weight over times were significant for groups 24-31 weeks, 37-38 weeks, and 39-40 weeks gestational age at delivery in women with GDM (Figure 2). The results appeared to be no significant change in the absolute values of birth mean weight between offspring of women with GDM and those without GDM, although there was a statistically significant difference due to the large sample size. However, the z-score for birth weight showed that GDM offspring had higher birth weight than non-GDM offspring, and both groups demonstrated a decreasing trend (Table 2). When we further restricted the analysis to full-term singleton live births, similar results were observed (Supplementary Table 1).

Among women with GDM, the prevalence of macrosomia and LGA reduced significantly during the study period (from 5.1% to 3.0% in macrosomia and from 11.8% to 7.7% in LGA, respectively) (Table 3). The prevalence of macrosomia and LGA in offspring of women with GDM was higher than that of non-GDM women. Despite fluctuations in the prevalence of macrosomia over the past 10 years, the prevalence of macrosomia did not significantly decrease in non-GDM offspring, while it showed a relatively significant reduction in GDM offspring. The prevalence of LGA showed a decreasing trend in both groups (Table 3). Figure 3 revealed that prevalence of macrosomia and LGA was significantly higher in multiparous women with GDM than those nulliparous women across the time course examined. The prevalence of macrosomia and LGA showed decreased trends with time in both nulliparous and multiparous. Women with GDM were risk factors for macrosomia and LGA. Compared to women without GDM, women with GDM had 1.30 (95% CI: 1.23 - 1.38) times odds for LGA, and the odds remained stable over the study years (Table 4).

Discussion

GDM is becoming more prevalent, and it is imperative to gain a better understanding of the evolution of adverse outcomes. In the management of pregnancy complicated by GDM, birth weight and LGA are important outcome measures. Therefore, our study updated the 10-year trends in the birth weight and LGA among women with GDM in southern China. This large, hospital-based study documented a high prevalence of GDM with fluctuations over time. The birth weight appeared decrease trends in women with GDM, and also found a concomitant decline in LGA prevalence from 2012 to 2021.

The overall prevalence of GDM was 16.8% during the 10-year study period, which was contrast with those of a previous report evaluating trends in GDM prevalence in China (16) and other parts of the world (19). A recent clinical update on GDM by Sweeting et al. also highlighted the increasing prevalence of GDM globally, with estimates suggesting that GDM affects around 2% to 19% for the IADPSG criteria of all pregnancies worldwide, and emphasized the importance of appropriate management of blood glucose levels in preventing

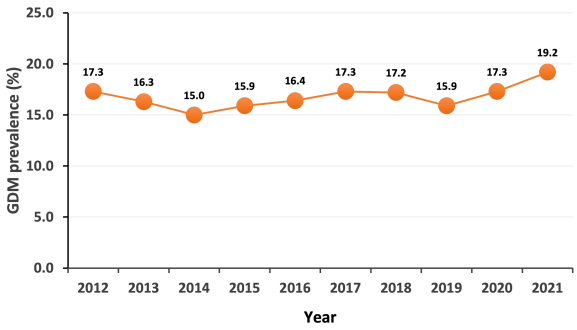

FIGURE 1
Trends of prevalence of GDM between 2012 and 2021.

TABLE 1 Characteristics of the study population.

Variables	Total (n= 115097)	Non-GDM (n= 95741)	GDM (n= 19356)	*P*-value
Maternal age at delivery, years	29.7 ± 4.6	29.4 ± 4.5	31.7 ± 4.8	< 0.001
18-24	13643 (11.9)	12620 (13.2)	1023 (5.3)	
25-29	45617 (39.6)	39950 (41.7)	5667 (29.3)	
30-34	37929 (33.0)	30600 (32.0)	7329 (37.9)	< 0.001
35-39	14746 (12.8)	10588 (11.1)	4158 (21.5)	
>=40	3162 (2.7)	1983 (2.1)	1179 (6.1)	
Parity				
Nulliparous	58582 (50.9)	50040 (52.3)	8542 (44.1)	
econd delivery	47359 (41.1)	38488 (40.2)	8871 (45.8)	< 0.001
Third and more delivery	9156 (8.0)	7213 (7.5)	1943 (10.0)	
Mode of delivery				
Vaginal	71953 (62.5)	60990 (63.7)	10963 (56.6)	
Cesarean	43144 (37.5)	34751 (36.3)	8393 (43.4)	
Gestation at delivery, weeks	38.99 ± 1.86	39.04 ± 1.85	38.75 ± 1.89	< 0.001
24-31	1689 (1.5)	1361 (1.4)	328 (1.7)	
32-36	7249 (6.3)	5678 (5.9)	1571 (8.1)	
37-38	33691 (29.3)	27427 (28.6)	6264 (32.4)	< 0.001
39-40	65004 (56.5)	54304 (56.7)	10700 (55.3)	
41-42	7464 (6.5)	6971 (7.3)	493 (2.5)	
Newborn sex				
Male	61706 (53.6)	51131 (53.4)	10575 (54.6)	0.002
Female	53391 (46.4)	44610 (46.6)	8781 (45.4)	
Birth weight, kg	3.171 ± 0.497	3.172 ± 0.491	3.167 ± 0.525	0.148
Low birth weight (<2.5 kg)	7767 (6.7)	6243 (6.5)	1524 (7.9)	< 0.001
Macrosomia (≥ 4.0 kg)	3789 (3.3)	2962 (3.1)	827 (4.3)	
Z score for birthweight	0.001 ± 0.883	-0.014 ± 0.873	0.078 ± 0.928	< 0.001
Small for gestational age (≤ 10th centile)	8039 (7.0)	6797 (7.1)	1242 (6.4)	< 0.001
Large for gestational age (≥ 90th centile)	8530 (7.4)	6630 (6.9)	1900 (9.8)	

Values are presented as n (%) or mean ± SD.
P-value for comparing variable between Non-GDM and GDM group.

adverse outcomes in pregnancies complicated by GDM (20). GDM affects 17.6% of all pregnant women from 2011 to 2018, with high and stable trend in the prevalence of GDM in Xiamen, China (21). Another study conducted in Beijing during 2013-2018 reported that the prevalence of GDM was 24.2% according to the IADPSG criteria (22). After applying the IADPSG criteria in China, the prevalence of GDM was substantially increased due to more pregnant women with mild hyperglycemia were diagnosed as GDM. Although these studies conducted to be in line with the same IADPSG criteria in China, there were some deficiencies in these previous studies, which could be partly relevant to China with a large population in different regions, ethnicities, diets, and living habits (16).

Although multiple studies had evaluated GDM prevalence in China at some point, few examined trends of birth weight and LGA prevalence for 10-year period after employing the new criteria. Our study showed that birth weight was decreased in women with GDM during this study period. Trends in the prevalence of macrosomia (birth weight ≥ 4.0 kg) and LGA were declined throughout the study period in women with GDM. Positive changes over this time period, such as improved antenatal care and progressed in managing blood glucose levels, may be contributed to the decreasing trends in LGA. This finding is contrary to previous study surveyed in the UK which have reported that average birth weight is greatly increased in the offspring of mothers with diabetes, despite receiving increased

FIGURE 2
Trends of mean birth weight in women with and without GDM between 2012 and 2021.

intervention in pregnancy between 1998 and 2013 (9). It may be interpreted as numbers of pregnancy women with type 1 and type 2 diabetes have increased significantly over that study period (23). The prevalence of LGA decreased during our study period, but the risk for LGA in women with GDM was found no significant change. The metabolic abnormalities of GDM during pregnancy are mainly due to increased insulin resistance and β-cell defects (24), which most commonly involve hyperglycemia with the attendant risk of fetal overgrowth (25). However, women with GDM often have other risk factors for LGA, including increasing age, maternal overweight, excessive gestational weight gain and insulin administration (26–28). Our present study did not investigate the comprehensive effects of GDM. Thus, the findings could not be determined whether in relation to risk factors for LGA associated with GDM were due to maternal hyperglycemia or other risk factors.

Our study is mainly limited by its retrospective design. We used routinely collected data in hospital information system that were unable to measure some factors assessed in the previous studies, such as maternal gestational weight gain, antenatal care and glycemic control status during pregnancy across the study period. Second, the study was conducted using non-random population-based sampling. The data may have been affected by selection bias,

TABLE 2 Trends in singleton liveborn birth weight in women with and without GDM between 2012 and 2021.

Year	Total No.	GDM No.	Birth weight (kg)		*P*-value	Birth weight z score		*P*-value
			Non-GDM	GDM		Non-GDM	GDM	
2012	8920	1539	3.164 ± 0.514	3.224 ± 0.504	< 0.001	0.039 ± 0.904	0.230 ± 0.905	< 0.001
2013	8637	1407	3.141 ± 0.530	3.149 ± 0.561	0.606	0.031 ± 0.884	0.144 ± 0.946	< 0.001
2014	10003	1501	3.145 ± 0.526	3.150 ± 0.574	0.757	-0.004 ± 0.891	0.112 ± 0.972	< 0.001
2015	10400	1650	3.158 ± 0.522	3.156 ± 0.565	0.884	-0.024 ± 0.892	0.078 ± 0.971	< 0.001
2016	11918	1951	3.177 ± 0.503	3.183 ± 0.528	0.641	0.018 ± 0.879	0.133 ± 0.913	< 0.001
2017	13819	2394	3.188 ± 0.474	3.151 ± 0.509	0.001	-0.001 ± 0.866	0.023 ± 0.905	0.232
2018	13012	2239	3.187 ± 0.475	3.183 ± 0.529	0.763	-0.019 ± 0.861	0.088 ± 0.944	< 0.001
2019	14113	2240	3.176 ± 0.469	3.169 ± 0.517	0.546	-0.06 ± 0.854	0.059 ± 0.920	< 0.001
2020	12193	2111	3.202 ± 0.459	3.173 ± 0.503	0.010	-0.006 ± 0.861	0.043 ± 0.926	0.019
2021	12082	2324	3.163 ± 0.459	3.134 ± 0.490	0.006	-0.085 ± 0.850	-0.037 ± 0.885	0.015
P-value for trend			0.045	0.019		0.027	< 0.001	

TABLE 3 Trends of prevalence of singleton liveborn macrosomia and LGA in women with and without GDM between 2012 and 2021.

Year	Macrosomia, prevalence (95% CI)		*P*-value	Large for gestational age, prevalence (95% CI)		*P*-value
	Non-GDM	GDM		Non-GDM	GDM	
2012	3.4 (3.0 - 3.8)	5.1 (4.1 - 6.2)	0.002	8.2 (7.6 - 8.9)	11.8 (10.3 - 13.5)	< 0.001
2013	3.3 (2.9 - 3.7)	4.3 (3.4 - 5.5)	0.041	7.8 (7.2 - 8.5)	11.2 (9.7 - 13.0)	< 0.001
2014	3.0 (2.7 - 3.4)	4.8 (3.8 - 6.0)	< 0.001	7.1 (6.6 - 7.6)	11.2 (9.7 - 12.9)	< 0.001
2015	3.0 (2.7 - 3.4)	4.6 (3.7 - 5.7)	0.001	7.1 (6.6 - 7.7)	10.7 (9.2 - 12.2)	< 0.001
2016	3.4 (3.1 - 3.8)	4.9 (4.0 - 5.9)	0.002	7.4 (6.9 - 8.0)	10.4 (9.1 - 11.8)	< 0.001
2017	3.4 (3.1 - 3.8)	3.6 (2.9 - 4.4)	0.663	7.1 (6.6 - 7.5)	9.1 (8.0 - 10.3)	0.001
2018	3.0 (2.7 - 3.3)	4.6 (3.8 - 5.5)	< 0.001	6.9 (6.4 - 7.3)	9.8 (8.6 - 11.1)	< 0.001
2019	2.7 (2.4 - 3.0)	4.2 (3.4 - 5.0)	< 0.001	5.9 (5.5 - 6.4)	9.1 (8.0 - 10.4)	< 0.001
2020	3.5 (3.2 - 3.9)	4.5 (3.6 - 5.4)	0.034	6.9 (6.4 - 7.4)	9.2 (8.0 - 10.5)	< 0.001
2021	2.4 (2.1 - 2.7)	3.0 (2.3 - 3.7)	0.136	5.6 (5.1 - 6.0)	7.7 (6.7 - 8.8)	< 0.001
P-value for trend	0.665	0.030		0.009	< 0.001	

compromising its representativeness. However, continued monitoring of recent trends is needed to assess improvement made in reducing pregnancies complicated by GDM. It is also important for future studies to analyze the tendency of offspring birth weight in women with GDM over time, as well as exploring the causes. In addition, it is important to consider that diagnostic criteria for GDM may vary across different countries and racial/ethnic groups. The IADPSG criteria, which we used in our study, have been adopted by many countries, but other countries may use different criteria that could affect the reported prevalence of GDM (29). Our study was conducted in southern China where the population is predominantly Han Chinese, it is known that different racial/ethnic groups have different risks of developing and managing GDM (30). Studies have shown that South Asian and Hispanic women are at higher risk of developing GDM compared to non-Hispanic white women (31, 32). This may be attributed to differences in genetics, lifestyle factors, and socioeconomic status (33). Therefore, future studies should investigate the trends in birth weight and LGA in different racial/ethnic groups with GDM and compare outcomes using the same diagnostic criteria. This could help identify any disparities in the management and outcomes of GDM in different populations and

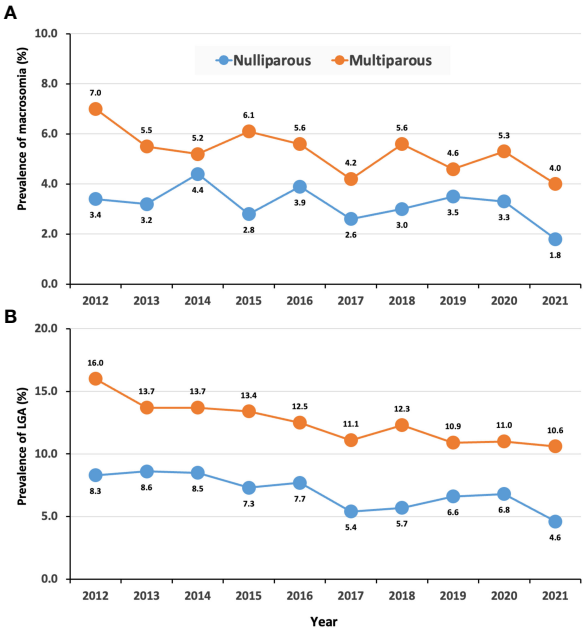

FIGURE 3
Trends in prevalence of macrosomia and LGA in women with GDM by parity. **(A)**, macrosomia; **(B)**, LGA.

TABLE 4 Trends in odds ratio of macrosomia and LGA in women with GDM.

Year	Macrosomia			Large for gestational age		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
2012	1.40	1.07 - 1.82	0.014	1.36	1.14 - 1.63	0.001
2013	1.20	0.90 - 1.61	0.221	1.34	1.10 - 1.62	0.003
2014	1.45	1.10 - 1.91	0.008	1.46	1.21 - 1.76	< 0.001
2015	1.34	1.02 - 1.75	0.034	1.33	1.11 - 1.60	0.002
2016	1.31	1.03 - 1.66	0.029	1.24	1.05 - 1.47	0.012
2017	0.95	0.75 - 1.22	0.701	1.16	0.99 - 1.36	0.071
2018	1.39	1.10 - 1.76	0.005	1.28	1.08 - 1.50	0.003
2019	1.43	1.12 - 1.82	0.004	1.39	1.17 - 1.64	< 0.001
2020	1.19	0.94 - 1.51	0.149	1.22	1.03 - 1.44	0.024
2021	1.20	0.91 - 1.59	0.192	1.33	1.11 - 1.59	0.002
Total	1.27	1.17 - 1.38	< 0.001	1.30	1.23 - 1.38	< 0.001

OR were adjusted for maternal age and parity.

inform the development of tailored interventions to improve maternal and fetal health.

Conclusions

Our study observed that there are decreased trends of birth weight in women with GDM and a concomitant decline in LGA prevalence between 2012 and 2021. Although these results partly represent improvements in avoiding fetal overgrowth for women with GDM over the 10-year period, the risk of LGA in women with GDM remains at relatively high level, and efforts are still needed to address regarding causes and effective interventions for adverse outcomes.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Guangdong Women 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

Conception and design of this study: L-RH, LY and YG. Data collection and analysis: L-RH and YG. The first draft of the manuscript was written by YG and all authors commented on previous versions of the manuscript. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1166533/full#supplementary-material

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Effect of gestational diabetes mellitus on pregnancy outcomes among younger and older women and its additive interaction with advanced maternal age

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Background: The prevalence of gestational diabetes mellitus (GDM) and advanced maternal age (AMA, ≥ 35 years) has shown an increasing trend worldwide. This study aimed to evaluate the risk of pregnancy outcomes among younger (20-34 years) and older (≥ 35 years) women with GDM and further analyze the epidemiologic interaction of GDM and AMA on these outcomes.

Methods: This historical cohort study included 105 683 singleton pregnant women aged 20 years or older between January 2012 and December 2015 in China. Stratified by maternal age, the associations between GDM and pregnancy outcomes were analyzed by performing logistic regression. Epidemiologic interactions were assessed by using relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI) with their 95% confidence intervals (95%CIs).

Results: Among younger women, individuals with GDM had a higher risk of all maternal outcomes, preterm birth (relative risk [RR] 1.67, 95%CI 1.50–1.85), low birthweight (RR 1.24, 95%CI 1.09–1.41), large for gestational age (RR 1.51, 95%CI 1.40–1.63), macrosomia (RR 1.54, 95%CI 1.31–1.79), and fetal distress (RR 1.56, 95%CI 1.37–1.77) than those without GDM. Among older women, GDM increased the risk of gestational hypertension (RR 2.17, 95%CI 1.65–2.83), preeclampsia (RR 2.30, 95%CI 1.81–2.93), polyhydramnios (RR 3.46, 95%CI 2.01–5.96), cesarean delivery (RR 1.18, 95%CI 1.10–1.25), preterm birth (RR 1.35, 95%CI 1.14–1.60), large for gestational age (RR 1.40, 95%CI 1.23–1.60), macrosomia (RR 1.65, 95%CI 1.28–2.14) and fetal distress (RR 1.46, 95%CI 1.12–1.90). Additive interactions of GDM and AMA on polyhydramnios and preeclampsia were found, with RERI of 3.11 (95%CI 0.05-6.16) and 1.43 (95%CI 0.09-2.77), AP of 0.51 (95%CI 0.22-0.80) and 0.27 (95%CI 0.07-0.46), and SI of 2.59 (95%CI 1.17-5.77) and 1.49 (95%CI 1.07-2.07), respectively.

Conclusion: GDM is an independent risk factor for multiple adverse pregnancy outcomes, and may exert additive interactions with AMA on the risk of polyhydramnios and preeclampsia.

KEYWORDS

gestational diabetes mellitus, advanced maternal age, pregnancy outcomes, additive interaction, polyhydramnios, preeclampsia

Introduction

Gestational diabetes mellitus (GDM), a state of hyperglycemia that is first recognized during pregnancy, has an overall incidence of 14 cases per 100 persons globally per year, and its regional standardized prevalence ranges from 7.1% in the Caribbean and North America to 27.6% in North Africa and the Middle East (1). The prevalence of GDM was 14.8% in mainland China, varying from 2.3% to 24.2% in different regions, and has been dramatically increasing over the past decades (2–5). GDM has caused an enormous health and economic burden in China. Population-based studies demonstrated that GDM was associated with an elevated risk of adverse outcomes for mothers and their infants (6, 7). For example, GDM may increase the risk of cesarean delivery, gestational hypertension, and preeclampsia for the mothers, as well as the risk of fetal distress, preterm birth, and macrosomia for their infants (6, 8–10).

The associations of GDM with pregnancy outcomes may change by maternal age. A historical cohort study of 8844 singleton pregnancies observed that GDM elevated the risk of preterm birth and macrosomia among women aged < 35 years, while the increased risk for the two outcomes was not found in women aged 35 years or older (8). A registry-based study in Finland showed that the risk of preterm birth was increased in younger women with insulin-treated GDM but did not rise in older women affected by GDM (11). However, linear relationships between fasting plasma glucose and the risk of preterm birth and macrosomia in both maternal age groups were also demonstrated in a population-based study from Southern China (12). Therefore, it is necessary to further evaluated the associations between GDM and pregnancy outcomes stratified by maternal age.

In the past decades, the proportion of advanced maternal age (AMA, ≥ 35 years) has elevated rapidly, not only in developed countries, but also in some developing countries, including China (13). An increasing number of studies have suggested that pregnant women with AMA were at a higher risk of adverse pregnancy outcomes (14–16). To our knowledge, the separate effect of GDM or AMA on pregnancy outcomes has been well-studied; however, few studies have yet documented the combined impact of GDM and AMA on these outcomes. Our objective was to assess the individual or combined effects of GDM and AMA on pregnancy outcomes using a historical cohort study. This investigation would help us comprehensively estimate the risk of adverse outcomes among pregnant individuals with both GDM and AMA.

Methods

Study design and participants

A historical cohort study of pregnant women aged 20–54 years old was conducted in 27 hospitals located in central urban areas of Nanning, Guangxi province, from January 2012 to December 2015. All studied population derived from a universal GDM screening. Participants were categorized as younger (20-34 years) and older (≥ 35 years) women. We further allocated each of them to a group with GDM and a group without GDM according to the results of 75 g oral glucose tolerance test. Individuals with pregestational diabetes or hypertension, multiple pregnancy, induced abortion, delivery before 20 weeks of gestation, and birthweight less than 300 g were excluded. Study flow chart is shown in Figure 1.

This study was approved by the Ethics Committee of Nanning Maternal and Child Health Hospital.

Data collection

The clinical characteristics and pregnancy outcomes data were collected retrospectively from the Guangxi Woman and Child Health Information Management System. With the guidelines and regulations of the Guangxi Health Commission, all eligible hospitals in Nanning were required to extract information about antenatal care, delivery and infant outcomes from the medical records and input them into this provincial database system. The data entry and management methods were implemented per the previous study (17). Clinical characteristics assessed were: gravidity, parity, obesity (pre-pregnancy body mass index ≥ 30 kg/m^2), examination at first trimester, number of prenatal visits, previous cesarean history, prior spontaneous or induced abortion and assisted reproductive technology (ART).

Variables and definitions

We defined GDM as fasting plasma glucose ≥ 5.1 mmol/l or the 75 g oral glucose tolerance test value ≥ 10.0 mmol/l at 60 min or ≥

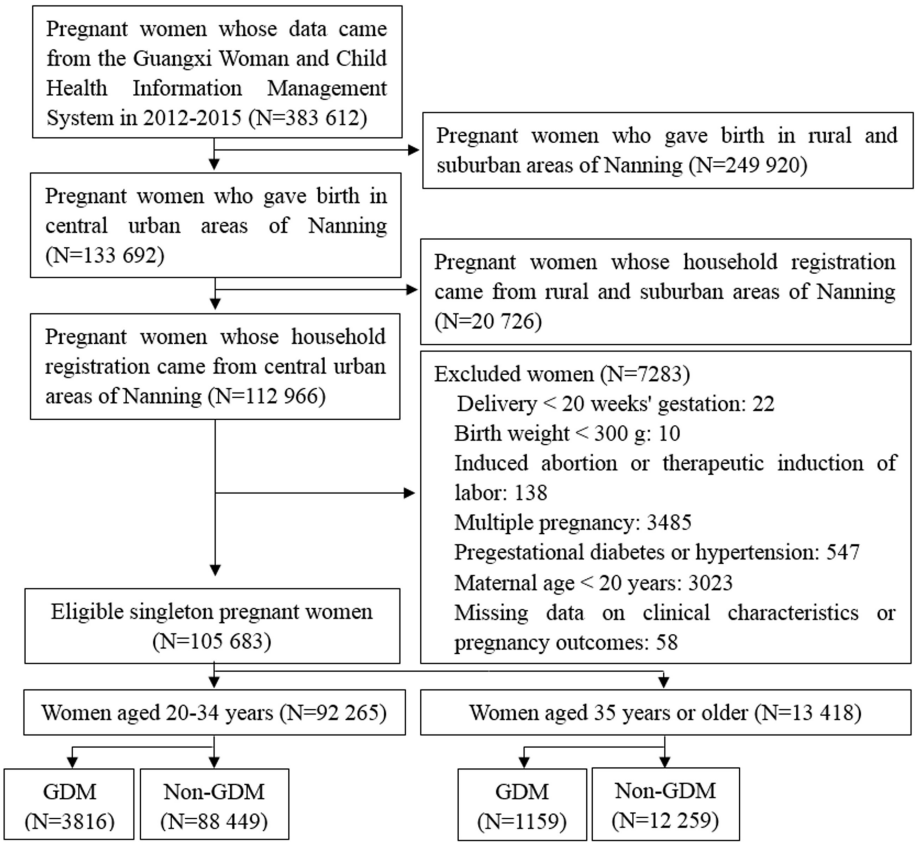

FIGURE 1
Study flow diagram. GDM, gestational diabetes mellitus.

8.5 mmol/l at 120 min when conducted at 24-28 gestational weeks (18). AMA was defined as being 35 years or older at the time of giving birth. Pregnancy outcomes included maternal outcomes and infant outcomes.

For maternal outcomes variables, gestational hypertension was diagnosed by blood pressure (BP) monitoring performed after 20 gestational weeks, with a systolic BP ≥ 140 mmHg or a diastolic BP ≥ 90 mmHg. Gestational hypertension with proteinuria was diagnosed as preeclampsia (19). Placental abruption referred to a part or all of the placenta separation from the uterine wall after 20 weeks of gestation (20). Placenta previa referred to a state where the placenta partially or completely covered the opening of the cervix (21). Polyhydramnios was defined as an amniotic fluid volume of over 2000 ml when giving birth. Cesarean delivery referred to a way of giving birth through abdominal and uterine incision.

For infant outcomes variables, we defined small for gestational age (SGA) as a birthweight less than the 10th percentile for its gestational age, large for gestational age (LGA) as greater than the 90th percentile, preterm birth as less than 37 weeks of pregnancy, macrosomia as a birthweight not less than 4000 g, low birthweight as less than 2500 g, low Apgar score as the score at 5 min less than 7, respectively. Fetal distress referred to a syndrome in which the fetus was suffering from insufficient oxygen supply (22). Auricle malformation or external auditory canal atresia was diagnosed as congenital microtia.

Statistical analysis

Pearson's chi-square test was used to compare the distributions of clinical characteristics and pregnancy outcomes among two groups, stratified by maternal age. Logistic regression models were implemented to explore the associations between GDM, AMA and adverse pregnancy outcomes.

Given that the odds ratio (OR) always overestimates the relative risk (RR) and it does not have as intuitive an interpretation as the RR (23), we decided to use RR with a 95% confidence interval (95% CI) to assess the association between two categorical variables. RR was calculated by using a formula: $RR = OR/[(1 - P_0) + (P_0 \times OR)]$, and P_0 refers to the incidence of the outcome of interest in the reference group (24). Epidemiologic interactions between GDM and AMA on the risk of adverse pregnancy outcomes were assessed via the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI). The RERI, AP, and SI were separately defined as follows: $RERI = RR_{11} - RR_{10} - RR_{01} + 1$, $AP = RERI/RR_{11}$, and $SI = [RR_{11} - 1]/[(RR_{10} - 1) + (RR_{01} - 1)]$, where RR_{11}, RR_{10}, and RR_{01} represented the RR with both GDM and AMA, with GDM only, and with AMA only, respectively. No additive interaction was defined as 95% CI of RERI and AP including 0 and 95% CI of SI comprising 1. The 95% CIs for RERI, AP, and SI were calculated using the method of Hosmer et al. (25) and Andersson et al. (26). The binary and

categorical variables were presented as numbers (percentage). All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). $P < 0.05$ was considered statistical significance.

Results

Population characteristics of the participants

In total, 105 683 singleton pregnancies of women aged 20 years or older were included in our study. The prevalence of GDM was 4.71%, and the proportion of AMA was 12.70%. As depicted in Table 1, the two groups were comparable in term of gravidity ($P > 0.05$), but differed in both younger and older women with regard to parity, obesity, examination at first trimester, number of prenatal visits, previous cesarean history, ART, and number of prior spontaneous or induced abortions (all $P < 0.001$). Pregnant individuals with GDM were more likely to have higher proportions of primiparity, obesity, examination at first trimester, prenatal visits ≥ 5 times, previous cesarean history, ART, and prior spontaneous or induced abortion ≥ 3 times when compared to those with normal glucose level regardless of maternal age (all $P < 0.001$).

TABLE 1 Baseline characteristics of women with gestational diabetes mellitus, stratified by maternal age.

Characteristics	Total (n=105 683)	20-34 Years			35 Years or Older		
		GDM (n=3816)	Non-GDM (n=88 449)	*P*-value	GDM (n=1159)	Non-GDM (n=12 259)	*P*-value
Obesity				<0.001			<0.001
No	105 055 (99.41)	3742 (98.06)	88 051 (99.55)		1126 (97.15)	12 136 (99.00)	
Yes	628 (0.59)	74 (1.94)	398 (0.45)		33 (2.85)	123 (1.00)	
Examination at first trimester				<0.001			<0.001
No	45 673 (43.22)	1456 (38.16)	38 090 (43.06)		426 (36.76)	5701 (46.50)	
Yes	60 010 (56.78)	2360 (61.84)	50 359 (56.94)		733 (63.24)	6558 (53.50)	
Number of prenatal visits				<0.001			<0.001
0-4	69 087 (65.37)	2321 (60.82)	57 421 (64.92)		719 (62.04)	8626 (70.36)	
5 or More	36 596 (34.63)	1495 (39.18)	31 028 (35.08)		440 (37.96)	3633 (29.64)	
Gravidity				0.774			0.955
1-2	68 573 (64.89)	2625 (68.79)	61 038 (69.01)		425 (36.67)	4485 (36.59)	
3 or More	37 110 (35.11)	1191 (31.21)	27 411 (30.99)		734 (63.33)	7774 (63.41)	
Parity				<0.001			<0.001
Nulliparous	57 522 (54.43)	2608 (60.60)	51 390 (54.12)		407 (35.12)	3117 (25.43)	
Parous	48 161 (45.57)	1208 (39.40)	37 059 (45.88)		752 (64.88)	9142 (74.57)	
Previous caesarean history				<0.001			<0.001
No	99 655 (94.30)	3485 (91.33)	84 424 (95.45)		912 (78.69)	10 834 (88.38)	
Yes	6028 (5.70)	331 (8.67)	4025 (4.55)		247 (21.31)	1425 (11.62)	
Prior spontaneous or induced abortion				<0.001			<0.001
0-1	100 297 (94.90)	3531 (92.53)	84 742 (95.81)		950 (81.97)	11 074 (90.33)	
2	3586 (3.39)	200 (5.24)	2572 (2.91)		110 (9.49)	704 (5.74)	
3 or More	1800 (1.70)	85 (2.23)	1135 (1.28)		99 (8.54)	481 (3.92)	
ART				<0.001			<0.001
No	104 972 (99.33)	3764 (98.64)	88 025 (99.52)		1109 (95.69)	12 074 (98.49)	
Yes	711 (0.67)	52 (1.36)	424(0.48)		50 (4.31)	185 (1.51)	

GDM, gestational diabetes mellitus; ART, assisted reproductive technology.
Data are n (%) unless otherwise specified.

Prevalence of pregnancy outcomes among younger and older women with gestational diabetes mellitus

The incidence of pregnancy outcomes among younger and older women with GDM is manifested in Table 2. For younger women, the prevalence of all the selected maternal outcomes, preterm birth, low birthweight, LGA, macrosomia, and fetal distress was significantly higher in individuals with GDM than those without GDM (all $P < 0.001$). For older women, individuals with GDM were at a greater incidence of gestational hypertension, preeclampsia, polyhydramnios, cesarean delivery, preterm birth, low birthweight, LGA, macrosomia, and fetal distress compared with those who did not have GDM (all $P < 0.05$). However, a lower prevalence of SGA was observed in individuals with GDM compared to individuals with normal glucose level regardless of maternal age ($P < 0.05$).

Risk of pregnancy outcomes among younger and older women with gestational diabetes mellitus

Table 3 shows that the associations in the binary regression analyses after adjusting for potential confounders were consistent with crude regression analyses. Among women aged 20-34 years, GDM was associated with an increased risk of all the selected maternal outcomes, preterm birth (relative risk [RR] 1.67, 95%CI 1.50–1.85), low birthweight (RR 1.24, 95%CI 1.09–1.41), LGA (RR 1.51, 95%CI 1.40–1.63), macrosomia (RR 1.54, 95%CI 1.31–1.79), and fetal distress (RR 1.56, 95%CI 1.37–1.77), as well as a decreased risk of SGA (RR 0.76, 95%CI 0.68–0.85). Among women aged 35 years or older, individuals with GDM had a higher risk of gestational hypertension (RR 2.17, 95%CI 1.65–2.83), preeclampsia (RR 2.30, 95%CI 1.81–2.93), polyhydramnios (RR 3.46, 95%CI 2.01–5.96), cesarean delivery (RR 1.18, 95%CI 1.10–1.25), preterm birth (RR 1.35, 95%CI 1.14–1.60), LGA (RR 1.40, 95%CI 1.23–1.60), macrosomia (RR 1.65, 95%CI 1.28–2.14) and fetal distress (RR 1.46, 95%CI 1.12–1.90) and were less likely to have SGA (RR 0.78, 95%CI 0.62–0.97) when compared to individuals with normal glucose level.

Epidemiologic interaction between gestational diabetes mellitus and advanced maternal age on adverse pregnancy outcomes

As shown in Figure 2, the logistic regression models with adjustment for parity, obesity, and number of prenatal visits manifested that the RR of polyhydramnios was 2.34 for individuals with GDM only, 1.61 for individuals with AMA only, and 6.06 for individuals with both GDM and AMA when compared to those without GDM aged 20-34 years. The combined effect of GDM and AMA on polyhydramnios was markedly greater than the sum of the separate effect, with a RERI of 3.11 (95%CI 0.05-6.16),

TABLE 2 Prevalence of adverse pregnancy outcomes in women with gestational diabetes mellitus, stratified by maternal age.

Outcomes	Total (n=105 683)	20-34 Years			35 Years or Older		
		GDM (n=3816)	Non-GDM (n=88 449)	*P*-value	GDM (n=1159)	Non-GDM (n=12 259)	*P*-value
Gestational hypertension	1281 (1.21)	126 (3.30)	806 (0.91)	<0.001	65 (5.61)	284 (2.32)	<0.001
Preeclampsia	1697 (1.61)	137 (3.59)	1142 (1.29)	<0.001	79 (6.82)	339 (2.77)	<0.001
Placental abruption	338 (0.32)	23 (0.60)	247 (0.28)	<0.001	7 (0.60)	61 (0.50)	0.626
Placenta previa	1046 (0.99)	60 (1.57)	716 (0.81)	<0.001	27 (2.33)	243 (1.98)	0.421
Polyhydramnios	308 (0.29)	21 (0.55)	216 (0.24)	<0.001	18 (1.55)	53 (0.43)	<0.001
Cesarean delivery	34 133 (32.30)	1658 (43.45)	25 885 (29.27)	<0.001	726 (62.64)	5864 (47.83)	<0.001
Preterm birth	6400 (6.06)	352 (9.22)	4840 (5.47)	<0.001	139 (11.99)	1069 (8.72)	<0.001
Low birthweight	5835 (5.52)	252 (6.60)	4606 (5.21)	<0.001	101 (8.71)	876 (7.15)	0.049
SGA	9772 (9.25)	283 (7.42)	8394 (9.49)	<0.001	76 (6.56)	1019 (8.31)	0.037
LGA	11268(10.66)	567(14.86)	8853(10.01)	<0.001	212(18.29)	1636(13.35)	<0.001
Macrosomia	3209 (3.04)	167 (4.38)	2545 (2.88)	<0.001	65 (5.61)	432 (3.52)	<0.001
Fetal distress	3982 (3.77)	241 (6.32)	3245 (3.67)	<0.001	64 (5.52)	432 (3.52)	<0.001
Apgar score < 7 at 5 min	764 (0.72)	19 (0.50)	604 (0.68)	0.172	10 (0.86)	131 (1.07)	0.511
Congenital microtia	95 (0.09)	4 (0.10)	70 (0.08)	0.551	2 (0.17)	19 (0.15)	0.885

GDM, gestational diabetes mellitus; SGA, small for gestational age; LGA, large for gestational age.
Data are n (%) unless otherwise specified.

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TABLE 3 Risk of adverse pregnancy outcomes in women with gestational diabetes mellitus, stratified by maternal age.

Outcomes	20-34 Years			35 Years or Older		
	GDM (RR, 95% CI)	Non-GDM (RR, 95% CI)	*P*-value	GDM (RR, 95% CI)	Non-GDM (RR, 95% CI)	*P*-value
Gestational hypertension						
Model 1	3.62 (3.01-4.35)	1.00	<0.001	2.43 (1.86-3.13)	1.00	<0.001
Model 2	3.27 (2.71-3.94)	1.00	<0.001	2.17 (1.65-2.83)	1.00	<0.001
Preeclampsia						
Model 1	2.78 (2.34-3.31)	1.00	<0.001	2.46 (1.95-3.11)	1.00	<0.001
Model 2	2.50 (2.09-2.98)	1.00	<0.001	2.30 (1.81-2.93)	1.00	<0.001
Placental abruption						
Model 1	2.16 (1.41-3.30)	1.00	<0.001	1.22 (0.55-2.64)	1.00	0.626
Model 2	2.08 (1.36-3.20)	1.00	<0.001	1.35 (0.61-2.97)	1.00	0.457
Placenta previa						
Model 1	1.94 (1.49-2.52)	1.00	<0.001	1.18 (0.79-1.73)	1.00	0.421
Model 2	1.87 (1.43-2.42)	1.00	<0.001	1.03 (0.68-1.53)	1.00	0.900
Polyhydramnios						
Model 1	2.25 (1.44-3.52)	1.00	<0.001	3.59 (2.11-6.08)	1.00	<0.001
Model 2	2.21 (1.41-3.47)	1.00	<0.001	3.46 (2.01-5.96)	1.00	<0.001
Cesarean delivery						
Model 1	1.49 (1.43-1.54)	1.00	<0.001	1.31 (1.25-1.37)	1.00	<0.001
Model 2	1.36 (1.30-1.42)	1.00	<0.001	1.18 (1.10-1.25)	1.00	<0.001
Preterm birth						
Model 1	1.69 (1.52-1.87)	1.00	<0.001	1.38 (1.16-1.62)	1.00	<0.001
Model 2	1.67 (1.50-1.85)	1.00	<0.001	1.35 (1.14-1.60)	1.00	<0.001
Low birthweight						
Model 1	1.27 (1.12-1.43)	1.00	<0.001	1.22 (1.00-1.48)	1.00	0.050
Model 2	1.24 (1.09-1.41)	1.00	<0.001	1.18 (0.96-1.44)	1.00	0.108
SGA						
Model 1	0.78 (0.70-0.87)	1.00	<0.001	0.79 (0.63-0.99)	1.00	0.037
Model 2	0.76 (0.68-0.85)	1.00	<0.001	0.78 (0.62-0.97)	1.00	0.030
LGA						
Model 1	1.49 (1.37-1.60)	1.00	<0.001	1.37 (1.20-1.55)	1.00	<0.001
Model 2	1.51 (1.40-1.63)	1.00	<0.001	1.40 (1.23-1.60)	1.00	<0.001
Macrosomia						
Model 1	1.52 (1.31-1.77)	1.00	<0.001	1.59 (1.23-2.05)	1.00	<0.001
Model 2	1.54 (1.31-1.79)	1.00	<0.001	1.65 (1.28-2.14)	1.00	<0.001
Fetal distress						
Model 1	1.72 (1.52-1.96)	1.00	<0.001	1.57 (1.21-2.02)	1.00	<0.001
Model 2	1.56 (1.37-1.77)	1.00	<0.001	1.46 (1.12-1.90)	1.00	0.004

(Continued)

TABLE 3 Continued

Outcomes	20-34 Years			35 Years or Older		
	GDM (RR, 95% CI)	Non-GDM (RR, 95% CI)	*P*-value	GDM (RR, 95% CI)	Non-GDM (RR, 95% CI)	*P*-value
Apgar score < 7 at 5 min						
Model 1	0.73 (0.46-1.15)	1.00	0.174	0.81 (0.42-1.53)	1.00	0.512
Model 2	0.75 (0.47-1.19)	1.00	0.218	0.85 (0.44-1.63)	1.00	0.625
Congenital microtia						
Model 1	1.32 (0.48-3.62)	1.00	0.584	1.11 (0.26-4.76)	1.00	0.885
Model 2	1.41 (0.51-3.87)	1.00	0.508	1.00 (0.23-4.33)	1.00	0.996

GDM, gestational diabetes mellitus; SGA, small for gestational age; LGA, large for gestational age; RR, relative risk; CI, confidence interval.
Model 1: shows crude relative risk.
Model 2: Adjusted for parity, obesity, examination at first trimester, number of prenatal visits, previous cesarean history, ART, and number of prior spontaneous or induced abortions.

AP of 0.51 (95%CI 0.22-0.80), and SI of 2.59 (95%CI 1.17-5.77). In addition, the RR for concurrent GDM and AMA on preeclampsia was slightly higher than the sum of the individual effect, with a RERI of 1.43 (95%CI 0.09-2.77), AP of 0.27 (95%CI 0.07-0.46), and SI of 1.49 (95%CI 1.07-2.07).

Discussion

In this study, GDM was associated with an elevated risk of gestational hypertension, preeclampsia, polyhydramnios, cesarean delivery, preterm birth, LGA, macrosomia, and fetal distress and a decreased risk of SGA in both younger and older women. Interestingly, we observed the additive interactions between GDM and AMA on the risk of polyhydramnios and preeclampsia.

GDM is associated with an increased risk of various maternal outcomes. Some evidences manifested that GDM elevated the occurrence of gestational hypertension and preeclampsia, which were in accordance with our study (7, 9, 27). As all we know, insulin resistance play a role in the pathogenesis of hypertension in pregnancy (28). Among younger women with GDM, increased risk was found for placental abruption. Hyperglycemia during pregnancy may induce a condition of placental thickening, and this constant state was associated with placental abruption (29). GDM also increased the incidence of placenta previa in younger women. The greater proportions of prior abortions, using ART, and previous cesarean history may help explain this outcome (30). However, the elevated risk of placental abruption and placenta previa was not observed in older individuals, implying that the association of GDM with the two outcomes may be modified by maternal age. In addition, a higher risk of polyhydramnios and cesarean delivery was found in patients with GDM compared to those without GDM. The findings were in accordance with studies in Ethiopia (9) and Ireland (31).

A relationship between GDM and adverse infant outcomes was also found in our study. Offspring of women with diabetes are considered to be at an elevated risk of fetal distress. In this study, the incidence of fetal distress was higher in offspring of mothers with GDM when compared to those unaffected by GDM, which was in line with the study of Zhuang et al. (10). Consistent with other studies (8, 32), the logistic regression model demonstrated that individuals with GDM had a higher risk of preterm birth than those with normal glucose tolerance. This may be explained by the higher rate of hypertension, placenta previa, and fetal distress (33, 34). We also observed a close association between GDM and the risk of developing LGA and macrosomia. Pregnant women with GDM had an over 1.4-fold risk of LGA and macrosomia compared to those without GDM. This is in accordance with studies in Germany (32), the United States (35), and Canada (36). The occurrence of these neonatal outcomes may be linked to maternal hyperglycemia and insulin resistance that subsequently resulted in fetal hyperinsulinemia and thus contributed to nutrient utilization and fetal overgrowth (37, 38). Individuals with GDM had a higher incidence of low birthweight than non-GDM counterparts. As GDM was associated with an elevated risk of preterm birth and a decreased risk of SGA, it was suggested that preterm birth rather than intrauterine growth restriction was the primary cause of low birthweight. Similar to our findings, population-based studies conducted in Taiwan (39) and mainland of China (40) indicated that GDM increased the risk of low birthweight by 64% and 37%, respectively.

This study shows that the interactions between GDM and AMA were more strongly associated with the risk of polyhydramnios than the sum of the separate effect. GDM and AMA were both independent risk factors for polyhydramnios (31, 41), however, further researches about their interactions on polyhydramnios were scarce. The causal relationship between GDM, AMA, and polyhydramnios occurrence may be explained by the following evidences. First, maternal hyperglycemia is usually accompanied by an increased level of fetal blood sugar, and this condition induces osmotic diuresis and subsequently leads to polyhydramnios (42). Second, increasing maternal age is followed by a significantly elevated concentration of human brain natriuretic peptide, where brain natriuretic peptide plays a role in the pathogenesis of polyhydramnios (43, 44). Third, AMA also significantly increases the risk of maternal hyperglycemia (45), further promoting the occurrence of polyhydramnios. In addition, a slightly additive interaction of GDM and AMA on preeclampsia incidence was uncovered. We hypothesized that the excretion of proteinuria increased with increasing age-related glomerular sclerosis (46),

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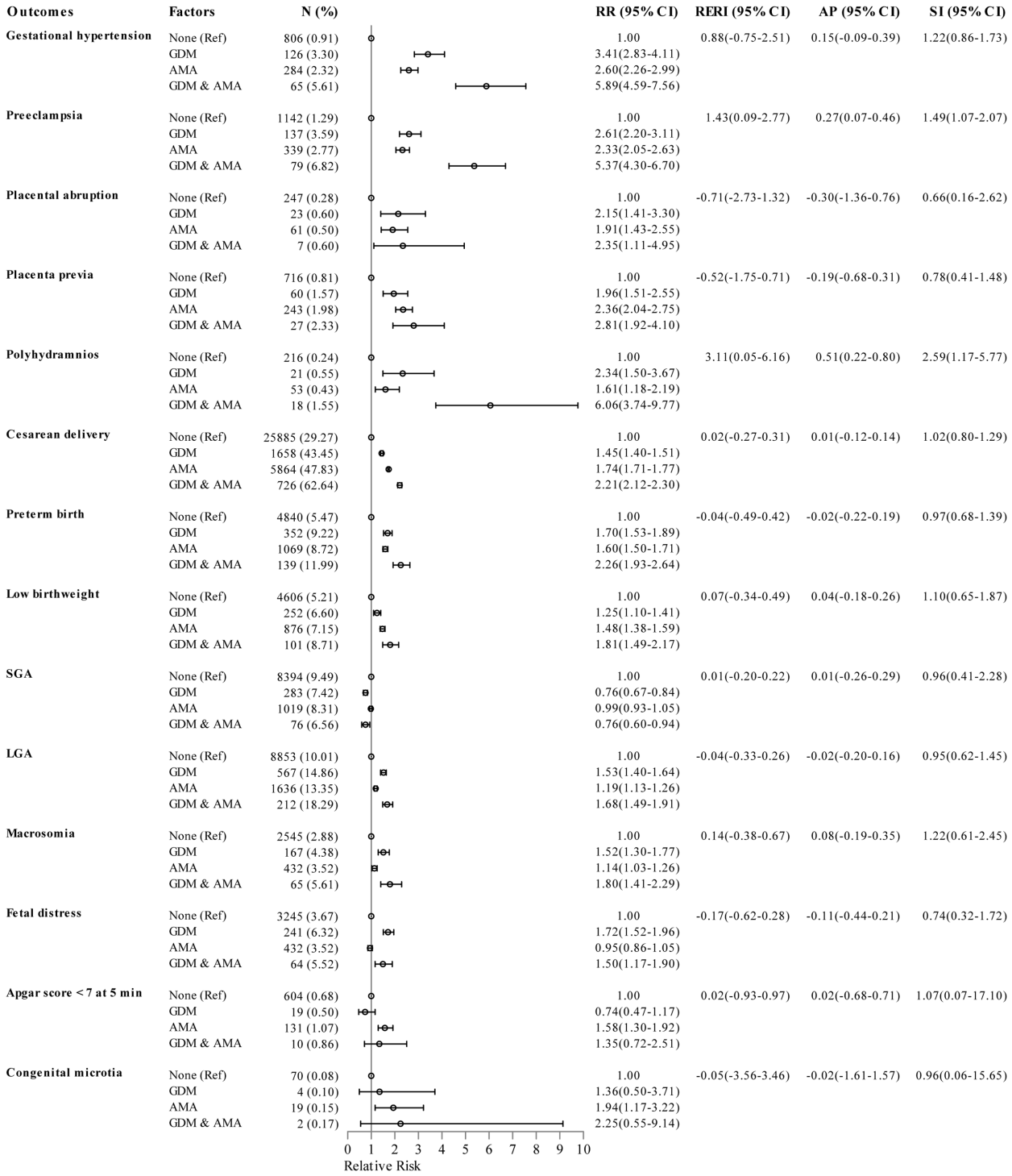

FIGURE 2
Epidemiologic interaction of gestational diabetes mellitus and advanced maternal age on the risk of pregnancy outcomes. RRs (95% CIs) were adjusted for parity, obesity, and number of prenatal visits. GDM, gestational diabetes mellitus; AMA, advanced maternal age; SGA, small for gestational age; LGA, large for gestational age; Ref, reference group; RR, relative risk; CI, confidence interval; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index.

along with the hypertension induced by insulin-resistance, ultimately resulted in preeclampsia for women with GDM aged 35 years or older. Similarly, a registry-based study of 230 003 pregnant women in Finland indicated that combining GDM and AMA clearly had an increasing impact on preeclampsia, but the study lacked data of their interactions (11). All in all, our study provides evidences that there is a synergistic effect between GDM and AMA on polyhydramnios or preeclampsia, which may help us comprehensively estimate the health hazard of GDM and AMA.

The main strengths of our study were the large population-based register data, the maternal-age-stratified risk of adverse pregnancy outcomes, and the assessment of interactions between GDM and AMA on these outcomes. However, some limitations of this study were also present. Firstly, we did not distinguish between diet- and insulin-treated GDM. Secondly, an extremely small portion of maternal and infant outcomes data was missing during the retrospective collection. Thirdly, several confounding factors, such as maternal lifestyle and educational level, were absent and not included in the adjusted logistic model, which may affect the results of this study.

In conclusion, GDM was an independent risk factor for a wide range of adverse pregnancy outcomes. Women with GDM were more likely to have gestational hypertension, preeclampsia, polyhydramnios, cesarean delivery, preterm birth, LGA, macrosomia, and fetal distress when compared to those without GDM regardless of maternal age. More importantly, GDM and AMA may cooperate in a more than additive way in significantly elevating the risk of developing polyhydramnios and preeclampsia, which we should pay enough attention to in clinical practice. It is very necessary to prevent the occurrence of severe adverse pregnancy outcomes by strengthening prenatal care and diet or insulin treatment for women with both GDM and AMA.

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 Nanning Maternal and Child Health Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JL, MZ, and WJ designed the study and revised the manuscript. JL, JY, LM, and YH contributed to the data collection. JL analyzed data and drafted the manuscript. 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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Lights and shadows on the use of metformin in pregnancy: from the preconception phase to breastfeeding and beyond

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During pregnancy, the complex hormonal changes lead to a progressive decrease of insulin sensitivity that can drive the onset of gestational diabetes (GDM) or worsen an already-known condition of insulin resistance like type 2 diabetes, polycystic ovarian syndrome (PCOS), and obesity, with complications for the mother and the fetus. Metformin during pregnancy is proving to be safe in a growing number of studies, although it freely crosses the placenta, leading to a fetal level similar to maternal concentration. The aim of this literature review is to analyze the main available evidence on the use of metformin during, throughout, and beyond pregnancy, including fertilization, lactation, and medium-term effects on offspring. Analyzed studies support the safety and efficacy of metformin during pregnancy. In pregnant women with GDM and type 2 diabetes, metformin improves obstetric and perinatal outcomes. There is no evidence that it prevents GDM in women with pregestational insulin resistance or improves lipid profile and risk of GDM in pregnant women with PCOS or obesity. Metformin could have a role in reducing the risk of preeclampsia in pregnant women with severe obesity, the risk of late miscarriages and preterm delivery in women with PCOS, and the risk of ovarian hyperstimulation syndrome, increasing the clinical pregnancy rate in women with PCOS undergoing *in vitro* fertilization (IVF/FIVET). Offspring of mothers with GDM exposed to metformin have no significant differences in body composition compared with insulin treatment, while it appears to be protective for metabolic and cardiovascular risk.

KEYWORDS

gestational diabetes, insulin resistance, pregnancy, metformin, offspring, fertilization

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Introduction

During pregnancy, the human body faces complex hormonal changes leading to a physiologic progressive decrease of insulin sensitivity (1). The physiologic factors responsible for the decrease of insulin sensitivity or insulin resistance of pregnancy are not completely understood, but they are partially related to the metabolic effects of maternal plasma progesterone, human placental lactogen, free cortisol, and estrogens that are elevated in the maternal circulation during pregnancy (2).

The decrease in insulin sensitivity in physiological pregnancy leads to higher glucose output and lower glucose uptake and utilization with the purpose to ensure fetal energy requirements (3).

In some cases, the imbalance of these metabolic changes can lead to the onset of gestational diabetes (GDM), which can manifest itself according to three different phenotypes: fasting hyperglycemia, postprandial hyperglycemia, and mixed hyperglycemia (4).

In some other cases, the physiological reduction of insulin sensitivity is established on an initial picture already characterized by insulin resistance as in the case of pregnancies that occur in obese patients, patients with polycystic ovarian syndrome (PCOS), and patients with already diagnosed type 2 diabetes (T2DM) (5–7).

The unbalanced insulin resistance that is developed in all these pathologies during pregnancy causes high glucose levels in maternal and fetus blood that can result in the fetus suffering, leading to complications such as early fetal death, congenital anomalies, macrosomia, and maybe long-term complications on the offspring (8, 9); in fact, according to the new concept of "metabolic memory", the intrauterine hyperglycemia may act on the fetal hypothalamus and create a sort of "metabolic memory" that programs obesity and metabolic syndrome in the offspring during adulthood (10).

Therefore, a key role in the management of all these conditions, which, while implying a different pathological substrate, is linked by a common end effect (insulin resistance), could be played by metformin (Figure 1) (11).

In fact, metformin is a biguanide compound that has been shown to reduce hepatic glucose production, increase hepatic sensitivity to insulin, increase muscle glucose transport, and reduce hepatic steatosis by acting according to a complex picture in which a key role is played by AMP-activated protein kinase (AMPK) activation that activates a cascade of mechanisms including a reduction in acetyl-CoA carboxylase activity (12).

These mechanisms lead to a decrease in blood glucose level without a correlated elevated risk of hypoglycemia or weight gain (13).

Furthermore, because of its chemical and physical characteristics, metformin freely crosses the placenta, leading to a fetal level similar to maternal concentration (14). In addition, the safety of metformin in pregnancy is corroborated by a growing number of randomized clinical trials (15).

These characteristics make metformin a capital treatment for people with T2DM and an attractive drug for use in pregnancy (16). Not only that, but the characteristic properties of this small molecule could also allow us to use it in other conditions related to pregnancy such as lactation and fertilization.

Therefore, the aim of this literature review is to analyze the main available evidence on the use of metformin during, throughout, and beyond pregnancy. We included RCT studies and studies with an adequate sample size (at least 90 subjects, except for studies of particular relevance to our opinion).

Metformin and gestational diabetes

One of the first studies to compare safety and efficacy of metformin vs. insulin in 63 women with gestational diabetes and similar baseline characteristics was published in 2007 by Moore et al. (17). Preliminary data showed no statistically significant difference in the rate of cesarean delivery (p = 0.102) and of neonatal characteristics at birth [birth weight, neonatal hypoglycemia, respiratory distress syndrome, hyperbilirubinemia, Apgar score at 5 min, and neonatal intensive care unit (NICU) admission (p = 0.144–0.373)].

After that, one of the most important studies on metformin in GDM was published in the *New England Journal of Medicine* in 2008 (18). The Metformin versus Insulin for the treatment of Gestational diabetes (MiG) study was an Australian off-label randomized trial including 751 women with GDM at 20 to 33 weeks of gestation to open treatment with metformin (373/751 patients) or insulin (378/751 patients). Inclusion criteria were 18–45 years of age, diagnosis of GDM with a single fetus between 20 and 33 weeks of gestation, and, after lifestyle intervention consisting of advice about diet and exercise, had more than one capillary blood glucose measurement >97.2 mg/dl after an overnight fast or more than one 2-h postprandial blood glucose measurement >120.6 mg/dl. The primary outcome was a composite of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-min Apgar score <7, or prematurity. Secondary outcomes included neonatal anthropometric measurements, maternal glycemic control, maternal hypertensive complications, postpartum glucose tolerance, and acceptability of treatment. The trial was designed to rule out a 33% increase (from 30% to 40%) in this composite outcome in infants of women treated with metformin as compared with those treated with insulin. Note that 168 women in the metformin arm (46%) required supplemental insulin. Those requiring insulin supplement had a higher body mass index (BMI) (p = 0.01), higher enrollment fasting glucose (p < 0.001), higher hemoglobin A1c (Hba1c) (p < 0.001), more frequent history of miscarriages (p < 0.001), less frequent nulliparous women (p = 0.003), and a higher representation of Polynesian ethnicity (p < 0.001).

The women clearly preferred metformin to insulin treatment and there was no difference in the composite primary outcomes (p = 0.95), and even in the single outcomes included in the composite, severe hypoglycemia was less common in the metformin group (p = 0.008), but preterm birth was more common in the metformin group (p = 0.04). Statistical significance in the secondary outcomes was found in the gestational age at birth (38.3 weeks in the metformin group vs. 38.5 weeks in the insulin group) and in the overall mean maternal 2-h postprandial glucose levels that were

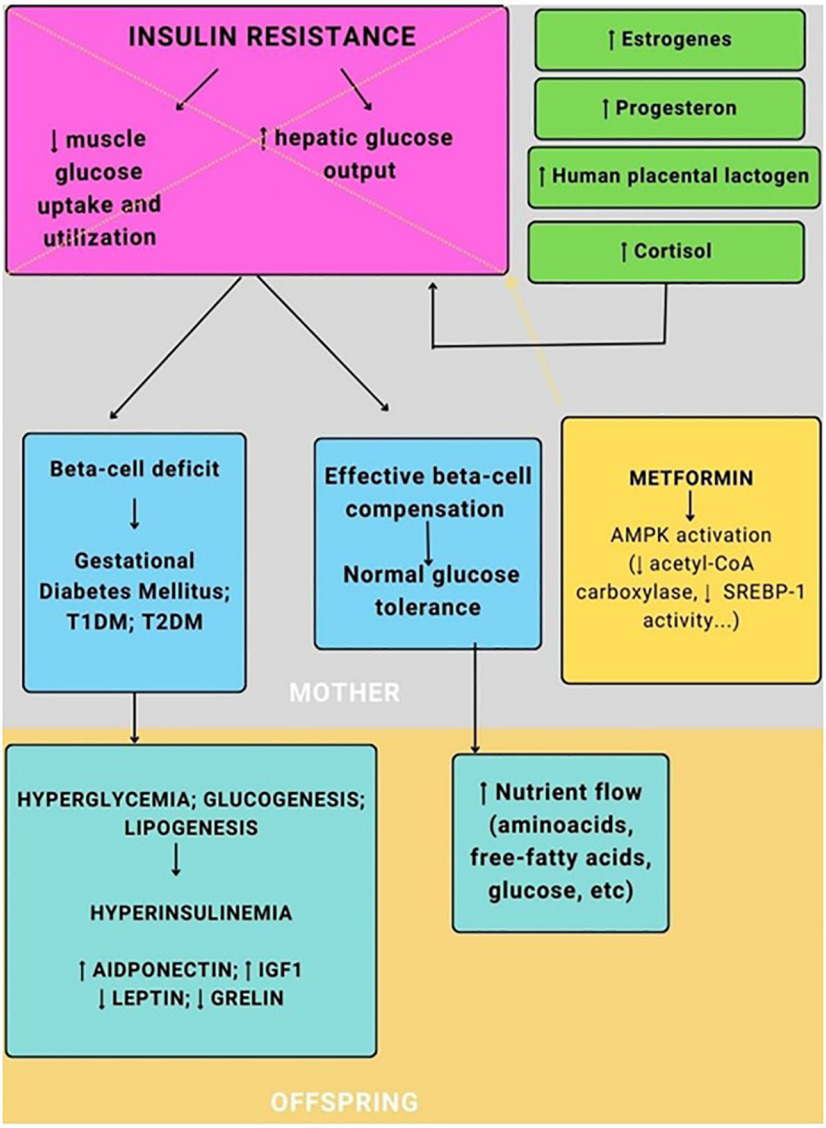

FIGURE 1
The pathogenesis of gestational diabetes and the role of metformin.

slightly lower in the metformin group (111.6 vs. 115.2 mg/dl); furthermore, women in the metformin group had greater weight loss between the time of enrollment and the postpartum visit (p = 0.006) and less weight gain between the time of enrollment and 36 weeks of gestation than did women in the insulin group ($p < 0.001$).

This important study, even with the limits of a wide enrollment range (20–33 weeks), a 2-year follow up that does not take into account lifestyle and feeding habits, and the fact that 46% of the women in metformin treatment required supplemental insulin, clearly shows that metformin is safe during pregnancy and is not associated with increased perinatal complications as compared with insulin.

Then, an open-label prospective randomized controlled trial (RCT) was published in 2010 involving 100 women with singleton pregnancies between 12 and 34 weeks of gestation with GDM in a secondary- and tertiary-level hospital in Finland who did not attain euglycemia with diet (<95 mg/dl fasting glucose and <120 mg/dl 2 h after meals) (19). They were randomized to therapy with insulin (n = 50) or oral metformin (n = 50).

The primary outcome was the incidence of macrosomia, defined as a birth weight >4,000 g, or large for gestational age (LGA). Neonatal complications, such as admission to NICU, hyperbilirubinemia treated with phototherapy, birth injuries (clavicular fracture or brachial nerve injury), and neonatal hypoglycemia requiring intravenous glucose treatment, were the secondary outcomes. The results show no statistically significant differences in the incidence of LGA (p = 0.97), mean birth weight, mean cord artery pH, or neonatal morbidity between the insulin and metformin groups. Fifteen out of 47 (31.9%) women randomized to metformin therapy needed supplemental insulin. The women needing supplemental insulin had higher mean BMIs (35.7 ± 7.2 vs. 29.6 ± 5.3 kg/m^2, p = 0.002), had higher fasting

capillary glucose concentrations (p = 0.001), and needed pharmacological treatment at earlier gestational age than women who were normoglycemic with metformin (26 ± 5.9 versus 31 ± 3.1 weeks), and their infant had higher birth weight (3,919 ± 400 versus 3,615 ± 417 g, p = 0.022).

In 2011, an observational study of all women with GDM who delivered after 20 weeks' gestation at National Women's Health from January 2007 to December 2009 was published (20). Since June 2007, women requiring glucose-lowering therapy could choose either metformin or insulin therapy, except for women with a fetal abdominal circumference < 10th percentile, who were not eligible for metformin. The study prospectively analyzed results from 1,269 women with GDM; 371 women were treated with diet, 399 women were treated with insulin, and 465 were treated with metformin (249 metformin alone and 216 metformin and insulin). Compared with those in the diet group, women taking metformin and/or insulin had higher fasting glucose at diagnosis (p < 0.001) and higher BMIs (p < 0.001). Women under insulin treatment had higher rates of cesarean section (CS) (45.6% insulin, 37% metformin, 34% diet, p = 0.02) than women under metformin or diet. Women under insulin treatment also had higher rates of preterm births (19.2% insulin, 12.5% metformin, 12.1% diet, p = 0.005), neonatal intravenous dextrose use (11.1% insulin, 5.1% metformin, 7.4% diet, p = 0.004), customized LGA infants (18.5% insulin, 12.5% metformin, 12.4% diet, p = 0.02), and NICU admissions (18.7% insulin, 12.7% metformin, 14.0% diet, p = 0.04).

An interesting finding is that, if we compare the patients on metformin plus insulin and the patients only on insulin, the group on metformin plus insulin had higher percentage of women with BMI > 30 (62.8 vs. 45.3%), a higher fast plasma glucose (5.7 vs. 5.4 mmol/L) on oral glucose tolerance test (OGTT), a higher percentage of CS (45.6% vs. 38%), and a higher percentage of preterm births (19.2 vs. 12.8%).

Niromanesh et al. in 2012 compared the efficacy of metformin and insulin in women with GDM (metformin n = 80, insulin n = 80), singleton pregnancy, and gestational age between 20 and 34 weeks, who did not achieve glycemic control and comparable maternal characteristics (21). The primary outcomes were maternal glycemic control and birth weight, while the secondary outcomes were neonatal and obstetric complications. Child born to women included in the metformin group had a lower rate of birth weight centile >90 than the insulin group (RR 0.5, 95% CI 0.3–0.9, p = 0.012) and maternal weight gain was reduced in the metformin group (p < 0.001), with comparable neonatal and obstetric complications (p > 0.05). Supplemental insulin was needed by 14% of women taking metformin in order to achieve glycemic control.

Metformin was, thus, indicated as an effective and safe alternative to insulin in women with GDM.

In 2012, a study was published to compare metformin with insulin as treatment of GDM and, furthermore, to characterize metformin-treated patients needing additional insulin to achieve prespecified glucose targets (99 mg/dl fasting glucose and 140 mg/dl 1 h after meal) (22).

It was a single-center randomized controlled study with a non-inferiority design comparing metformin and insulin in the treatment of 217 GDM patients. The primary outcome variable was the birth weight. No significant differences were found in the primary outcome. In the metformin group, 20.9% of the patients needed additional insulin. Factors predicting the need of additional insulin in metformin-treated patients were older age (p = 0.04), earlier gestational weeks at randomization (p = 0.004), earlier gestational week at OGTT (p = 0.01), higher Hba1C at randomization (5.6% vs. 5.44%, p = 0.01), and higher fructosamine at randomization (218.4 vs. 207.1 µmol/L, p < 0.001). Mothers with fructosamine concentration above the median before starting medication had a 4.6-fold (p = 0.006) higher probability for additional insulin than mothers having fructosamine below the median; the respective risk ratio for HbA1c between the patients having HbA1c above and below the median value was not significant (p = 0.09), leading us to hypothesize that fructosamine could be more useful than HbA1c in predicting the need of additional insulin.

A 2013 randomized trial of metformin vs. insulin in the management of GDM (23) including 97 pregnancy patients with GDM assigned to receive insulin (n = 47) or metformin (n = 47) showed lower weight gain (p = 0.002) and, moreover, a lower incidence of neonatal hypoglycemia (p = 0.032) in the metformin arm even if 26% of the metformin arm required an addition of insulin to their therapy.

It also showed that the probability of no response to metformin monotherapy was linked to earlier gestational age at diagnosis (p = 0.032) and mean pretreatment glucose level (p = 0.046).

A meta-analysis of five RCTs (some of them described above) was published in 2013 (24). It included 1,270 participants. Analysis of baseline characteristics showed that women requiring additional insulin had significantly higher fasting glycemic concentrations in OGTT (p = 0.0006).

The pooled results of main outcomes revealed that in the metformin group, there was a lower average weight gain after enrollment (p = 0.003), lower average gestational age at delivery (p = 0.02), higher incidence of preterm birth (p = 0.01), and lower incidence of pregnancy-induced hypertension (p = 0.02).

The limitations of this meta-analysis are linked not only to the high variability between the studies in the incidence of requiring additional insulin (especially high in the study of Rowan (18), 46.3%) but also to the high variability in metformin dose, the criteria of GDM's diagnosis, and the glycemic targets.

Further confirmation on safety and efficacy of metformin treatment in pregnant women with GDM comes from a systematic review and meta-analysis of 24 studies published in 2021 (25). There were both maternal and neonatal outcomes. The neonatal outcomes comprehend birth weight, LGA, neonatal hypoglycemia, small for gestational age (SGA), macrosomia, NICU, Apgar score (<7) at 5 min, hyperbilirubinemia, respiratory distress syndrome (RDS), congenital anomalies, and umbilical cord pH. Maternal outcomes included gestational age at delivery, premature delivery, preeclampsia, pregnancy-induced hypertension (PIH), CS, maternal weight gain, and maternal glycemic control. Metformin was linked to lower risk of pregnancy-induced hypertension (p = 0.03), LGA babies (p = 0.04), macrosomia (p = 0.01), neonatal hypoglycemia (p = 0.001), and NICU admission (p = 0.01).

Another prospective trial published in 2021 (26) by a Spanish group evaluated metformin vs. insulin in 200 women with GDM (n = 100 in the metformin arm and n = 100 in the insulin arm). It was a multicenter, open-label, parallel-arm, randomized clinical trial enrolling women with singleton pregnancy, aged 18–45 years, with a gestational age between 14 and 35 weeks, and with GDM who needed pharmacologic treatment. The main outcomes of this study were glycemic control (mean glycemia and hypoglycemic events) and maternal and neonatal complications (hypertensive disorders of pregnancy, induced or spontaneous labor, preterm birth, fetal growth, neonatal care unit admission, respiratory distress syndrome, neonatal hypoglycemia, or jaundice requiring phototherapy). Metformin was started at 425 to 850 mg/day once or twice daily, and increased if necessary up to 2,550 mg/day. The insulin group was treated with detemir (0.2 UI/kg) plus, when necessary, aspart (0.1 UI/kg/meal).

This study confirmed that metformin was linked to less maternal weight gain (p = 0.011) and that there were no significant differences in birth weight, SGA, or LGA rates. The results show, differing from the MiG trial, that metformin was associated with lower postprandial glycemia and also reduced the rate of delivery by CS compared to those treated with insulin (p = 0.001).

A slightly different role of metformin was explored in the double-blind, multicenter, randomized trial of Valdes et al. published in 2019 in the *Journal of Obstetrics and Gynecology Research* (27). The aim of this study was to evaluate the role of metformin in the prevention of GDM in pregnant women with pregestational insulin resistance. They recruited 140 patients randomly assigned to take metformin (n = 68) or placebo (n = 73). The results show that patients in the metformin group did not have a decrease in the incidence of GDM as compared to placebo (37.5% vs. 25.4%, respectively; p = 0.2), but they experienced a higher incidence of drug intolerance (p = 0.02).

Mean results of the most important studies mentioned above are listed in Table 1.

These studies show that, in GDM, metformin is safe and effective; it is linked to less weight gain and a lower risk of neonatal hypoglycemia compared to insulin treatment.

The limitation of these lines of evidence is linked to a scarcity of randomized clinical trials, most with a small number of patients included, and no clinical studies designed with the purpose of evaluating the efficacy and safety of the metformin and insulin combination treatment, and that data from metformin and insulin combined use are derived from metformin vs. insulin comparison studies or retrospective data (non-randomized controlled trials).

The positive effects of metformin are linked to the increase in the hepatic and peripheral uptake of glucose, the reduction in hepatic output of glucose, and the increase in insulin sensitivity. Also not to be underestimated is the fact that metformin, in addition to being safe and effective in this subgroup, is a low-cost molecule, with a low risk of hypoglycemia, and does not require educational programs or intensive control of glycemia.

Concerns about the use of metformin in GDM are linked to the transplacental passage of this molecule and to the high concentration in the umbilical artery and vein.

The disadvantages of metformin are moreover linked to collateral effects like nausea and/or vomiting, diarrhea, and the uncertainty on fetus' long-term effects.

TABLE 1 Metformin for the treatment of women with GDM.

Trial	*N*	Gestational week at inclusion	Metformin dose (mg)	Comparator	CS	PE	GWG	BW	LGA	SGA	Preterm births	Other neonatal outcomes
Moore 2007 (17)	63	24–30	1,000–2,000	Insulin	=	/	/	=	/	/	/	=
MiG 2008 (18)	751	20–33	2,500 ± insulin	Insulin	/	=	<	=	=	=	>	< Neonatal hypoglycemia
Ijäs 2010 (19)	100	12–34	2,250 ± insulin	Insulin	>	=	=	=	=	/	=	=
Goh 2011 (20)	1,269	/	2,500 ± insulin	Insulin/dayt	<	=	/	=	<	=	<	< NICU ≥ 2 days
Niromanesh 2012 (21)	160	20–34	1,000–2,500 ± insulin	Insulin	=	=	<	<	<	=	=	=
Tertti 2012 (22)	217	22–34	1,500 ± insulin	Insulin	=	=	=	=	=	/	=	=
Spaulonci 2013 (23)	97	/	1,700–2,550	Insulin	=	=	<	=	=	=	=	< Neonatal hypoglycemia
Picón-César 2021 (24)	200	14–35	425–2,550	Insulin	<	/	<	=	=	=	=	=

N, number; CS, cesarean section; PE, preeclampsia; GWG, gestational weight gain; BW, birth weight; LGA, large for gestational age; SGA, small for gestational age.
< increased incidence.
> decreased incidence.
= unchanged incidence.
/ variable not analyzed.

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Metformin treatment in pregnant women with T2DM

The most important study to evaluate the safety and efficacy of metformin in pregnant women affected by T2DM is the MiTy trial, a randomized double-blind multicenter international placebo-controlled study involving 502 women with T2DM under insulin therapy between 18 and 45 years old and 6 to 22 weeks plus 6 days of pregnancy randomly assigned to take metformin 1 g twice daily (n = 253) or placebo one capsule twice daily (n = 249) published in 2020 (28). The primary outcome was a composite of fetal and neonatal outcomes (pregnancy loss, preterm birth, birth injury, moderate or severe respiratory distress syndrome, neonatal hypoglycemia, and NICU admission lasting >24 h). Secondary outcomes included maternal glycemic control, maternal hypertensive disorders, CS, gestational weight gain and insulin dose, LGA, extreme LGA, SGA, cord blood C-peptide, neonatal adiposity outcomes, gestational age at birth, and length of infant hospital stay.

They found no significant difference in the primary composite neonatal outcome between the two groups (40% vs. 40%, p = 0.86) but compared with women in the placebo group, metformin-treated women had lower levels of Hba1c, gained less weight, and had a lower incidence of CS; metformin-exposed infants had lower birth weight (p = 0.0016), a lower incidence of extreme LGA (22% vs. 27%, p = 0.041), and a higher incidence of SGA (13% vs. 7%, p = 0.026), and infants had slightly higher incidence of neonatal jaundice (23% vs. 16%, p = 0.06) (Table 2).

Metformin treatment in pregnant women with obesity

In 2015 the EMPOWaR was published, a randomized double-blind placebo controlled study involving 449 pregnant women (aged ≥16 years) between 12 and 16 weeks' gestation who had a BMI of 30 kg/m^2 or more and normal glucose tolerance in 15 National Health Service hospitals in the UK (29). Women were randomly assigned (1:1) to metformin (maximum 2,500 mg/day) or placebo. Demographic characteristics, comorbidities, and anthropometric parameters overlap between the two groups. Primary outcome was birth weight percentile. Secondary outcomes were insulin resistance at 36 weeks EG, maternal fasting glucose and insulin at 2 h of glucose load at 36 weeks CE, maternal and neonatal anthropometric parameters, maternal inflammatory markers, and incidence of IUGR. There were no significant differences in the primary outcome or in the secondary outcomes, which shows that metformin had no significant effect on birth weight percentile in obese pregnant women.

One of the most important studies to explore the role of metformin on obese pregnant patients was the GRoW trial, a randomized double-blind placebo-controlled study on 524 women with a BMI >25 kg/m^2 of 10–20 weeks of gestation; 256 women were randomly assigned to take metformin 2,000 mg/day, and 258 women took placebo (30). This study shows no differences in GDM incidence or in the incidence of other maternal complications like hypertension or preeclampsia except for a lower weight gain per week in the metformin group (p = 0.006). No differences were found either in the incidence of perinatal adverse outcomes including macrosomia or LGA.

In 2020, a randomized clinical trial involving 357 obese (BMI >30 kg/m^2) pregnant women without diabetes was published; 186 women were assigned to take placebo and 171 were assigned to take metformin (31). The main outcomes were absolute risk reduction and the number of women who needed treatment for CS and LGA. There were no differences in patients' baseline characteristics except for marital status.

The incidence rate of CS in the metformin group was 39.8% vs. 62.9% in the control group (p < 0.01). No differences were found in the LGA prevention. Between the maternal–fetal outcomes assessed in the secondary analysis (GDM, preeclampsia, prematurity, newborn weight, SGA, Apgar 1st and 5th min, and NICU), only the incidence of preeclampsia seems to be reduced in the metformin group (p < 0.01).

In 2020, another study was published on metformin to analyze its role in the lipid profile, BMI, and weight gain of pregnant women with obesity (32). This study was a randomized clinical trial involving 436 obese pregnant women randomly assigned to low-dose metformin (n = 206) or control (n = 218). The inclusion criteria were pregnant women with obesity ≥18 years, single pregnancy, negative screening for GDM in early pregnancy, and gestational age <20 weeks.

There was no difference in lipid profile, BMI, and weight gain values between groups during the 1st, 2nd, and 3rd evaluation. A significant difference was observed only in the BMI, high-density-lipoprotein (HDL), and triglycerides (TG) values from the 1st to 3rd evaluation.

We can conclude that in obese women, even if metformin seems to be potentially useful in the inflammatory response modulation

TABLE 2 Metformin for the treatment of pregnant women with T2DM.

Trial	N	Gestational week at inclusion	Metformin dose (mg)	Comparator	CS	PE	GWG	BW	LGA	SGA	Preterm births	Other neonatal outcomes
Mity trial (28)	502	6–22	2,000 + insulin	Placebo + insulin	<	=	<	<	=	>	=	=

N, number; CS, cesarean section; PE, preeclampsia; GWG, gestational weight gain; BW, birth weight; LGA, large for gestational age; SGA, small for gestational age.
< increased incidence.
> decreased incidence.
= unchanged incidence.

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and in the severe obesity to reduce the risk of preeclampsia, there is no evidence that, in this subgroup of patients, metformin has a role in fetal growth; it does not reduce the risk of GDM, it does not improve maternal lipidic profile, and benefits have only been observed in some of the outcomes addressed (Table 3).

Metformin treatment in pregnant women with PCOS

A prospective, randomized, double-blind, placebo-controlled pilot study to investigate a possible effect of metformin on androgen levels in pregnant women with PCOS was published in 2004 (33). Forty pregnant women with PCOS were randomly assigned to receive diet and lifestyle counseling plus metformin 850 mg/day twice daily or plus placebo.

Primary outcome measures were dehydroepiandrosterone sulfate (DHEAS), androstenedione, testosterone, SHBG, and free testosterone index (FTI). Secondary outcome measures were pregnancy outcome and pregnancy complications. Metformin had no effect on maternal androgen levels in pregnant women with PCOS. Moreover, while none of the 18 women in the metformin group experienced a severe pregnancy or post-partum complication, 7 of the 22 (32%) women in the placebo group experienced severe complications (p = 0.01), showing promising results for overall pregnancy complications.

The PregMet study was published in 2010 (34). It was a prospective, randomized, double-blind, multicenter trial comparing metformin 2,000 mg daily with placebo in 257 women with a history of PCOS aged 18–42 years and enrolled in the first semester of pregnancy. Primary outcomes were the prevalence of preeclampsia, preterm delivery, GDM, and a composite of these three outcomes. Secondary outcomes included weight, blood pressure, heart rate, and mode and length of delivery.

The results show no differences between the groups in the prevalence of preeclampsia, preterm delivery, GDM, or the composite of these three pregnancy complications, contradicting the previous pilot study mentioned above. Between secondary outcomes, they only found a significant difference in weight gain with a lower increase in the metformin group.

Pooled data from these two studies showed a significant reduction in the combined endpoint of late miscarriage and preterm birth in favor of metformin (35).

One of the biggest studies involving pregnant women with PCOS is the PregMet2, a randomized, double-blind, placebo-controlled study involving 487 singleton pregnant PCOS women aged 18–45 years randomly assigned to metformin (n = 244) or placebo (n = 243) published in 2019 (36). The primary outcome of this intention-to-treat analysis was incidence of late miscarriage (EG 13 -22 + 6) and preterm birth (EG 23 -36 + 6); the secondary outcomes were incidence of GDM, preeclampsia, pregnancy-induced hypertension, and admission of the neonate to the NICU, and tertiary outcome was weight gain in pregnancy, from inclusion until week 36. Women in need of assisted reproductive technology (15%–20%) were equally distributed between the treatment groups. The different phenotypes of PCOS were equally

TABLE 3 Metformin for the treatment of pregnant women with obesity.

Trial	N	Gestational week at inclusion	Metformin dose (mg)	Comparator	CS	PE	GWG	Maternal lipid assessment	BW	LGA	SGA	Preterm births	Other maternal/neonatal outcomes
EMPOWaR 2015 (29)	449	12–16	2,500	Placebo	=	=	=	=	=	/	=	=	< Admission to neonatal unit
GRoW 2019 (30)	524	10–20	2,000	Placebo	<	=	<	/	=	=	=	=	=
Nascimento 2020 (31)	357	<20 weeks	1,000	Placebo	<	<	/	/	/	=	/	=	=
Dienstmann 2020 (32)	436	<20 weeks	1,000	Placebo	/	/	=	=	/	/	/	/	=

N, number; CS, cesarean section; PE, preeclampsia; GWG, gestational weight gain; BW, birth weight; LGA, large for gestational age; SGA, small for gestational age.
> decreased incidence.
= unchanged incidence.
/ variable not analyzed.

distributed between the treatment groups. Metformin's starting dose was 500 mg twice daily during the first week of treatment, increased to 1,000 mg twice daily from week 2 until delivery. Treatment was started in the first trimester as soon as possible, and at the latest 7 days after, the inclusion visit. If necessary because of side effects, doses were adjusted to an acceptable level. All women received diet and lifestyle advice according to national guidelines. The results of PregMet2 showed a non-significant reduction in the incidence of late miscarriage or preterm delivery (primary outcome). No substantial between-group differences were found in maternal and offspring adverse events (secondary outcomes). Women in the metformin group gained less weight from inclusion to gestational week 36 compared with those in the placebo group ($p < 0.001$).

An interesting study was made on a subgroup of PregMet2 enrolled women ($n = 73$) who agreed to provide serum sample at three time points in pregnancy (gestational weeks 19, 28, and 32) and once in postpartum, (either 2, 4, or 8 weeks after delivery) (37). The study showed an increase of 32% in metformin concentration already during the first 2 weeks postpartum, probably linked to the resolution of the pregnancy hemodilution. These results may impact both the therapeutic efficacy during pregnancy and the risk of adverse drug reactions that could be higher postpartum.

The results of PregMet2 partially contradict a previous meta-analysis based on 13 studies including 5 RCTs and 8 cohort studies involving 1,606 pregnant women with PCOS published in 2016 (38).

The primary outcomes of this meta-analysis included early pregnancy loss, preterm delivery, term delivery, and GDM; secondary outcomes included pregnancy-induced hypertension (PIH), intrauterine growth restriction (IUGR), fetal malformation, vaginal delivery (VD), CS, and metformin's side effects, such as nausea or gastrointestinal discomfort. Taking metformin seems to reduce the risk of miscarriage, preterm delivery, complications like GDM, hypertensive disorders, and CS. However, the positive effect on GDM incidence was not confirmed in sub-analysis including only the randomized trials.

Mean results of the three most important studies mentioned above are listed in Table 4.

Metformin and fertilization

PCOS is among the most common endocrinopathies associated with reproductive and metabolic disorders and affects 9% to 18% of women (37). According to the World Health Organization, it belongs to group II of ovulation disorders and accounts for 80% of women with anovulatory syndrome (39).

The Rotterdam criteria (2003) for the diagnosis of PCOS require that women must meet two of the following items: oligo-ovulation or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries (40).

Among the most frequent clinical manifestations of PCOS, there are irregular periods, infertility, hirsutism, acne, obesity, inappropriate gonadotropin secretion (i.e., elevated levels of circulating luteinizing hormone), pregnancy complication, cardiovascular disease, and metabolic features including especially insulin resistance with compensatory hyperinsulinemia (40, 41).

The reduction of insulin resistance has been proven to improve ovulation and fertility in women with PCOS, and this led to many studies regarding the possible role of insulin-sensitizing agents, particularly metformin, in the treatment of PCOS (41, 42). Metformin reduces hyperinsulinemia and suppresses the excessive ovarian production of androgens (43). It is suggested that, as a consequence, metformin could improve assisted reproductive technique (ART) outcomes, such as ovarian hyperstimulation syndrome (OHSS), pregnancy, and live birth rates.

Despite the multitude of RCTs conducted, high-quality RCTs designed to answer the specific question of the comparative efficacy of metformin in patients with PCOS and with or without obesity are still lacking (39). Some limited studies have found that BMI may affect the efficacy of metformin (44, 45).

Wu et al. conducted a study that aimed to systematically review the literature and performed a meta-analysis in 2020 to clarify whether metformin is associated with improved outcomes in women with PCOS undergoing *in vitro* fertilization or intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) cycles (41). It included 12 studies involving 1,123 women with PCOS undergoing IVF/ICSI-ET, and its outcomes were OHSS rate, clinical pregnancy rate, live birth rate, and miscarriage rate.

TABLE 4 Metformin for the treatment of pregnant women with PCOS.

Trial	*N*	Gestational week at inclusion	Metformin dose (mg)	Comparator	CS	PE	GWG	BW	LGA	SGA	Preterm births	GDM
Pilot study 2004 (33)	40	5–12	1,700 mg	Placebo	/	/	/	=	/	/	/	/
PregMet 2010 (34)	257	5–12	2,000	Placebo	=	=	<	=	/	/	=	=
PregMet 2 2019 (36)	487	6–12	2,000	Placebo	=	=	<	=	/	/	=	=

N, number; CS, cesarean section; PE, preeclampsia; GWG, gestational weight gain; BW, birth weight; LGA, large for gestational age; GDM, gestational diabetes; SGA, small for gestational age.
< increased incidence.
> decreased incidence.
= unchanged incidence.
/ variable not analyzed.

Women in the metformin group had lower odds of OHSS than women in the control group (OR 0.43; 95% CI 0.24–0.78); in particular, women in the subgroup with BMI > 26 had lower rates of OHSS if randomized with metformin (OR 0.25, 95% CI 0.12–0.51). No differences were observed in OHSS rate in the subgroup with BMI < 26.

Metformin was not associated with the clinical pregnancy rate (OR 1.24, 95% CI 0.82–1.86). Dividing two groups by BMI, there was a significant difference in clinical pregnancy rate (OR 1.7, 95% CI 1.12–2.60) in the subgroup with BMI > 26 treated with metformin.

There was no evidence of a difference in live birth rate between the metformin and control groups (OR 1.23 95% CI 0.74–2.04), even dividing the two subgroups by BMI, or in miscarriage rate (OR 0.58 95% CI 0.24–1.39).

Tso et al. conducted a systematic review published in the Cochrane Database to determine the effectiveness and safety of metformin as a co-treatment during IVF or ICSI in achieving pregnancy or live birth in women with PCOS (43). It included 13 studies for a total population of 1,132 women of reproductive age with anovulation due to PCOS with or without coexisting infertility factors. They stratified the analysis by type of ovarian stimulation protocol used [long gonadotropin-releasing hormone agonist (GnRH agonist) or short gonadotropin-releasing hormone antagonist (GnRH antagonist)] to determine whether the type of stimulation used influenced the outcomes.

The review showed uncertainty of the effect of metformin on live birth rate when compared to placebo/no treatment (RR 1.30, 95% CI 0.94–1.79) for the GnRH-agonist group, while it may reduce live birth rate for the GnRH-antagonist group.

Metformin could reduce the incidence of OHSS (RR 0.46, 95% CI 0.29–0.72), while regarding the clinical pregnancy rate, it demonstrated an increase in women of the GnRH-agonist group (RR 1.32, 95% CI 1.08–1.63), and uncertainty for the GnRH–antagonist group.

Metformin may also result in an increase in side effects (mainly gastrointestinal) compared with placebo/no treatment (RR 3.35, 95% CI 2.34–4.79).

The overall quality of evidence ranged from very low to low.

In conclusion, this review found no conclusive evidence that metformin improves live birth rates; in a long GnRH-antagonist protocol, it is uncertain whether metformin improves live birth rates, but it may increase the clinical pregnancy rate; in a short GnRH-antagonist protocol, metformin could reduce live birth rates, with uncertainty on clinical pregnancy rate. Metformin could also reduce the incidence of OHSS in the long GnRH-agonist protocol but not in the GnRH-antagonist ovarian stimulation protocol (Table 5).

Another meta-analysis summarized 47 studies and concluded that metformin could lower triglyceride levels in patients with PCOS who did not have diabetes, possibly through improving oxidative stress status (46).

One guideline (42) pointed out that stopping metformin treatment at the initiation of gestation did not influence the live birth rate; however, the already mentioned study of PregMet2 (36) stated that metformin could reduce the incidence of late miscarriage and preterm birth when the treatment is prolonged to the late first trimester to delivery.

Metformin and breastfeeding

Maternal obesity is consistently associated with delayed lactogenesis (47, 48). Recent studies revealed the different insulin sensitivity of the mammary gland during pregnancy and lactation (49).

Nommsen et al. designed a metformin-versus-placebo randomized clinical trial involving 15 women with insulin resistance and low milk production despite regular breast emptying; their hypothesis was that an intervention targeting insulin action could improve milk production (49). Metformin is considered compatible with lactation, with milk concentrations from 0.1 to 0.4 mg/L and undetectable or very low detection of metformin (<0.08 mg/L) in the serum of breastfed infants. Women took metformin at a dosage of 750 mg/day from day 1 to 7, 1,500 mg/day from day 8 to 14, and 2,000 mg/day from day 14 to 28. They measured breast milk production by having participants weigh their infants on a specialized scale immediately before and after feeding on each breast over 24 h for 14–28 days. They found that maximum milk production improved from baseline in 60% of the participants who were assigned metformin and in 20% of the placebo group. Median change in milk production was 68 ml greater in participants assigned metformin as compared to placebo participants, with a non-statistically significant difference. *Post-hoc* results led to the conclusion that an intervention aimed at improving insulin sensitivity could improve milk production (median peak change in milk output +22 in metformin completers $n = 8$, versus −58 ml/24 h placebo + non-completers, $n = 7$), even though absolute milk

TABLE 5 Metformin to improve fertilization.

Study	*N*	Comparator	OHSS		Clinical pregnancy rate		Live birth rate		Miscarriage
Wu et al. 2020 (41)	12 studies 1,123 women	Metformin vs. control	BMI < 26	BMI > 26	BMI < 26	BMI > 26	=		=
			=	<	/	>			
Tso et al. 2020 (43)	13 studies 1,132 women	Metformin vs. placebo/no treatment	<		GNRH-antagonist	GNRH-agonist	GNRH-antagonist	GNRH-agonist	/
					U	>	<	U	

N, number; BMI, body mass index; OHSS, ovarian hyperstimulation syndrome; GNRH, gonadotropin releasing hormone; U, uncertain.

output remained very low even in the participants who completed the metformin course.

Metformin and offspring

It is known that offspring of women with diabetes have an increased fat mass at birth but not an increase in fat-free mass (50), an explanation could be the continued exposure to nutrient excess in the uterus that may cause an overload of the subcutaneous fat stores and, thus, the development of leptin and insulin resistance and a deposit of excess nutrients as ectopic fat (51). Reduced insulin sensitivity has been demonstrated in cord blood of infants exposed to maternal hyperglycemia (52).

Moreover, large-scale epidemiological studies have highlighted how the offspring of obese women have an increased incidence of reduced cognitive performance (53), attention deficit hyperactivity disorder (ADHD) (54), psychiatric disorders (55), cerebral paralysis (56), and autism spectrum disorders (57).

Women with insulin resistance then need to achieve strict glycemic control to avoid pregnancy complications resulting from hyperglycemia (58), and insulin is proven to reduce complications for both the mother and the fetus (5).

GDM not properly controlled with diet is commonly treated with insulin, although there are different guidelines: the American Diabetes association recommends using insulin as first-line treatment for GDM, the National Institute for Health and Care Excellence (NICE) proposes the use of metformin as first-line treatment, and the Society for Maternal Fetal Medicine considers metformin a reasonable and safe first-line pharmacologic alternative to insulin (57, 59, 60).

Metformin use during pregnancy has been studied mainly for PCOS and GDM, and the main worries come from the fact that it freely crosses the placenta and reaches a fetal level similar to maternal concentration (61). It is possible that metformin exposure in the uterus might lead to improved insulin action in the fetus, resulting in a metabolically healthier pattern of growth, but it remains extremely important to examine longer-term outcomes (24). A lack of long-term offspring follow-up data has led to caution about using metformin routinely in GDM.

The MiG-TOFU is a series of studies that, starting from the results of the MIG trial (17), tried to assess potential effects on growth of the children.

Rowan et al. led an offspring follow-up (TOFU) investigating the body composition at 2 years of age (62). In Auckland and Adelaide, women who had participated in the MiG trial were reviewed when their children were 2 years old and the children were assessed with anthropometrics, bioimpedance, and DEXA. There were no differences between groups in the baseline characteristics of mothers at the randomization of treatment, and there were no differences between groups in measurements at birth, maternal glucose control during pregnancy, and rates of breastfeeding at 6/8 weeks postpartum. Their first hypothesis was that metformin exposure in the uterus would be associated with less central fat and, then, less insulin resistance in the offspring. Body composition measurements at 2 years of age showed three significant differences: the upper arm circumference was larger in the metformin group, and subscapular skinfolds and biceps skinfolds were bigger, while there were no differences in DEXA and bioimpedance measures. Their first hypothesis was not confirmed though, since they found no differences between the two groups in central fat measures, total fat mass, percentage body fat, or central to peripheral fat. Anyway, the larger skin folds may suggest that exposure to metformin has led to more fat being stored in subcutaneous sites, which may, in turn, mean that there is less ectopic or visceral fat in these children.

The importance of these findings lies in the fact that size and location of the fat cells are important predictors of insulin resistance and adverse metabolic consequences of obesity (51, 63, 64). They provide feedback about food intake and satiety, and in situations of excessive nutrient intake, the adipocytes become large and dysfunctional and excess fat is deposited in visceral adipocyte depots, which release fatty acids and inflammatory adipocytokines, associated with insulin resistance (64).

The same authors led another study, investigating body composition and metabolic outcomes at 7–9 years of age of the same children of the previous MiG TOFU (65). Its aim was to compare body composition and markers of insulin sensitivity between the groups treated with metformin and insulin.

The Adelaide subgroup was assessed at 7 years of age and all measures of body composition, adjusted for age, gender, and ethnicity, were similar in the two groups. In the Auckland subgroup, at 9 years of age, the metformin group was still larger on several measures, including weight, mid-upper arm circumference, waist circumference, and waist-to-height ratio. They also had a trend toward higher fat-free mass and fat mass. In conclusion, that study reported similar total and abdominal fat body percentage and metabolic measures in 7- to 9-year-old offspring of women randomized to metformin or insulin treatment during pregnancy, even if 9-year-old offspring of women randomized to metformin were larger than those whose mothers had been randomized to insulin.

Paavilainem et al. compared the lipid and glucose metabolism in 9-year-old offspring of mothers treated with metformin or insulin for GDM, beyond anthropometrics (66). It was the result of a longitudinal follow-up study of two previously published Finnish RCTs with a similar study design, including a total of 172 children, already mentioned above (19, 22).

Neonatal measures, such as birth weight, crown–heel length, ponderal index, and sex distribution, did not differ significantly between the two groups. Maternal baseline characteristics, pregnancy outcomes, and neonatal measures were also found to be similar in the two groups. At the follow-up evaluation, all the 9-year-old children were prepubertal. There were no significant differences between the metformin and insulin groups in terms of weight, height, BMI, proportion of overweight or obese children, waist circumference, waist-to-height ratio, and systolic or diastolic blood pressure. Data were consistent with existing literature.

Regarding the metabolic profile, the offspring on the metformin group were found to have a more favorable lipid profile. Their HDL cholesterol concentration was higher, whereas their low-density-lipoprotein (LDL) and apolipoprotein B concentrations were lower,

although the significance in HDL increased concentration was reached only in boys. The glucose metabolism values (fasting glucose, fasting insulin, fasting C peptide, HbA1C, and OGTT) were similar.

Mean results of the three studies mentioned above are listed in Table 6.

Exploring the cardiovascular profile in the offspring, Panagiotopoulou et al. designed a follow-up study, including 151 children from the Metformin (vs. Placebo) in Obese Pregnant Women trial (67) to assess whether prenatal exposure to metformin can improve the cardiovascular profile and body composition in the offspring of obese mothers (68). Consistently with other studies, they found no differences in weight, height, body mass index, skinfolds, and body fat distribution measurements. The rate of weight gain from birth to early childhood (children were about 4 years old at the time of the evaluation) was also comparable.

On the cardiovascular side, children in the metformin group had shorter isovolumetric relaxation time and smaller left atrial area and higher pulmonary vein peak systolic Doppler velocity value. Measures of cardiac systolic function were similar.

Regarding hemodynamic parameters and vascular phenotype, there was no significant difference in peripheral systolic blood pressure and diastolic blood pressure. After multivariable adjustments, children exposed to metformin had lower aortic pulse pressure and aortic systolic blood pressure, suggesting a reduced central blood pressure with an improvement in central hemodynamics and left ventricular diastolic indices. These results suggest a putative beneficial and protective effect of metformin to the cardiovascular system of the offspring.

The PedMet study (69), led by Hanem et al., was conducted with different results exploring the cardiometabolic risk factors in children during a follow up of the PregMet study, a randomized, placebo-controlled, double-blind study that investigated the role of metformin in women with PCOS during pregnancy in terms of reduction of pregnancy complications (34). They re-evaluated children after 5/10 years and concluded that children in metformin groups vs. placebo had a higher BMI *Z* score, a higher measure of abdominal adiposity, and a higher weight. There was no difference in height *Z* score, head circumference *Z* score, adiponectin, cholesterol, TG, HDL cholesterol, non-HDL cholesterol, alanine aminotransferase, glucose, HbA1c, insulin, c-peptide, Homeostasis Model Assessment 2-Insulin Resistance (HOMA2-IR), blood pressure, or heart rate.

As with the majority of the studies available in literature, all the aforementioned studies did not differentiate metformin use alone or in combination with insulin, in comparison with insulin or placebo.

Brand et al. instead designed a register-based cohort study, including more than 10,000 children with maternal exposure to metformin or insulin regardless of the indication (GDM, presentational T2DM, or PCOS), classified into three exposure groups: metformin, insulin, and combination treatment (15). As primary outcomes, they demonstrated that for obesity and hypoglycemia, the incidence was higher for the combination treatment; for hyperglycemia, there were no marked differences between the groups. Moreover, for motor–social development, no significant difference was observed. No events of hypertension or PCOS were observed in the metformin or combination treatment groups.

TABLE 6 Impact of metformin treatment during pregnancy on offspring.

Trial	Comparator	Subgroups	Measures	Results
MIG-TOFU 2 years 2011 (62)	Metformin vs. insulin		Upper arm circumference	>
			Subscapular skinfolds	>
			Biceps skinfolds	>
			Central fat measures	=
			Total fat mass	=
			Percentage body fat	=
			Central to peripheral fat	=
MIG-TOFU 7–9 years 2017 (65)	Metformin vs. insulin	Adelaide group 7-year-olds	Body composition	=
		Auckland group 9-year-olds	Weight Mid-upper arm circumference Waist circumference Waist-to-height ratio Fat-free mass	>
Paavilainen 9 years 2022 (66)	Metformin vs. insulin		Weight Height BMI Overweight/obese % Waist circumference Waist-to-height ratio	=

< increased incidence.
= unchanged incidence.

As secondary outcomes, exposure to metformin was associated with significantly lower mean birth weight, and compared with insulin, no differences were observed for the other secondary outcomes (LGA, SGA, preterm birth, neonatal mortality, neonatal hypoglycemia and hyperglycemia, and major congenital anomalies).

In the CogMet study, Greger et al. explored whether metformin (vs. placebo) exposure in the uterus had any effect on offspring cognitive function (70). The study was designed as a follow-up of two randomized, placebo-controlled studies [the pilot study (33) and the PregMet study (34)], and included 93 children with a mean age of 7.7 years. There was no difference between participants and nonparticipants regarding maternal baseline data, pregnancy outcomes, and neonatal data. All anthropometric measures, including Tanner stage development of the children at follow-up, were also comparable in the two groups.

The mean full-scale intelligence quotient (FIQ) in the metformin and placebo groups were similar and corresponded to the average FIQ score in the background population. There were no statistically significant differences on the subscales (verbal comprehension, working memory, perceptual organization, or processing speed), and the results did not change after adjustment for maternal/paternal educational level.

Conclusion

What do the results of these studies tell us?

Clinical and scientific evidence presented above support the safety and efficacy of metformin during pregnancy. In pregnant women with GDM and T2DM, metformin improves obstetric and perinatal outcomes, but there is no evidence that metformin prevents GDM in women with pregestational insulin resistance (27). In addition, no improvement in lipid profile and risk of GDM was demonstrated in pregnant women with PCOS or obesity (32). Metformin could have a role in reducing the risk of preeclampsia in pregnant women with severe obesity (31) and the risk of late miscarriages and preterm delivery in women with PCOS (38). In women with PCOS undergoing IVF/FIVET, taking metformin seems to be associated with a lower risk of OHSS (40).

Offspring of mothers exposed to metformin have no significant differences in long-term outcomes compared to those born to mothers exposed to insulin (63, 64, 68).

Maternal exposure to metformin and combination treatment of metformin and insulin was not associated with long-term increased risk of obesity, hypoglycemia, hyperglycemia, diabetes, or challenges in MSD compared with insulin. The analyses of adverse outcomes at birth showed significantly lower birth weight and significantly increased risk of SGA associated with exposure to metformin, compared with insulin; combination treatment was associated with increased risk of LGA, preterm birth, and hypoglycemia (15).

Metformin in pregnancy appears to be protective for metabolic risk in babies to mothers with GDM (66) and cardiovascular risk in babies born to obese mothers (68).

Metformin in pregnancy appears to increase metabolic risk in babies born to mothers with PCOS (69).

It would be of great interest to evaluate glycemic profiles with subcutaneous continuous monitoring devices and also to compare new long-acting formulations of insulin among them and with metformin (26).

Furthermore, there are not enough studies reporting long-term data nowadays, and whether the effect of metformin will continue until adulthood is an important point to explore.

What do the guidelines tell us?

Despite the clinical and scientific lines of evidence listed above, the Italian standards for the treatment of diabetes mellitus 2018 declare that in all women with GDM or T2DM in whom the glycemic target is not achievable by diet alone, insulin therapy should be promptly instituted; oral antidiabetics and non-insulin injection therapy are currently not recommended in pregnancy; a possible introduction of metformin into the GDM therapy remains suspended pending reliable data on its long-term safety in the fetus and offspring (71).

The global guideline on pregnancy and diabetes published in 2017 instead declares that women with T2DM who are taking metformin during pregnancy need information about the potential advantages and disadvantages of these medications; for women with GDM not controlled by diet, insulin is the treatment of choice; however, metformin can be considered a safe and effective alternative (72).

The National Institute for Health and Clinical Excellence (NICE) and the Canadian Diabetes Association include metformin as an option for treatment of GDM, and NICE also includes metformin as an option for the treatment of T2DM in pregnancy, even if it is not licensed for these indications (61, 73).

A clinical approach

An interesting review recently published proposed a clinical targeted approach in the use of metformin in pregnant women (74).

In obese pregnant women, even if on a small evidence base, metformin could have a role in very obese women (BMI >35 kg/m^2) to minimize weight gain with no effect on infant size at birth. However, personalized decisions with risks and benefits (particularly long-term fetal outcome and gastrointestinal side effects) have to be discussed.

In pregnant women with PCOS, consider continuing metformin especially in those with a BMI ≥30 kg/m2, even if in this group of women, metformin also does not reduce infant size.

In pregnant women with GDM, consider metformin in very obese women who are likely to need insulin as metformin will reduce the dose needed and gestational weight gain.

In pregnant women with T2DM already on metformin, consider continuing metformin throughout pregnancy; however, stop taking metformin if there is evidence of fetus being SGA; consider initiating treatment in obese women who are insulin naïve and consider adding it to those on large dose of insulin to reduce dose.

They concluded that, owing to increasing rates of maternal obesity, GDM, and T2DM, metformin use in pregnancy is increasing; overall, it appears safe and effective but further research is needed to examine mechanisms linking metformin to obesity reported during childhood in some follow-up studies.

An interesting work was made by Tarry-Adkins et al. in a recent big meta-analysis (75). They have included 35 RCTs reporting pregnancy outcomes in women randomized to metformin versus any other treatment for any indications. The sample included 8,033 patients and the analysis showed that metformin use is associated with lower gestational weight gain and a modest reduced risk of preeclampsia, but increased gastrointestinal side effects compared to other treatments.

Metformin is safe and effective in pregnant women with insulin resistance. Currently, there remain a lot of blind spots in the use of metformin in pregnant women; some interesting clinical trials are ongoing (76), though, with the hope of providing us more clinical evidence and certainties on metformin use in this field.

Author contributions

DP contributed to conception and design of the study. DP, AB, and GT researched and selected the articles of interest. GT and AB (that share first authorship) wrote the first draft of the manuscript and wrote sections of the manuscript. All authors (AB, GT, LT, LV, AP, SD, AR, MD, AL, DP, and AS) contributed to manuscript revision. All authors contributed to the article and approved the submitted version.

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.

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Composition of the intestinal microbiota and its variations between the second and third trimesters in women with gestational diabetes mellitus and without gestational diabetes mellitus

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Objective: This study was designed to explore the composition of the intestinal microbiota and its longitudinal variation between the second trimester (T2) and the third trimester (T3) in women with gestational diabetes mellitus (GDM) and pregnant women with normal glucose tolerance.

Methods: This observational study was conducted at Peking Union Medical College Hospital (PUMCH). Women with GDM and pregnant women with normal glucose tolerance were enrolled in the study, and fecal samples were collected during T2 (weeks 24~28) and T3 (weeks 34~38). Fecal samples were analyzed from 49 women with GDM and 42 pregnant women with normal glucose tolerance. The 16S rRNA gene amplicon libraries were sequenced to analyze the microbiota and QIIME2 was used to analyze microbiome bioinformatics.

Results: The four dominant phyla that *Firmicutes*, *Bacteroidetes*, *Actinobacteria* and *Proteobacteria* which accomplish about 99% of the total relative abundance did not significantly change between the T2 and T3 in the GDM and healthy groups. At the genus level, the relative abundance of *Scardovia* (0 vs. 0.25%, P = 0.041) and *Propionibacterium* (0 vs. 0.29%, P = 0.041) increased significantly in the control group, but not in the GDM group. At the phylum level, the relative abundance of *Firmicutes* and *Actinobacteria* was significantly different between women with GDM and pregnant women with normal glucose tolerance in both T2 and T3. In T2 and T3, the relative abundances of *unidentified_Lachnospiraceae*, *Blautia*, and *Parabacteroides* were significantly higher in the GDM group than in the control group (P<0.05). The relative abundance of *Bifidobacterium* in the GDM group was lower than in the control group in both T2 and T3.

Conclusions: The intestinal microbiota composition was stable from T2 to T3 in the GDM and control groups; however, the intestinal microbiota composition was different between the two groups.

KEYWORDS

gut microbiota, gestational diabetes mellitus, normal glucose tolerance, healthy pregnant normal glucose tolerance women, second trimester, third trimester

Introduction

The intestinal microbiota, which plays an important role in maintaining human health, colonizes the human intestinal tract (1). In general, the gut microbiota participates in various activities, such as metabolism (2). The gut microbiota can play a role by producing short-chain fatty acids, such as butyrate and propionate (3). The alteration of the intestinal microbiota is associated with many diseases, such as type 2 diabetes and obesity (4–8). Some researchers have recently explored the association between gut microbiota and pregnancy (9–11). The gut microbiota is characterized mainly by an increase in *Actinobacteria* and *Proteobacteria*, with a reduction in the diversity of microbiota and butyrate-producing bacteria during pregnancy (9). Gestational diabetes mellitus (GDM) is a common complication during pregnancy, characterized by the incapability of pancreatic beta cells to respond sufficiently to the increased insulin requirements of pregnancy leading to different degrees of hyperglycemia (12). GDM can pose important short- and long-term health risks for both the mother and the offspring. Although insulin resistance and inflammatory processes have been suggested to be involved in the development of GDM, the specific pathogenesis of GDM remains unclear (13). Therefore, researchers have conducted various studies to explore the gut microbiota characteristics in women with GDM and found differences in the gut microbiota compared with pregnant women with normal glucose tolerance. In women with GDM, opportunistic pathogens in the gut microbiota, such as *Bacteroides* and *Firmicutes* increase, and beneficial bacteria decrease (14).

Various factors, such as dietary intervention and probiotics, influence gut microbiota composition (1). Metabolism can change with the progression of trimesters during pregnancy (15). Koren et al. (9) found that the intestinal microbiota changed dramatically from the first to the third trimester, with a general increase in *Proteobacteria* and *Actinobacteria*, and the microbiota in the third trimester induced greater insulin adiposity than in the first trimester. Abdullah et al. (16) showed that lower α-diversity indices in the GDM group than in the control group, higher abundances in the genera *Acidaminococcus, Clostridium, Megasphaera, and Allisonella*, and lower abundances in *Barnesiella* and *Blautia* but no differences by trimester. Sun et al. (17) found that a decrease in the diversity of intestinal microbial species and changes in the composition of intestinal microbiota with advancing gestation was founded in the control group but not in the GDM group. The gut microbiota in women with GDM may be more stable than that of control group.

To date, the differences in gut microbiota composition between women with GDM and pregnant women with normal glucose tolerance have been explored in various studies, and the conclusions have been similar (18–20). However, a comparison of the intestinal microbiota in women with GDM between different trimesters is lacking. We conducted this prospective observational cohort study to investigate the longitudinal variations of the intestinal microbiota composition from the second (T2) to the third trimester (T3) in women with GDM and pregnant women with normal glucose tolerance.

Methods

Ethical approval

This prospective observational cohort study was conducted at the Peking Union Medical College Hospital (PUMCH) between April 2019 and May 2020. This study was reviewed and approved by the Ethics Review Board at PUMCH (approval number HS-1875). Women who met the inclusion criteria and signed an informed consent form were recruited. This study was registered at clinicaltrial.gov (NCT03916354, 04/12/2019). All the procedures were performed in accordance with the Declaration of Helsinki.

Population and groups

Fifty women with GDM and fifty pregnant women with normal glucose tolerance were enrolled in the study at T2 (24~28 weeks), and basic characteristics such as age, parity, pre-pregnancy body mass index (BMI), height, pre-pregnancy weight and gestational week were collected. Pre-pregnancy BMI was defined as the weight (kg) divided by the square of height (m). The inclusion criteria were as follows: (1) pregnant women, (2) natural pregnancy, (3) singleton pregnancy, and (4) provision of informed consent. Exclusion criteria were: (1) women with pre-pregnancy hypertension, diabetes, and dyslipidemia; (2) severe complications during pregnancy; (3) administration of antibiotics/prebiotics/probiotics during or in the last month before recruitment; (4) any situation of preexisting chronic diseases; and (5) refusal to sign the informed consent.

Definition

GDM was diagnosed using recommendations of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG), based on the result of a 75 g oral OGTT. Pregnant women who exhibited one or more markers of blood glucose levels higher than the cutoff values (fasting venous plasma glucose levels ≥ 5.1 mmol/L and/or 1 h glucose level ≥ 10.0 mmol/L and/or 2h glucose level ≥ 8.5 mmol/L) were diagnosed with GDM.

Fecal sample collection

Participants were asked to collect at least 250 mg of feces into a sterile test tube (PSP® Spin Stool DNA Plus Kit) with preservation solution at 24~28 and 34~38weeks. Researchers would instruct the subjects to store the samples in an environment of 4°C and send the samples to hospital within 24 hours. After that, researchers would store the samples at -80°C for DNA extraction.

Sequencing and analysis of 16S rRNA gene amplicon

DNA was extracted using a QIAamp Fast DNA Stool Mini Kit (Qiagen, Hilden, Germany). The V4 region of the 16S rRNA bacterial gene was amplified by PCR. A TruSeq® DNA PCR-free Sample Preparation Kit was used for library construction and the Illumina NovaSeq 6000 platform was used for sequencing. According to barcode sequence and the PCR amplification primer sequence, each sample data was separated from disembarkation data. After the amputation of barcode and primer sequences using FLASH (V1.2.7, http://ccb.jhu.edu/software/FLASH/) (21) to splice reads of each sample, the splicing sequence for the original tags data (raw tags). Raw tags obtained by splicing need to undergo strict filtering (22) to obtain the high-quality tag data (clean data). According to the QIIME (V1.9.1 http://qiime.org/scripts/split_libraries_fastq.html) (23) tags quality control process, the procedures were as follows: (a) tags to intercept: The raw tags were truncated from the first low-quality base site whose number of consecutive low-quality values (default quality threshold ≤ 19) reached the set length (default length value 3). (b) Tags length filtering: Tags data set obtained by intercepting tags were filtered out tags whose continuous high-quality base length was less than 75% of the length of tags. The tags obtained after the above processing need to be processed to remove the chimeric sequence. The Tags sequence (24) shall be compared with the series annotation database to detect the chimeric sequence, and finally remove the chimeric sequence. Using Uparse software (Uparse v7.0.1001, http://www.drive5.com/uparse/) (25) to cluster all effective tags of all samples. By default, sequences are grouped into operational taxonomic units (OTU) with 97% identification. According to the algorithm principle, the sequences with the highest frequency among OTUs were selected as representative sequences of OTUs. OTU annotation analysis was performed using the Mothur (26) and SSUrRNA databases of SILVA132 (27) (threshold 0.8–1). The Shannon and Simpson indices were calculated using QIIME (version 1.9.1). Beta diversity was calculated using unweighted UniFrac with QIIME. Principal coordinate analysis (PCoA) was performed to obtain the principal coordinates and visualize the complex multidimensional data, and PCoA plots based on unweighted UniFrac distance analysis were used to evaluate beta diversity.

Statistical analyzes

All statistical analyzes were performed with IBM SPSS 25.0. Clinical baseline characteristics are presented as medians (interquartile range). Continuous variables not normally distributed were reported as medians (interquartile distance), and compared using the Wilcoxon test. The relative abundances of taxa at the phylum and genus levels were compared using the Wilcoxon test. A false discovery rate (FDR)- corrected $P < 0.05$ was considered statistically significant. All statistical analyzes were performed using two-sided tests.

Results

Clinical characteristics of the participants

The baseline characteristics of the women with GDM and pregnant women with normal glucose tolerance are summarized in Table 1. Fifty women with GDM and fifty controls were enrolled in this study. One person in the GDM group was excluded due to the use of antibiotic drugs. In the control group, two participants were excluded because they experienced serious obstetric complications during pregnancy, four used antibiotic drugs, and two were lost to follow-up (Figure 1). The final sample for analyzes included data from 49 women with GDM and 42 pregnant women with normal glucose tolerance. Fecal samples from all participants in the GDM group (n = 49) were collected in T2 (SGDM) and T3 (TGDM). In the control group, one stool sample in T2 and three stool samples in T3 were not received, and eventually 41 and 39 fecal samples were collected in T2 (SHC) and T3 (THC), respectively,.

Women with GDM were more likely to be older (33 (32–36.5) vs. 32 (29–34), P = 0.018) and deliver at lower gestational age (39 (38–39) vs. 39 (38–40), P = 0.006). Other clinical characteristics were not significantly different between the groups (Table 1).

Dynamics in intestinal microbiota in the GDM and control group from T2 to T3

From T2 to T3 in the GDM group, at the phylum level (Figure 2A), although not statistically significant, the relative abundances of > 1% of the dominant bacteria, *Firmicutes* (60.31% vs. 57.62%, P = 0.772), *Actinobacteria* (5.43% vs. 4.37%, P = 0.772), and *Proteobacteria* (3.47% vs. 3.27%, P = 0.772), showed a downward trend. *Bacteroides* (29.85% vs. 33.53%, P = 0.772)

TABLE 1 Comparison of clinical characteristics in the study groups.

Characteristic	GDM (n=49)	Health women (n=42)	*P* value
Age (year)	33 (32~36.5)	32 (29~34)	0.018*
Parity (number)	1 (1~2)	1 (1~2)	0.438
Pre-pregnancy BMI (kg/m^2)	22.46 (19.78 ~24.28)	21.05 (19.65~22.68)	0.112
Height(cm)	163.00 (160.00 ~167.00)	163 (162~166.5)	0.592
OGTT-0 hours	4.90 (4.50 ~ 5.25)	4.40 (4.18 ~ 4.60)	< 0.05
OGTT-1 hours	9.80 (8.85 ~ 10.70)	7.55 (6.38 ~8.45)	< 0.05
OGTT-2 hours	8.80 (7.45 ~ 9.40)	6.20 (5.40 ~ 7.23)	< 0.05
Pre-pregnancy Weight (kg)	58 (53.25~64.5)	56.5 (52.5~61.25)	0.217
Gestational week (weeks)	39 (38~39)	39 (38~40)	0.006*

Data presented as median (first quartile, third quartile).
GDM gestational diabetes mellitus, BMI body mass index.
*Statistically significant at P < 0.05.

showed an increasing trend (Supplement File 1). The same trend at the genus level (Figure 2B), among the top 10 dominant bacteria in the GDM group, although not statistically significant, the relative abundances of *Bacteroides* (20.18% vs. 22.68%, P = 0.791), *Faecalibacterium* (8.25% vs. 9.84%, P = 0.392), *unidentified_Lachnospiraceae* (4.88% vs 5.16%, P = 0.820), *Parabacteroides* (2.28% vs. 2.73%, P = 0.791) showed an increase from T2 to T3, whereas, the relative abundances of *unidentified_Ruminococcaceae* (4.86% vs. 3.54%, P = 0.392), *Blautia* (4.13% vs. 3.83%, P = 0.520), *Roseburia* (3.61% vs. 3.52%, P = 0.791), *Lachnospira* (3.90% vs. 2.89%, P = 0.502), *Bifidobacterium* (3.72% vs. 2.80%, P = 0.392), *Megamonas* (2.81%

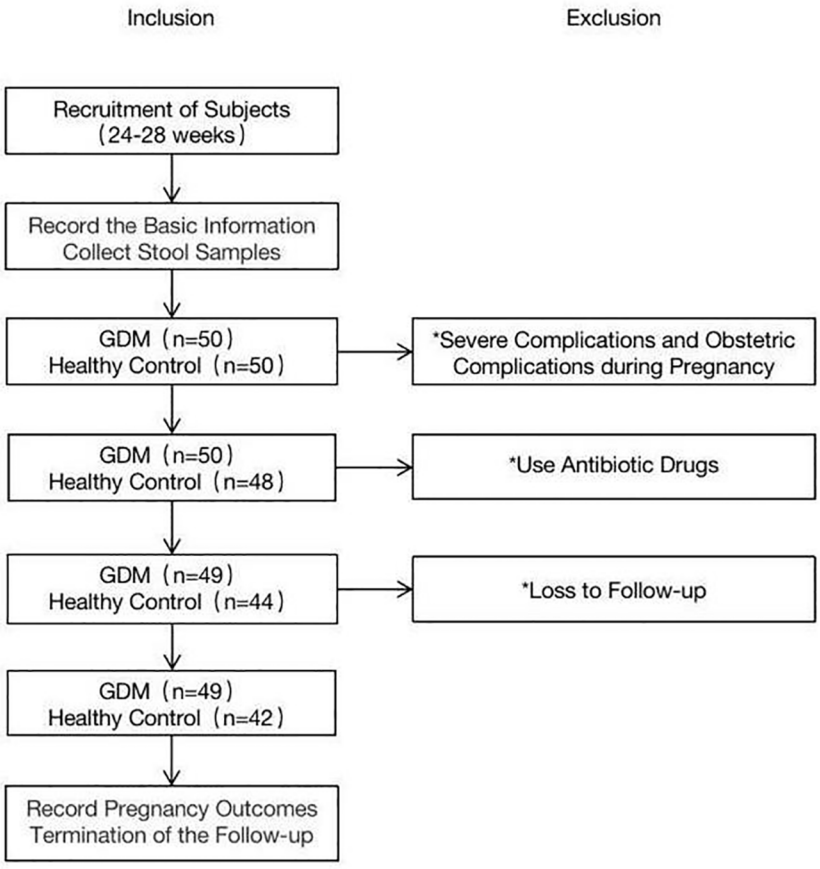

FIGURE 1
The flow chart of the study. * emphasis on exclusion.

vs. 1.30%, P = 0.502) showed a decrease from T2 to T3, as illustrated in Supplement File 2.

From T2 to T3 in the control group, at the phylum level (Figure 2A), although not statistically significant, the relative abundances of *Firmicutes* (47.84% vs. 49.46%, P = 0.969), *Bacteroides* (29.31% vs. 31.44%, P = 0.969), and *Proteobacteria* (5.35% vs. 5.38%, P = 0.915) showed an increasing trend. The relative abundance of *Actinobacteria* (16.59% vs. 12.63%, P = 0.946) showed a downward trend; however, the differences of other bacteria were not statistically significant (Supplement File 1). At the genus level (Figure 2B), among the top 10 dominant bacteria in the control group, *Bacteroides* (16.31% vs. 16.73%, P = 0.918), *Faecalibacterium* (7.62% vs. 9.70%, P = 0.734), *Bifidobacterium* (10.37% vs. 6.36%, P = 0.637), *Collinsella* (5.52% vs. 5.05%, P = 0.611), *unidentified_Ruminococcaceae* (4.67% vs. 5.09%, P = 0.833), *Subdoligranulum* (3.19% vs. 3.55%, P = 0.611), *Roseburia* (2.90% vs. 3.20%, P = 0.918), *Lachnospira* (2.15% vs. 2.73%, P = 0.918), *Streptococcus* (2.81% vs. 2.02%, P = 0.820), and *unidentified_Lachnospiraceae* (2.54% vs. 2.10%, P = 0.637) (Supplement File 2) were both no significant differences from T2 to T3. The relative abundance of *Scardovia* (0 vs. 0.25%, P = 0.041) and *Propionibacterium* (0 vs. 0.29%, P = 0.041) in pregnant women with normal glucose tolerance was significantly higher in T3 than in T2 (Supplement File 2).

In T2, at the phylum level (Figure 2A), the relative abundance of *Firmicutes* in the GDM group was significantly higher than that in the control group (60.31% vs. 47.84%, P < 0.001), and the relative abundance of *Actinobacteria* in the GDM group was significantly lower than that in the control group (5.43% vs. 16.59%, P = 0.009). The abundance of other bacteria is described in Supplement File 1. At the genus level (Figure 2B), the relative abundances of *unidentified_Lachnospiraceaee* (4.88% vs. 2.55%, P < 0.001), *Roseburia* (3.61% vs. 2.90%, P = 0.041), *Lachnospira* (3.90% vs. 2.15%, P = 0.004), *Blautia* (4.13% vs. 2.76%, P = 0), and *Parabacteroides* (2.27% vs. 0.73%, P = 0) in the GDM group were higher than those in the control group. The relative abundance of *Bifidobacterium* in the GDM group was lower than that in the control group (3.72% vs. 10.37%, P = 0.012). The relative abundances of other bacteria were lower in the GDM group than in the control group (Supplement File 2).

In T3, at the phylum level (Figure 2A), the relative abundance of *Firmicutes* (57.62% vs. 49.46%, P = 0.044) in the GDM group was significantly higher than that in the control group. The relative abundance of *Actinobacteria* (4.37% vs. 12.63%, P = 0.007) in the GDM group was significantly lower than in the control group. The relative abundances of other bacteria are detailed in Supplement File 1. At the genus level (Figure 2B), the relative abundances of *unidentified_Lachnospiraceae* (5.16% vs. 2.11%, P = 0), *Blautia* (3.83% vs.1.46%, P = 0), *Parabacteroides* (2.73% vs. 1.18%, P = 0), and *Megamonas* (1.31% vs. 0.21%, P = 0.038) in the GDM group were significantly higher than those in the control group. The relative abundance of *Bifidobacterium* (2.80% vs. 6.36%, P = 0.022) in the GDM group was significantly lower than that in the control group (Supplement file 2). The relative abundances of other bacteria are detailed in Supplement File 2.

OTUs

Venn diagrams were drawn on the basis of the number of OTUs of samples in the GDM and control groups (Figure 3). As shown in the figure, in the GDM group, the total number of OTUs in T2 and T3 was 3412 and 3806, respectively. The number of common OTUs in T2 and T3 was 2447; the number of unique OTUs in T2 and T3 was 965 and 1359, respectively (Figure 3A). The number of unique OTUs in T2 represented 28.28% of the total OTUs in T2 and 35.71% of the total OTUs in T3. In the control group, the total number of OTUs in T2 and T3 was 4619 and 4618, respectively. The number of common OTUs in T2 and T3 was 2883, and the unique numbers of OTUs in T2 and T3 were 1736 and 1735, respectively (Figure 3B). Unique OTUs in T2 accounted for 37.58% of the total OTUs in T2 and 37.57% of the total OTUs in T3.

The alpha and beta diversity

In the GDM group, there was no significant differences in the Chao index (P=0.123) (Figure 4A) and ACE index (P=0.201) (Figure 4B) were observed from T2 to T3. The same trend in the

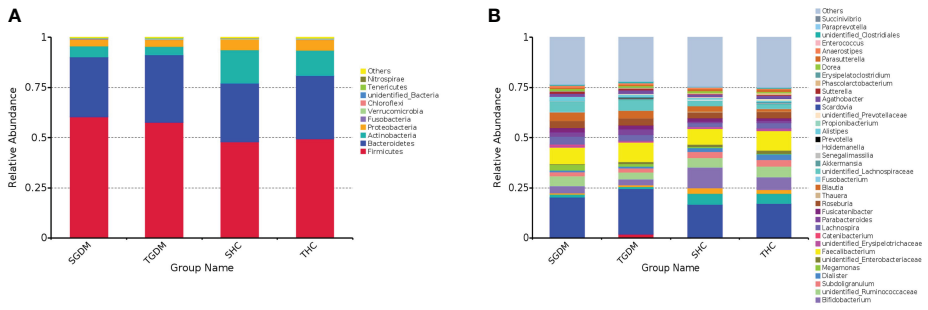

FIGURE 2
The dynamics in intestinal microbiota in the GDM and control group from T2 to T3 at the phylum and genus level. **(A)** Relative abundance of the top 10 bacterial taxa at the phylum level; **(B)** Relative abundance of the top 40 bacterial taxa at the level of bacterial. GDM, Gestational diabetes mellitus; T2, second trimester; T3, third trimester; SGDM, Second trimester in the GDM group; TGDM, Third trimester in the GDM; SHC, Second trimester in the control group; THC, Third trimester in the control group.

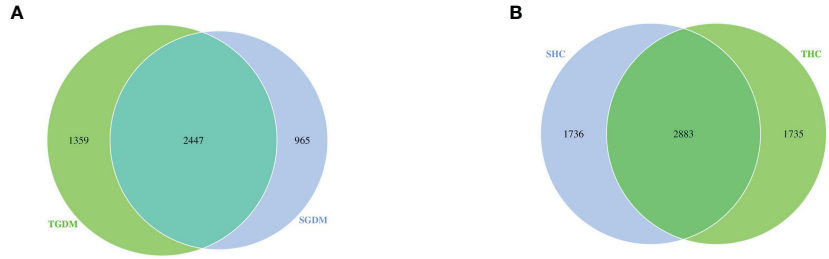

FIGURE 3
Venn diagram among the GDM and control groups. **(A)** The overlaps of OTUs in the GDM group. **(B)** The overlaps of OTUs in the control groups. GDM, Gestational diabetes mellitus; SGDM, Second trimester in the GDM group; TGDM, Third trimester in the GDM group; SHC, Second trimester in the control group; THC, Third trimester in the control group.

control group. In the GDM group, there was no significant difference in changes in the Shannon index (Figure 4C) (6.039 vs 5.822, P = 0.078) and the Simpson index (Figure 4D) was observed from T2 to T3 (0.953 vs 0.937, P = 0.177). The Shannon index (Figure 4C) (5.188 vs. 5.043, P=0.795) and the Simpson index (Figure 4D) (0.904 vs. 0.880, P = 0.824) in the control group from T2 to T3 were not statistically significant. The Shannon index in T2 (6.039 vs 5.188, P = 0) and T3 (5.822 vs 5.043, P = 0) in the GDM group were both significantly higher than those in the control group, and the Simpson index in T2 (0.953 vs. 0.904, P < 0.001) and T3 (0.937 vs. 0.880, P <.001) in the GDM group were both significantly higher than those in the control group.

PC1 was the main coordinate component that caused the largest difference in the samples, with an explanatory degree of 20.74%, followed by PC2, with an explanatory degree of 9.09% (Figure 5). According to the AMOVA analysis, there were no significant differences in the gut composition microbiota in T2 and T3 in the GDM (P = 0.265) and control groups (P = 0.593). However, there was a significant difference in the composition of the gut microbiota between the GDM and control groups (P < 0.001). The distribution of the intestinal microbiota in T2 and T3 was similar in the GDM and control groups; however, the distribution distance of the GDM group was relatively far compared to that of the control group.

Discussion

This study explored the composition of the intestinal microbiota and its alternative characteristics from T2 to T3 in women with GDM and pregnant women with normal glucose tolerance. The results showed that *Scardovia* and *Propionibacterium* were significantly higher in T3 than in T2 in the control group, but not in the GDM group. The changes in the relative abundance of the remaining bacteria from T2 to T3 were stable in the GDM and control

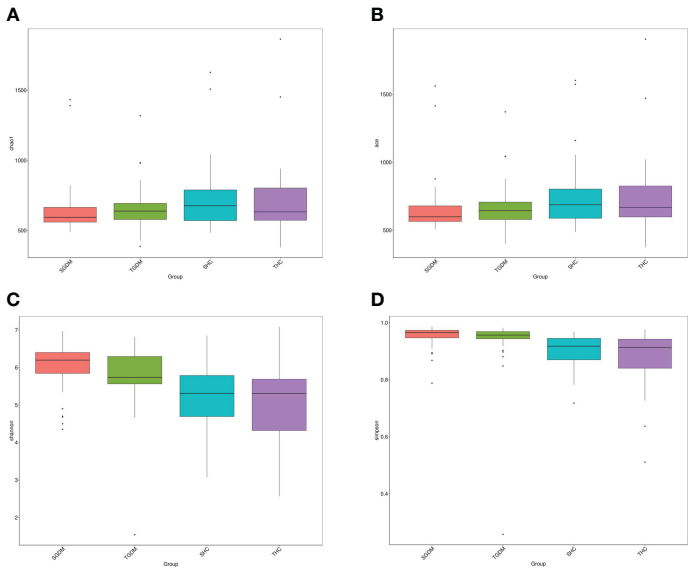

FIGURE 4
The alpha diversity of intestinal microbiota in the GDM and control groups. **(A)** Chao1 estimator, **(B)** abundance-based coverage estimator (ACE), **(C)** Shannon, **(D)** Simpson. GDM, Gestational diabetes mellitus. SGDM: Second trimester in the GDM group; TGDM, Third trimester in the GDM group; SHC, Second trimester in the control group; THC, Third trimester in the control group.

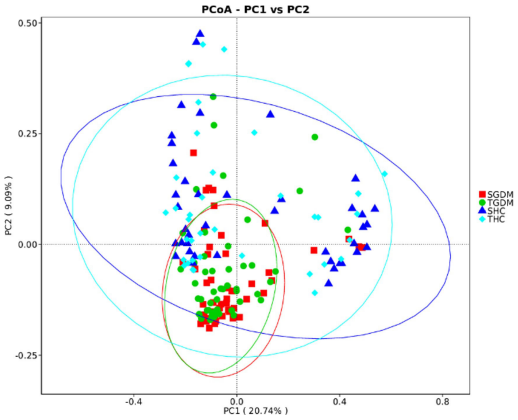

FIGURE 5
PCoA shows the dispersal of gut microbiota between trimesters in the GDM and healthy control groups. Red represents GDM samples in T2, green represents GDM samples in T3, dark blue represents samples of the control group in T2, and light blue represents samples of the control group in T3. SGDM, GDM group in the second trimester; TGDM, GDM group in the third trimester; SHC, control group in the second trimester; THC, control group in the third trimester; PCoA, Principal Coordinate Analysis. *P value < 0.05.

groups. Nevertheless, there were significant differences in the composition of the gut microbiota in the GDM and control groups in both T2 and T3.

We found that the dominant bacteria were composed of four phyla: *Firmicutes, Bacteroidetes, Proteobacteria*, and *Actinobacteria* at the phylum level in both the GDM and the control groups, which was consistent with the results of Tang et al. (28). Ma et al. (29) found that the four dominant phyla were *Firmicutes*, *Bacteroidetes, Proteobacteria*, and *Tenericutes*. *Actinobacteria* (30) act as markers of GDM and are positively correlated with fasting blood glucose levels; however, this association was not present after adjusting for pre-pregnancy body mass index (BMI). *Tenericutes* (31) are the dominant bacteria in the neonatal oral microbiota in babies of women with GDM. In our study, the relative abundance of *Tenericutes* was less than 1%, which may be explained by the type of samples studied and sample size. At the genus level, *Bacteroides, Faecalibacterium, unidentified_Lachnospiraceae*, *unidentified_Ruminococcaceae, Roseburia*, *Lachnospira*, and *Bifidobacterium* were the dominant bacteria in both the GDM and control groups. *Blautia, Parabacteroides*, and *Megamonas* were the dominant bacteria in the GDM group, while *Collinsella, Subdoligranulum*, and *Streptococcus* were the dominant bacteria in the control group.These GDM-enriched genus may participate in the development of GDM by influencing host immune status. *Blautia* (32), which is significantly associated with host dysfunctions, such as obesity, diabetes, and various inflammatory diseases, is a genus of biotransformative bacteria with probiotic properties that can regulate host health and alleviate metabolic syndrome. *Parabacteroides* are enriched in overweight women (30) and in women with GDM (18), which is consistent with our findings. *Megamonas* is enriched in obese women (16, 18) and has a positive relationship with glucose tolerance (18). *Megamonas* was the dominant bacterium specific to women with GDM; however, women with GDM were not classified by pre-pregnancy weight class in our study. Women with a history of GDM have a high abundance of *Collinsella* in their postpartum gut microbiota, and *Collinsella* has the potential to be a marker for the future development of type 2 diabetes in women with a history of GDM (30). However, previous studies have reported that *Collinsella* increases in healthy pregnancies (33, 34). In the present study, the relative abundance of *Collinsella* was higher in the control group. This difference may need the studies that enroll more subjects to explain. *Subdoligranulum*, which produces short-chain fatty acids such as butyrate, is negatively associated with human fat accumulation, insulin resistance, insulin, CRP, IL6, and other markers (35). A study (36) found that the relative abundance of *Streptococcus* in overweight, obese, and diabetic patients was lower than that of healthy controls, and Hajifaraji et al. (37) found that the combination of *Streptococcus* with other probiotics had a positive outcome in the treatment of metabolic diseases.

In our study, we found that the composition of the intestinal microbiota in the GDM and pregnant women with normal glucose tolerance was relatively stable from T2 to T3. Only the relative abundance of *Scardovia* and *Propionibacterium* in T3 was significantly higher than in T2 in pregnant women with normal glucose tolerance. Members of *Scardovia* are one of the seven genera of the *Bifidobacteriaceae* family and recognized as the healthy gut microbiota (38). *Scardovia* can produce acetic acid from glucose, together with small amounts of lactic and formic acid (39). It is reported that *Propionibacterium* can ameliorate insulin resistance by obesity (40).Insulin resistance, which is emphasized in the development of GDM in the late pregnancy, is associated with a reduced abundance of butyrate-producing bacteria (41–43). Ferrocino et al. found that an increase in *Firmicutes* and a reduction in *Bacteroidetes* and *Actinobacteria* from T2 to T3 in women with GDM who adhered to dietary recommendations showed a better metabolic and inflammatory pattern at the end of the study and a clear decrease in *Bacteroidetes* (44). We found that at the phylum level, the *Firmicutes*/*Bacteroidetes* ratio both decreased in the GDM group and control group from T2 to T3. The increased *Firmicutes*/*Bacteroidetes* ratio is associated with obesity and inflammation (45), and the decreased *Firmicutes*/*Bacteroidetes* ratio in our study may be related to factors such as

dietary modifications. However, Sun et al. (17) found a phenomenon that with advancing gestation, decreasing trends in the *Firmicutes*/*Bacteroides* ratio were observed in the control group but not in the GDM group. In addition, they also found that time-dependent alterations in gut microbiota composition were found in the control group but not in the GDM group. Compared to women with normal glucose, women with GDM tended to have a reduced intestinal microbiota diversity in the first trimester, while differences in intestinal microbiota composition were consistent in T2 and T3. Our research does not observe the composition of the gut microbiota in the first trimester and our study also observed the stable composition of the gut microbial in T2 and T3 in women with GDM. Women who develop GDM may have alterations in intestinal microbial composition from early pregnancy, explained by metabolic status. *Bacteroides*, a Gram-negative bacterium, can produce large amounts of LPS, leading to inflammation. LPS mainly activates inflammation via the Toll-like receptor 4 signaling pathway (46). From the first to the third trimester, women gain adiposity and have higher circulating levels of insulin (9). In women with GDM, two main inflammatory pathways, nuclear factor kappa B (NF-kB) and signal transducers and activators of the transcription 3 (STAT3) pathways, have been identified (13). The findings of this study provide evidence to explain the stable status of GDM.

In this study, the Shannon and Simpson indices of the GDM and healthy pregnancy groups both decreased from T2 to T3; however, the Shannon and Simpson indices of the GDM women were significantly higher than those of pregnant women with normal glucose tolerance. Our study was consistent with previous researches, showing the decreased microbial diversity with advancing gestation (9). This phenomenon might be due to the metabolic modifications occurring pregnancy, including changes of blood glucose and hormone. Higher α diversity values were associated with a lower incidence of type 2 diabetes, which was not affected by energy intake, exercise, education, smoking, or medication (47). Insulin resistance and elevated blood glucose levels can increase the risk of type 2 diabetes (48). With increasing gestational age, the level of insulin resistance increases to meet the nutritional supply of the mother and child (49). A lower Shannon index significantly correlated with blood glucose levels in patients with diabetes (19). The high Shannon and Simpson indices of the GDM group in this study could be explained by the inherent differences between the GDM and control groups. According to previous studies, β diversity is associated with insulin resistance and plasma OGTT levels (19, 47). Different methods to investigate beta diversity can influence the results. Unweighted UniFrac is sensitive to the absence and presence of low abundant bacteria, while both weighted Unifrac and Bray Cruits are more sensitive to the more abundant bacteria. In our study, unweighted Unifrac is used to investigate beta diversity. More methods should be used to claim beta diversity.

Our study explored the alterations of gut microbiota with the increasing gestational age in women with GDM and pregnant women with normal glucose tolerance. So far, few studies have explored the changes of intestinal microbiota composition in women with GDM during different trimesters. The longitudinal study will contribute to the understanding of the association between gut microbiota and GDM and provide the thinking way to predict the occurrence of GDM during early pregnancy. There are also some limitations in our study. First, this study was conducted at a single center with a limited sample size, and larger studies are needed in the future to verify the results of the study. Second, our study is an observational study and data may lack causality. There need more randomized control tests to research the association of dynamic gut microbiota composition between different trimesters in women with GDM. Third, lifestyle management is the first-line treatment for GDM but the diet patterns of the participants in this study were lack.

Conclusion

Our study indicated that the composition of the gut microbiota was stable with advancing gestation in women with GDM compared with the control group and gut microbiota composition was obviously different between women with GDM and controls. These findings may help explore the etiology of GDM from new perspective of the relationship between gut microbiota and glucose metabolism.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: [https://www.ncbi.nlm.nih.gov//PRJNA937449].

Ethics statement

The studies involving human participants were reviewed and approved by Peking Union Medical College Hospital (PUMCH). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study design: YS and LM. Sample and data collection: SZ and HL. Analysis and interpretation of data: NL and YW. Drafting the manuscript: NL. Critical revision of the manuscript for important intellectual content: YS. Statistical analysis: NL and YW. Obtained funding: LM. Study Supervision: YS and LM. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1126572/full#supplementary-material

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Association between the triglyceride to high-density lipoprotein cholesterol ratio and the risk of gestational diabetes mellitus: a second analysis based on data from a prospective cohort study

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Background: Although there is strong evidence linking triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio to insulin resistance and diabetes mellitus, its clinical importance in pregnant women has not been well determined. This study sought to determine the connection between the TG/HDL-C ratio in the first trimester and the eventual onset of gestational diabetes mellitus (GDM).

Methods: We performed a secondary analysis of open-access data from a prospective cohort study. This present study included 590 singleton pregnant women at 10-14 weeks who visited the outpatient clinics for prenatal checks and were recorded at Incheon Seoul Women's Hospital and Seoul Metropolitan Government Seoul National University Boramae Medical Center in Korea. A binary logistic regression model, a series of sensitivity analyses, and subgroup analysis were used to examine the relationship between TG/HDL-C ratio and incident GDM. A receiver operating characteristic (ROC) analysis was also conducted to assess the ability of the TG/HDL-C ratio to predict GDM.

Results: The mean age of the included individuals was 32.06 ± 3.80 years old. The mean TG/HDL-C ratio was 1.96 ± 1.09. The incidence rate of GDM was 6.27%. After adjustment for potentially confounding variables, TG/HDL-C ratio was positively associated with incident GDM (OR=1.77, 95%CI: 1.32-2.38, P=0.0001). Sensitivity analyses and subgroup analysis demonstrated the validity of the relationship between the TG/HDL-C ratio and GDM. The TG/HDL-C ratio was a good predictor of GDM, with an area under the ROC curve of 0.7863 (95% CI: 0.7090-0.8637). The optimal TG/HDL-C ratio cut-off value for detecting GDM was 2.2684, with a sensitivity of 72.97% and specificity of 75.05%.

Conclusion: Our results demonstrate that the elevated TG/HDL-C ratio is related to incident GDM. The TG/HDL-C ratio at 10-14 weeks could help identify pregnant women at risk for GDM and may make it possible for them to receive early and effective treatment to improve their prognosis.

KEYWORDS

sensitivity analysis, logistic models, ROC curve, triglyceride to high-density lipoprotein cholesterol, diabetes, gestational

Introduction

The most common metabolic disorder during pregnancy is gestational diabetes mellitus (GDM), which is defined as diabetes found in the second or third trimester that was previously unknown (1). Aggravating physiological alterations in glucose metabolism during pregnancy may contribute to GDM. 15% to 22% of pregnancies globally are afflicted by it, and its occurrence is rising (2). As one of the most prevalent pregnancy medical complications, GDM raises the risk of pregnancy complications and unfavorable perinatal outcomes, including pregnancy-induced hypertension, abortion, preeclampsia, premature delivery, premature rupture of membranes, large-for-gestational-age infants, and others. Additionally, it raises the mother's chance of developing type 2 diabetes and affects the long-term metabolism of offspring (3, 4), posing a financial and public health burden.

It is a common phenomenon that maternal dyslipidemia during pregnancy is significantly higher than the physiological range (5). Hyperlipidemia is frequently found in the second half of pregnancy and is considered a biologically necessary mechanism to supply the fetus with fuel and nutrients (6). Early pregnancy causes a minor increase in lipid levels, whereas later pregnancy causes a considerable boost. Determining if a lipid rise is pathogenic or physiological might be challenging. The connection between lipid profiles and GDM is still up for debate. Although lipid levels during pregnancy have been extensively investigated, the findings are inconsistent (7). Some researchers confirm the significant increase in serum lipid profile, including concentrations of triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio and low-density lipoprotein cholesterol to high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio in mothers with GDM compared to healthy pregnancies (8, 9). However, some studies have reported no significant differences in serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and TG/HDL-C ratio between women with and without GDM (10, 11). Researchers have previously found a link between insulin resistance (IR), diabetes mellitus, and TG/HDL-C ratio (12, 13). However, few studies have also been done to determine whether TG/HDL-C ratio is linked to GDM and whether TG/HDL-C ratio in the first trimester can be used clinically to identify women at risk of GDM later. In the current study, we investigated whether early pregnancy TG/HDL-C ratio was associated with a later risk of developing gestational diabetes mellitus.

Abbreviations: TG/HDL-C ratio, triglyceride to high-density lipoprotein cholesterol ratio; GDM, gestational diabetes mellitus; ROC, receiver operating characteristic; LDL-C/HDL-C ratio, low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; GCT, glucose challenge screening test; BMI, body mass index; LDL-C, low-density lipid cholesterol; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment-insulin resistance; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; TC, total cholesterol; FPG, fasting plasma glucose; IR, insulin resistance; TG, triglycerides; GAM, Generalized additive models; AUC, area under the curve; OR, odds ratios; SD, standard deviation; CI, confidence interval.

Methods

Data source

We downloaded the raw data freely from (https://journals.plos.org/plosone), provided by Lee SM et al. (14). From: Nonalcoholic fatty liver disease is a risk factor for large-for-gestational-age birthweight. The Creative Commons Attribution License, which allows unrestricted use, distribution, and reproduction in any format as long as the original author and source are credited, was used to publish this open-access research.

Study population

The original study enrolled 663 singleton pregnant women presenting for prenatal care before 14 weeks of gestation at Incheon Seoul Women Hospital and Seoul Metropolitan Government Seoul National University Boramae Medical Center in Seoul, Korea from November 2014 to July 2016, from the ongoing 'Fatty Liver in Pregnancy' registry (ClinicalTrials.gov registration no. NCT02276144). Before enrollment, all participants provided written informed consent according to the original study (14). In a non-selective approach, the initial researchers gathered the subsequent cases. The initial researchers used untraceable codes to encrypt participant identity information to protect their privacy.

The Institutional Review Board of the Seoul Metropolitan Government Seoul National University Boramae Medical Center and the Public Institutional Review Board of the Ministry of Health and

Welfare of Korea approved the research ethics (14). Therefore, there was no need for ethical approval of this secondary analysis. Also, the Declaration of Helsinki was followed in conducting the initial study.

Patients who (1): had underlying chronic liver disease, high alcohol consumption, or pre-gestational diabetes (2); were lost to follow-up; or (3) had a premature birth before 34 weeks were omitted from the final analysis. Consequently, the initial study contained 623 participants. In our present study, we further excluded missing values of HDL-C (n=20), TG (n=20), and lack of information on GDM (n=13). Finally, the present study included 590 eligible participants (Figure 1).

Variables

TG/HDL-C ratio

At 10–14 weeks gestation, an automated analyzer was used to measure the levels of HDL-C and TG in venous blood after fasting

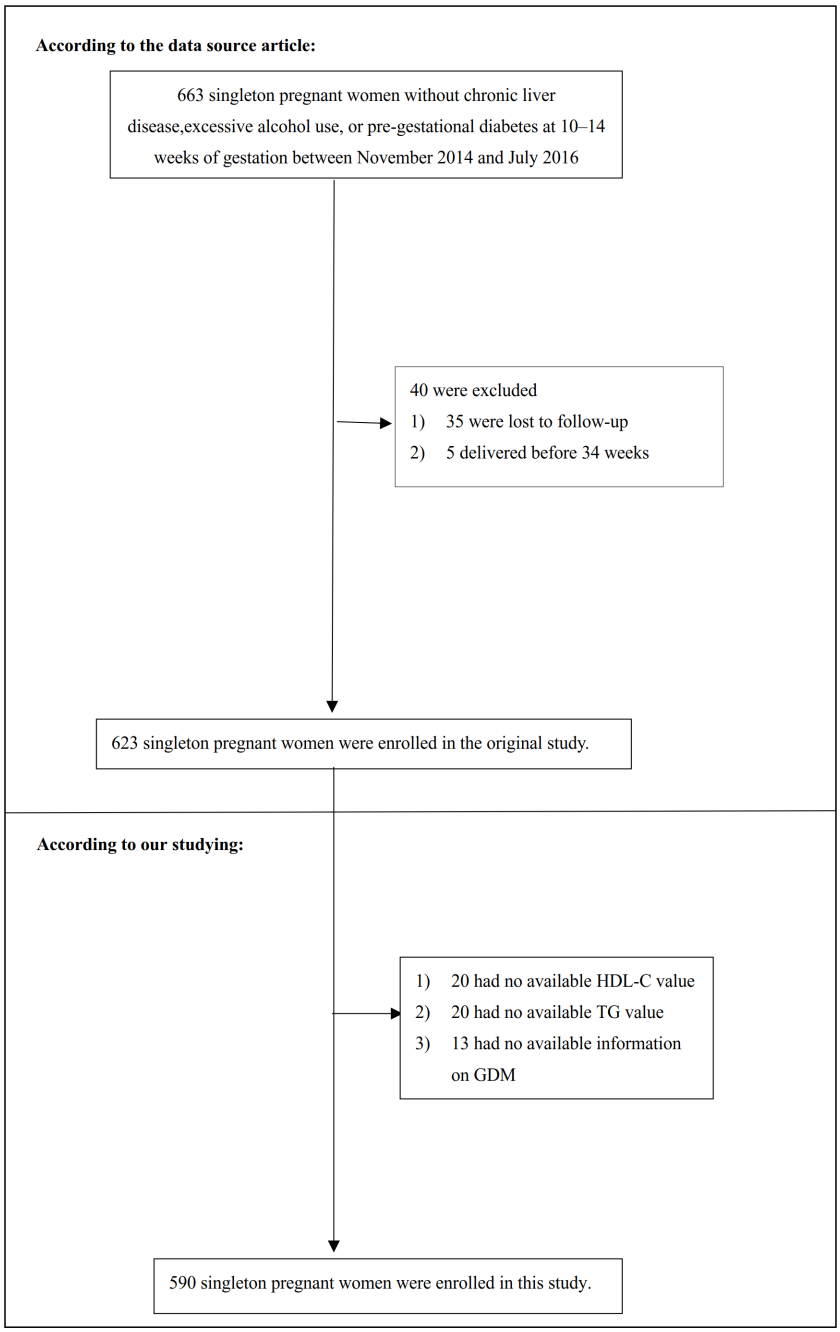

FIGURE 1
Flowchart of study participants. Figure 1 showed the inclusion of participants. 623 participants were assessed for eligibility in the original study. We excluded patients with missing values of HDL-C (n=20), TG (n=20), and lack of information on GDM (n=13). The final analysis included 590 subjects in the present study.

for at least 8 hours. [serum TG (mmol/L)]/[serum HDL-C (mmol/L)] was the formula used to calculate the TG/HDL-C ratio in detail.

Diagnosis of incident GDM

In accordance with the advice of the American College of Obstetricians and Gynecologists, all subjects were evaluated for the existence of GDM using the two-step method at 24-28 weeks (15). Serum glucose levels were assessed for the 50 g oral glucose challenge screening test (GCT) 1 hour following a 50 g oral glucose load in a non-fasting state. 7.8 mmol/l of serum glucose was considered to be a positive GCT. Those with a positive screening GCT underwent a follow-up 100 g oral glucose tolerance test. Two or more increased glucose levels-5.3 mmol/L for fasting glucose, 10 mmol/L for one hour, 8.6 mmol/L for two hours, and 7.8 mmol/L for three hours-were necessary for the diagnosis of GDM (16).

Covariates

The original study, our clinical experience, and previous studies on risk factors for GDM were all taken into consideration when choosing the variables for this investigation. Accordingly, the following variables were utilized as covariates based on the aforementioned concepts: (1) categorical variables: parity, hepatic steatosis; (2) continuous variables: age, pre-pregnancy body mass index (BMI), fasting plasma glucose (FPG), insulin, homeostasis model assessment-insulin resistance (HOMA-IR), alanine aminotransferase (ALT), adiponectin, aspartate aminotransferase (AST), TC, gamma-glutamyl transferase (GGT), LDL-C.

General clinical and demographic information was collected, including maternal age, parity, pre-gestational diabetes, a prior history of GDM, pre-gestational weight, height, alcohol consumption during pregnancy using the validated cut-annoyed-guilty-eye questionnaire, and a history of chronic liver diseases such as hepatitis B or hepatitis C, primary biliary cholangitis, autoimmune hepatitis, hemochromatosis, primary sclerosing cholangitis and Wilson's disease (14). At 10-14 weeks gestation, a venous blood sample was collected to measure hematological markers such as TC, TG, ALT, AST, GGT, FPG, insulin, and adiponectin after fasting for at least 8 hours. [FPG (mmol/L)×insulin (μIU/mL)/22.5] was the formula used to calculate HOMA-IR in detail (17). As in previous studies, a semiquantitative grading system (grades 0-3) was used to determine the severity of hepatic steatosis (18).

Statistical analysis

We first observed the distribution of baseline data based on tertiles of the TG/HDL-C ratio. The mean and standard deviation (SD) or median and quartile ranges (25th-75th percentile) were displayed for continuous variables, while frequencies and percentages were used to represent categorical variables. To examine differences between TG/HDL-C ratio groups, the one-way ANOVA, Kruskal Wallis H test, and the chi-square test were used. Incidence rates were expressed in cumulative incidence (19).

We created three models using univariate and multivariate logistic regression, including a non-adjusted model (Crude model: no covariates were adjusted), a model with minimal adjustments (Model I: only sociodemographic variables, such as age, pre-pregnancy BMI, and parity were adjusted), and a model with complete adjustments (Model II: covariates presented in Table 1 were adjusted, including age, pre-pregnancy BMI, parity, hepatic steatosis, AST, GGT, ALT, TC, LDL-C, HOMA-IR, and adiponectin). Adjusted odds ratios (OR) with a 95% confidence interval (CI) were estimated to evaluate the risk of GDM. The OR changed by at least 10% after the covariance was included in the model; hence, the covariance should be adjusted (20).

We conducted a number of sensitivity analyses to evaluate how reliable our findings were. To test the results of the TG/HDL-C ratio as a continuous variable and investigate the likelihood of non-linearity, we turned the TG/HDL-C ratio into a categorical variable based on the tertile and calculated the P for the trend. Obese and nonalcoholic fatty liver disease was linked to a higher incidence of GDM (19, 21). To investigate the link between the TG/HDL-C ratio and GDM risk, we thus excluded people with pre-pregnancy BMI≥24kg/m^2 or nonalcoholic fatty liver disease (grade of hepatic steatosis>0) in other sensitivity analyses. Besides, to ensure the robustness of the findings, we additionally added the continuity covariate as a curve to the equation (Model III) using a generalized additive model (GAM) (22). Further, by computing E-values, we investigated the possibility of unmeasured confounding between TG/HDL-C and GDM risk (23).

A stratified logistic regression model was used for the subgroup analysis across multiple subgroups (age, pre-pregnancy BMI, parity, hepatic steatosis, HOMA-IR). Firstly, continuous variable age (<35, ≥35 years) (24), pre-pregnancy BMI (<24, ≥24 kg/m2) (25), HOMA-IR FPG(≤2, >2) (26) were converted to a categorical variable based on the clinical cut point. Secondly, in addition to the stratification factor itself, we adjusted each stratification for all factors (age, pre-pregnancy BMI, parity, hepatic steatosis, AST, GGT, ALT, TC, LDL-C, HOMA-IR, adiponectin). Lastly, the likelihood ratio test of models with and without interaction terms was used to test for interactions (27).

Furthermore, we conducted receiver operating characteristic (ROC) analysis to evaluate the predictive ability of the TG/HDL-C ratio to GDM. We then calculated the area under the curve (AUC) of the ROC and the best cut-off point.

We used PASS15.0 for the sample size calculation. The sample size is calculated with reference to the preliminary study and based on the parameters, including power, Alpha, incidence rate, and odds ratios (28). The final sample size was calculated to require at least 106 cases. And a total of 590 participants were included in this study, which could satisfy the sample size requirement.

All the analyses in our study were performed with the statistical software package R (http://www.R-project.org, The R Foundation) and Empower-Stats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Characteristics of participants

In this study, 590 women without pre-gestational diabetes were enrolled. The average age was 32.06 ± 3.80 years. 37 women (6.27%) developed GDM at 24-28 weeks of gestation.

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TABLE 1 The Baseline Characteristics of participants.

TG/HDL-C ratio	T1(≤1.41)	T2(1.41 to ≤2.11)	T3(>2.11)	P-value
Participants	197	196	197	
Age(years)	31.55 ± 3.56	32.46 ± 3.56	32.18 ± 4.19	0.051
Pre-pregnancy BMI (kg/m^2)	21.24 ± 2.96	22.05 ± 3.56	22.82 ± 3.77	<0.001
Parity				0.050
No	117 (59.39%)	93 (47.45%)	100 (50.76%)	
Yes	80 (40.61%)	103 (52.55%)	97 (49.24%)	
Hepatic steatosis				<0.001
Grade 0	173 (87.82%)	167 (85.20%)	139 (70.56%)	
Grade 1	23 (11.68%)	23 (11.73%)	39 (19.80%)	
Grade 2	1 (0.51%)	4 (2.04%)	13 (6.60%)	
Grade 3	0 (0.00%)	2 (1.02%)	6 (3.05%)	
HDL-C (mg/dL)	74.09 ± 11.78	64.84 ± 10.90	55.82 ± 11.22	<0.001
TG (mg/dL)	81.88 ± 19.20	110.81 ± 21.68	164.24 ± 49.37	<0.001
TC (mg/dL)	171.14 ± 26.68	172.08 ± 26.35	175.36 ± 28.46	0.271
LDL-C (mg/dL)	80.68 ± 21.20	85.09 ± 20.06	86.31 ± 23.61	0.026
ALT (IU/L)	11 (8-14)	11 (8-15)	12 (8-18)	<0.001
AST (IU/L)	16 (14-18)	16 (14-19)	17 (14-21)	0.036
GGT(IU/L)	11 (9-14)	12 (10-15)	13 (10-17)	0.022
FPG ((mg/dL)	76.93 ± 10.25	76.88 ± 8.59	77.29 ± 10.29	0.903
Insulin (μIU/mL)	6.40 (4.27-9.53)	7.90 (5.50-10.90)	10.70 (7.50-15.30)	<0.001
HOMA-IR	1.59 ± 2.42	1.74 ± 1.13	2.34 ± 1.48	<0.001
Adiponectin (ng/mL)	7602.06 ± 4979.12	6234.51 ± 3705.93	4337.39 ± 3374.96	<0.001
TG/HDL-C ratio	1.11 ± 0.22	1.71 ± 0.20	3.05 ± 1.23	<0.001

Values were n(%) or mean ± SD or or median (quartile).
TG/HDL-C ratio, triglyceride to high-density lipoprotein cholesterol ratio; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipid cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance.

Table 1 presents the baseline characteristics of the population. The TG/HDL-C ratio was divided into three groups according to the tertiles (T1 ≤ 1.41; 1.41<T2 ≤2.11; T3>2.11). We found that in the T3 group, participants generally had higher levels of pre-pregnancy BMI, LDL-C, TG, ALT, GGT, AST, insulin, HOMA-IR, and higher rates of grade 3 hepatic steatosis. In contrast, participants in the T3 group had lower levels of HDL-C and Adiponectin.

The incidence rate of GDM

Table 2 displays the cumulative incidence rate of GDM. The cumulative incidence rate of GDM in the overall women and three TG/HDL-C ratio groups were specifically 6.27% (4.31%-8.23%), 1.52% (0.20%-3.25%), 3.57% (0.95%-6.19%), and 13.71% (8.86%-18.55%). Compared with the T1 group, participants in T3 had a higher incidence rate of GDM (P<0.001 for trend).

The results of univariate analyses using a binary logistic regression model

The results of the univariate analysis were shown in Table 3. The univariate analysis showed that pre-pregnancy BMI, grade of liver steatosis, TG, ALT, GGT, FPG, insulin, HOMA-IR, and TG/HDL-C ratio were positively associated with incident GDM. We also found that HDL-C was inversely associated with incident GDM.

The results of multivariate analyses using the binary logistic regression model

Table 4 showed that the binary logistic regression model was used to evaluate the association between TG/HDL-C ratio and incident GDM. In the non-adjusted model (Crude model), TG/HDL-C ratio showed a positive association with incident GDM (OR: 2.24, 95%: 1.68-

TABLE 2 Incidence rate of incident gestational diabetes mellitus.

TG/HDL-C ratio	Participants(n)	GDM events(n)	Cumulative incidence rate (95% CI) (%)
Total	590	37	6.27 (4.31-8.23)
T1	197	3	1.52 (0.20-3.25)
T2	196	7	3.57 (0.95-6.19)
T3	197	27	13.71 (8.86-18.55)
P for trend			<0.001

TG/HDL-C ratio, triglyceride to high-density lipoprotein cholesterol ratio; CI, confidence interval; GDM, gestational diabetes mellitus.

2.98, P <0.0001). When only demographic factors were taken into account in the minimally-adjusted model (Model I), the risk of GDM increased by 1.10 times for every additional unit of the TG/HDL-C ratio (OR= 2.10, 95%: 1.55-2.85, P <0.0001). In the fully-adjusted model (Model II), each additional unit of TG/HDL-C ratio was accompanied by a 77% increase in GDM risk (OR=1.77, 95%CI: 1.32-2.38, P=0.0001). The results were statistically significant.

Sensitive analysis

We used a number of sensitivity analyses to evaluate the robustness of our findings. We treated the TG/HDL-C ratio as a categorical variable and then reintroduced the categorical-transformed TG/HDL-C ratio into the model. After transforming the TG/HDL-C ratio into a categorical variable, the results showed

TABLE 3 The results of the univariate analysis.

	Statistics	OR (95% CI)	*P* value
Participants			
Age (years)	32.06 ± 3.80	1.04 (0.95, 1.13)	0.4304
Pre-pregnancy BMI (kg/m^2)	22.03 ± 3.50	1.28 (1.18, 1.39)	<0.0001
Parity			
No	310 (52.54%)	ref	
Yes	280 (47.46%)	1.05 (0.54, 2.05)	0.8809
Hepatic steatosis			
Grade 0	479 (81.19%)	ref	
Grade 1	85 (14.41%)	3.43 (1.46, 8.03)	0.0046
Grade 2	18 (3.05%)	28.94 (10.13, 82.68)	<0.0001
Grade 3	8 (1.36%)	17.36 (3.81, 79.04)	0.0002
HDL-C (mg/dL)	64.91 ± 13.54	0.97 (0.94, 0.99)	0.0094
TG (mg/dL)	118.99 ± 47.51	1.02 (1.01, 1.03)	<0.0001
TC (mg/dL)	172.86 ± 27.19	1.01 (1.00, 1.02)	0.0645
LDL-C (mg/dL)	84.03 ± 21.77	1.00 (0.99, 1.02)	0.9387
ALT (IU/L)	13.42 ± 9.58	1.04 (1.01, 1.06)	0.0017
AST (IU/L)	17.82 ± 8.10	1.02 (0.99, 1.05)	0.1354
GGT(IU/L)	14.04 ± 8.64	1.04 (1.01, 1.07)	0.0020
FPG ((mg/dL)	77.03 ± 9.73	1.07 (1.04, 1.10)	<0.0001
Insulin (μIU/mL)	9.56 ± 6.67	1.12 (1.07, 1.17)	<0.0001
HOMA-IR	1.89 ± 1.79	1.48 (1.22, 1.78)	<0.0001
Adiponectin (ng/mL)	6057.69 ± 4287.78	1.00 (1.00, 1.00)	<0.0001
TG/HDL-C ratio	1.96 ± 1.09	2.24 (1.68, 2.98)	<0.0001

Values are n(%) or mean ± SD.
TG/HDL-C ratio, triglyceride to high-density lipoprotein cholesterol ratio; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipid cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance.

that the trends in effect sizes (OR) between groups were equidistant. P for the trend matched the findings when TG/HDL-C ratio was continuous. Moreover, a GAM added the continuity covariate to the equation. We discovered that the GAM model's results aligned with the fully adjusted model (OR=1.85, 95%CI: 1.35-2.52, P=0.0001) (Table 4). Besides, this study also produced E-values to assess the influence of possible unmeasured confounding between the TG/HDL-C ratio and GDM risk. The E value for this study was 2.94. The E-value was higher than the relative risk of TG/HDL-C ratio and unmeasured confounders, indicating that the association between TG/HDL-C ratio and incident GDM was not significantly affected by unmeasured or unknown confounders.

In addition, we performed other sensitivity analyses on individuals with BMI<24kg/m^2. There was also a positive relationship between the TG/HDL-C ratio and GDM risk after adjusting for confounding covariates (OR=1.88, 95%CI: 1.26-2.81) (Table 5). Moreover, we included individuals with grade 0 hepatic steatosis for other sensitivity analyses. The findings revealed that the TG/HDL-C ratio remained positively linked with the risk of GDM after adjusting for age, pre-pregnancy BMI, parity, AST, GGT, ALT, TC, LDL-C, HOMA-IR, adiponectin (OR= 2.06, 95%CI: 1.34-3.16) (Table 5). The sensitivity analysis suggested that our results were well-robust.

The results of the subgroup analysis

Subgroup analysis was used to identify potential confounding factors that could have impacted the relationship between TG/HDL-C and the incident GDM (Table 6). Age, pre-pregnancy BMI, parity, hepatic steatosis, and HOMA-IR were chosen as stratification variables. The potential confounding variables mentioned above did not affect the relationship between TG/HDL-C ratio and GDM risk. The subgroup analysis showed that our results were well-robust.

ROC analysis

ROC analysis was further conducted to explore the ability of the TG/HDL-C ratio to predict GDM. The results showed that the AUC of the TG/HDL-C ratio was 0.7863 (95%CI: 0.7090-0.8637) (Table 7 and Figure 2). Compared to TG, HDL-C, TC, LDL-C, FPG, adiponectin, and HOMA-IR, the AUC of the TG/HDL-C ratio was predicted to be higher for DM. Youden's index determined that 2.2684 was the optimal cut-off point for using the TG/HDL-C ratio to predict GDM, with matching specificity and sensitivity values of 75.05 and 72.97%.

TABLE 4 Relationship between TG/HDL-C ratio and the incident GDM in different models.

Variable	Crude model (OR.,95% CI, P)	Model I (OR,95% CI, P)	Model II (OR,95% CI, P)	Model III (OR,95% CI, P)
TG/HDL-C ratio	2.24 (1.68, 2.98) <0.0001	2.10 (1.55, 2.85) <0.0001	1.77 (1.32, 2.38) 0.0001	1.85 (1.35, 2.52) 0.0001
TG/HDL-C ratio (tertile)				
Q1	Ref.	Ref.	Ref.	Ref.
Q2	2.40 (0.61, 9.40) 0.2104	1.86 (0.45, 7.64) 0.3922	2.00 (0.41, 9.71) 0.3902	1.41 (0.27, 7.35) 0.6849
Q3	10.27 (3.06, 34.44) 0.0002	7.54 (2.17, 26.23) 0.0015	4.38 (1.05, 18.29) 0.0429	4.75 (1.12, 20.07) 0.0341
P for trend	<0.0001	0.0001	0.0202	0.0108

Crude model: we did not adjust other covariants.
Model I: we adjusted age, pre-pregnancy BMI, parity.
Model II: we adjusted age, pre-pregnancy BMI, parity, hepatic steatosis, AST, GGT, ALT, TC, LDL-C, HOMA-IR, adiponectin.
Model III: we adjusted age(smooth), pre-pregnancy BMI(smooth), parity, hepatic steatosis, AST(smooth), GGT(smooth), ALT(smooth), TC(smooth), LDL-C(smooth), HOMA-IR(smooth), adiponectin(smooth).
HR, Hazard ratios; CI: confidence, Ref: reference; eGFR, evaluated glomerular filtration rate(mL/min·1.73 m2); NAFLD, non-alcoholic fatty liver disease.
OR, odds ratios; CI, confidence interval; Ref, Reference; TG/HDL-C ratio, triglyceride to high-density lipoprotein cholesterol ratio.

TABLE 5 Relationship between the TG/HDL-C ratio and incident GDM in different sensitivity analyses.

Exposure	Model I (OR,95%CI, P)	Model II (OR,95%CI, P)
TG/HDL-C ratio	1.88 (1.26, 2.81) 0.0018	2.06 (1.34, 3.16) 0.0010
TG/HDL-C ratio (tertile)		
T1	Ref.	Ref.
T2	0.35 (0.03, 4.18) 0.4101	0.80 (0.11, 6.06) 0.8312
T3	2.32 (0.43, 12.45) 0.3265	4.92 (1.00, 24.23) 0.0504
P for trend	0.1785	0.0150

Model I was sensitivity analysis after excluding those with pre-pregnancy BMI≥24kg/m^2. We adjusted age, parity, hepatic steatosis, AST, GGT, ALT, TC, LDL-C, HOMA-IR, and adiponectin.
Model II was sensitivity analysis after including those with grade 0 hepatic steatosis. We adjusted age, pre-pregnancy BMI, parity, AST, GGT, ALT, TC, LDL-C, HOMA-IR, and adiponectin.
OR, odds ratios; CI, confidence; Ref, reference; TG/HDL-C ratio, triglyceride to high-density lipoprotein cholesterol ratio.

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TABLE 6 Effect size of TG/HDL-C ratio on GDM in prespecified and exploratory subgroups.

Characteristic	No of patients	Effect size(95%CI)	P value	P for interaction
Age (years)				0.7797
<35	453	1.96 (1.39, 2.75)	0.0001	
≥35	137	1.71 (0.70, 4.15)	0.2392	
Pre-pregnancy BMI (kg/m^2)				0.9792
<24	457	1.78 (1.20, 2.66)	0.0046	
≥24	132	1.80 (1.07, 3.02)	0.0266	
Parity				0.3199
No	310	1.99 (1.32, 3.02)	0.0011	
Yes	280	1.46 (0.93, 2.31)	0.1010	
Hepatic steatosis				0.3922
Grade 0	479	2.03 (1.32, 3.12)	0.0012	
Grade 1-3	111	1.54 (0.98, 2.42)	0.0599	
HOMA-IR				0.2712
≤2	388	1.24 (0.59, 2.59)	0.5647	
>2	201	1.94 (1.32, 2.86)	0.0007	

Note 1: Above model adjusted for we adjusted for age, pre-pregnancy BMI, parity, hepatic steatosis, AST, GGT, ALT, TC, LDL-C, HOMA-IR, and adiponectin.
Note 2: The model is not adjusted for the stratification variable in each case.

Discussion

In the present study, we investigated the association between the TG/HDL-C ratio and the risk of GDM in the Korean population. Our findings showed that TG/HDL-C ratio was positively correlated with the incident GDM. We also demonstrated that TG/HDL-C ratio could predict GDM accurately with an AUC of 0.7863 (0.7090-0.8637), and the optimal cut-off point of TG/HDL-C ratio for predicting GDM was 2.2684, with a sensitivity of 75.05% and specificity of 72.97%. The TG/HDL-C ratio was superior to TG, HDL-C, TC, LDL-C, and HOMA-IR for predicting GDM in the population. Thus, TG/HDL-C ratio could be an effective noninvasive method for predicting DM.

The incidence of GDM increased to 12.70% in the general Korean population in recent years (29). The incidence of GDM in the present study was 6.27%, lower than the reported level. Since this study excluded women with chronic liver disease, excessive alcohol consumption, or pre-gestational diabetes, which are risk factors for GDM (21). Therefore, the fact that research participants had a lower incidence of GDM than the general population was acceptable. It's important to note that the incidence of GDM was still 6.27% in this population. It is still essential to aggressively search for additional potential risk factors for GDM.

In pregnant women, particularly in GDM pregnancies, a higher blood level of TG is typical. This may be related to oxidative stress, insulin resistance, and a relative lack of insulin secretion (30).

TABLE 7 Areas under the Receiver operating characteristic curves for each evaluated parameters in identifying GDM.

Test	AUROC	95%CI	Best threshold	Specificity	Sensitivity	Youden Index
TG/HDL-C ratio	0.7863	0.7090-0.8637	2.2684	0.7505	0.7297	0.4802
TG	0.7837	0.7092-0.8582	121.5000	0.6420	0.8378	0.4798
HDL-C	0.5923	0.4869-0.6977	49.2000	0.8843	0.3514	0.2357
TC	0.5810	0.4826-0.6794	181.5000	0.6618	0.5135	0.1753
LDL-C	0.5000	0.3968-0.6032	105.5500	0.8517	0.2162	0.0679
FPG	0.6584	0.5545-0.7623	90.5000	0.9566	0.3056	0.2622
Insulin	0.7702	0.6826-0.8578	13.9000	0.8659	0.6216	0.4875
Adiponectin	0.8202	0.7516-0.8887	2973.8000	0.7740	0.7838	0.5578
HOMA-IR	0.7649	0.6788-0.8510	2.7500	0.8752	0.5833	0.4585

TG/HDL-C ratio, triglyceride to high-density lipoprotein cholesterol ratio; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipid cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; AUROC, Areas under the Receiver operating characteristic curves.

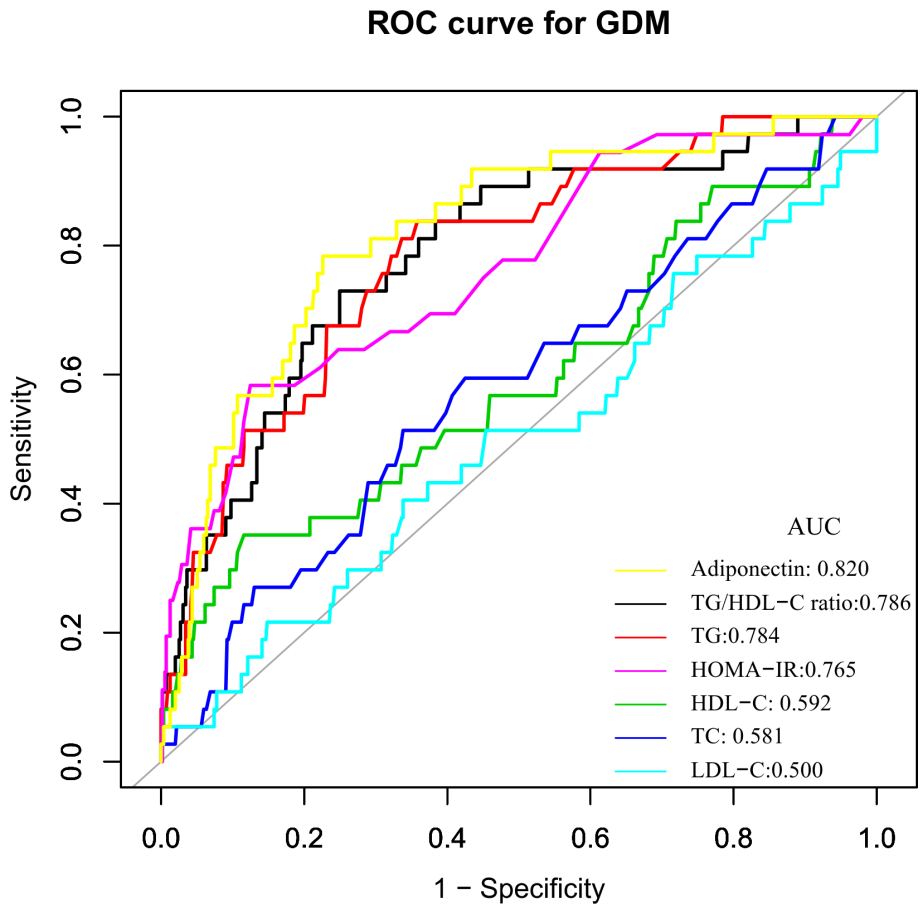

FIGURE 2
The TG/HDL-C ratio for predicting GDM in all participants by ROC analyses. ROC analysis was further conducted to explore the ability of the TG/HDL-C ratio to predict GDM. The results showed that the AUC of the TG/HDL-C ratio was 0.7863. Compared to TG, HDL-C, TC, LDL-C, FPG, insulin, and HOMA-IR, the AUC of the TG/HDL-C ratio for predicting DM was the highest.

According to some studies, hypertriglyceridemia, especially in the early stages of pregnancy, is linked to GDM and insulin resistance (31, 32). According to Enquobahrie et al. (33), the chance of developing GDM increases by 10% for every 20 mg/dl increase in TG concentration. Additionally, they showed that pregnant women with TG levels higher than 137 mg/dl had a 3.5-fold increased risk of having GDM (33). Furthermore, whether or not women have GDM, it has been demonstrated that the level of maternal TG has a solid and independent relationship with birth weight (34). The increased risk of macrosomia in pregnant women with hypertriglyceridemia has some pathophysiological causes. In the third trimester of pregnancy, there might be considerable variations in TG serum levels. Insulin sensitivity and lipoprotein lipase activity rise during the first trimester of pregnancy. In contrast, the third trimester of pregnancy sees a decrease in lipoprotein lipase activity due to an increase in insulin resistance. This condition is more common in GDM (35). Additionally, it has been found that a moderate increase in HDL-C concentration is a protective factor for GDM and that HDL-C levels in the blood are negatively correlated with GDM risk (36). Since TG/HDL-C ratio is an index that combines TG and HDL-C, it is related to GDM (37). In a prospective study involving 954 healthy pregnant women, after adjusting for age, history of diabetes in the first-degree family, and first trimester-body mass index, the relative risk of GDM in the top tertile of TG/HDL-C ratio was 3.87-folds of its risk in women in the bottom tertile (28). Another prospective study involving 202 healthy pregnant women found that the TG/HDL-C ratio was a risk factor for GDM when pregnant women were obese. When pregnant women are not obese, the TG/HDL-C ratio is not associated with GDM (38). Our study showed a positive association between TG/HDL-C ratio and GDM risk, which is consistent with previous studies. In addition, our research shows that compared with TG, HDL-C, TC, LDL-C, and HOMA-IR, TG/HDL-C ratio is the best predictor of GDM risk. At the same time, in the sensitivity analysis, we found that the relationship between TG/HDL-C ratio and GDM risk can still be detected in Korean women with BMI<24kg/m^2 or grade 0 hereditary steatosis. Compared with previous studies, our study included a different study population. In addition, we adjusted more covariates, such as hepatic steatosis, AST, GGT, ALT, TC, LDL-C, HOMA-IR, and adiponectin, which are all risk factors for GDM. More importantly, we used sensitivity and subgroup analysis methods to verify further the correlation between TG/HDL-C ratio and GDM. In short, our results further confirm the positive correlation between TG/HDL-C ratio and

GDM risk in participants with different BMI, age, and HOMA-IR levels. These efforts demonstrate the relationship's stability between the TG/HDL-C ratio and GDM risk. Therefore, this study further extends the application of the relationship between the TG/HDL-C ratio and GDM to the population. The results provide a reference for the clinical intervention of the TG/HDL-C ratio to reduce the risk of GDM. Therefore, this assay has excellent clinical value. The findings of this research should be conducive to future studies on establishing a predictive model of GDM risk.

According to Wang et al. (30), the area under the ROC curve for TG/HDL-C to detect GDM was 0.617 (95%CI: 0.548-0.686). With an AUC of 0.664 (0.595–0.733), TG/HDL-C was also found to potentially identify GDM risk in 352 Chinese women in single-center research (37). The logarithm of the TG/HDL-C ratio in early pregnancy has been proposed by Santos-Weis et al. as a valuable index to identify pregnant women with minimal risk of GDM before 24 weeks of gestation. In addition, our research shows that compared with TG, HDL-C, TC, LDL-C, FPG, and HOMA-IR, TG/HDL-C ratio is a better predictor of GDM risk. Clinical studies have revealed that hypoadiponectinemia is a risk factor of GDM (39, 40). Although the AUC was slightly larger for adiponectin than for TG/HDL-c in predicting GDM, the difference was not statistically significant (P=0.4931). Besides, after adjusting the HOMA-IR and adiponectin, we found that the TG/HDL-C ratio is still related to gestational diabetes. In addition, adiponectin is not routinely used in clinical practice to screen for GDM compared to lipids. Therefore, the use of TG/HDL-C for predicting the risk of GDM remains of general clinical value. Abnormal TG/HDL-C ratio can be a timely warning of GBM risk in clinical settings. Since 2.2684 is the best cut-off point for predicting GDM using the TG/HDL-C ratio, its corresponding specificity and sensitivity values were 75.05% and 72.97%, respectively. From a therapeutic perspective, it makes sense to maintain the TG/HDL-C ratio below the cut-off point.

The mechanism behind the association between the TG/HDL-C ratio and GDM is unknown, but IR may be involved. In pregnant women, elevated estrogen levels and insulin resistance can boost the liver's lipid synthesis (7). These modifications in fat metabolism point to a physiological change in pregnant women's bodies that prioritizes lipid metabolism over glucose metabolism. Pregnant women employ lipids as a source of energy to preserve glucose for the growth and development of the fetus. Bile acids, steroid hormones, and embryonic cell membranes can all be produced thanks to lipids (41). Early in pregnancy, there is an increase in the production of blood lipids and lipids, mainly triglycerides, which raises the blood levels of free fatty acids. High free fatty acids may impair insulin sensitivity (42), creating a vicious cycle between high TG levels and IR, which may lead to impaired glucose tolerance and the development of diabetes (43). Reduced insulin secretion, decreased insulin sensitivity, and reduced AMP-activated protein kinase activity are all possible effects of low HDL-C levels on glucose homeostasis (44–47). In addition, studies have shown that β-arrestin may be associated with metabolic disorders and may play a key role in the development of GDM (48). In addition, after adjusting the HOMA-IR, we found that the TG/HDL-C ratio is still related to gestational diabetes, indicating that the TG/HDL-C ratio may have other possible mechanisms to cause diabetes in addition to causing insulin resistance.

Our study has several following advantages. First, residual confounding factors were minimized by using strict statistical adjustments. Second, sensitivity analyses were conducted to ensure the robustness of the results. It included transforming the TG/HDL-C ratio into a categorical variable, using a GAM to insert the continuity covariate into the equation as a curve, and reanalyzing the association between the TG/HDL-C ratio and GDM after including participants with BMI<24kg/m^2 or grade 0 hereditary steatosis. Third, the present study conducted a subgroup analysis to assess other risk factors that might influence the connection between the TG/HDL-C ratio and GDM.

The present study does have certain restrictions. First, because the link between TG/HDL-C ratio and GDM may differ depending on ethnicity, the findings of our investigation should be verified in different ethnic groups. Second, because the present study is a secondary analysis, it is impossible to make adjustments for factors like uric acid, family history of diabetes, hypertension, and renal function that were not present in the initial dataset. The authors, however, determined that unmeasured confounders were unlikely to explain the data after calculating the E-value to assess the possible influence of unaccounted-for confounders. Third, the original study did not address preterm infants before 34 weeks and how TG and HDL-C fluctuate over time. Future designs of our investigation may include preterm infants before 34 weeks, capturing additional confounding variables and variations in TG and HDL-C during follow-up. We will also explore the external validity of our results in other populations.

Conclusion

In summary, the current study suggests that an elevated TG/HDL-C ratio has an independent and positive relationship with the risk of incident GDM and could be used as a predictor for GDM in the Korean population. Thus, the aberrant TG/HDL-C ratio facilitates the identification of Korean people at high risk of developing GDM. This would assist physicians in the early planning and implementation of care methods. The TG/HDL-C ratio may be an important routine screening test for gestational diabetes in pregnant women.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Seoul Metropolitan Government Seoul National University Boramae Medical Center and the Public Institutional Review Board of the Ministry of Health and

Welfare of Korea. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YY and HH contributed to the study concept and design, researched and interpreted the data, and drafted the manuscript. CC and YH analyzed the data and reviewed the manuscript. JT and HH oversaw the project's progress, contributed to the discussion and reviewed the manuscript. As guarantors, WZ, JT, and HH had full access to all study data and were responsible for its integrity and accuracy. All writers reviewed and approved the manuscript. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1153072/full#supplementary-material

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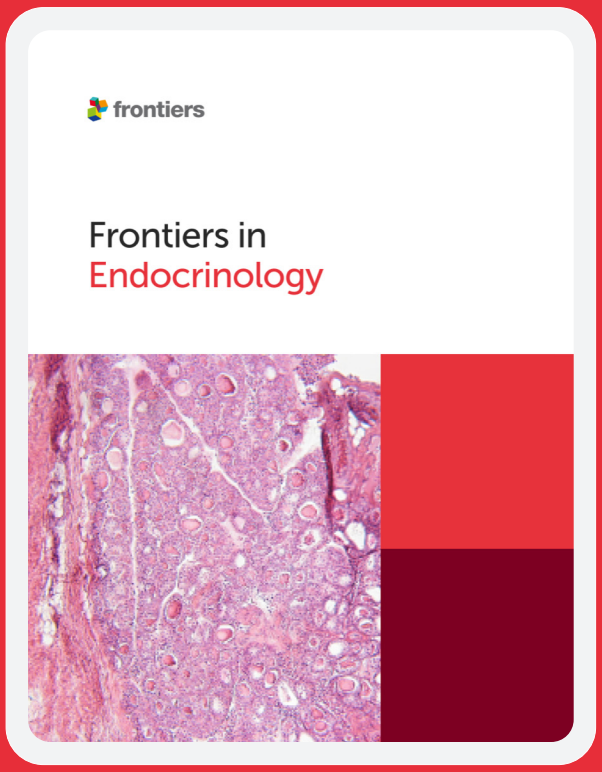

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