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Establishment of pregnancy-specific lipid reference intervals in pregnant women in a single-centre and assessment of the predictive value of early lipids for gestational diabetes mellitus: a prospective cohort study

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Abstract

Introduction: This study was aimed at establishing a pregnancy-specific lipid reference interval (RI) in pregnant women in a single-centre in the Beijing area of China, simultaneously exploring the predictive value of lipid levels in early pregnancy for gestational diabetes mellitus (GDM).

Material and methods: From October 2017 to August 2019, Peking University International Hospital established records for 1588 pregnant women, whose lipid profiles were determined during the first and third trimesters. The Hoffmann technique was used to calculate gestation-specific lipid RI. The 95% reference range for gestational lipids was also estimated for 509 healthy pregnant women screened according to the Clinical and Laboratory Standards Institute guideline. Multivariate logistic regression analysis was used to calculate odds ratios (OR) and their 95% confidence interval (CI), and the receiver operating characteristic (ROC) curve was applied to assess the predictive value of lipids in the first trimester for the diagnosis of GDM.

Results: Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were significantly higher in the third trimester ($p < 0.05$). Hoffmann technique RI of the lipid profiles and the 95% reference range of the lipid profiles in healthy pregnant women did not differ statistically ($p > 0.05$). TC, TG, and LDL-C levels were higher in the GDM group in the first trimester ($p < 0.05$), and the risk of GDM was 2.1 times higher in women with higher TG (95% CI: 1.13–3.77, $p < 0.05$). The optimal ROC cut-off for TG to predict GDM was 2.375 mmol / L, and the area under the ROC curve was 0.622 (95% CI: 0.592–0.751), with a sensitivity of 73.7% and a specificity of 59.3%.

Conclusions: This study established pregnancy-specific lipid RI for pregnant women in a single centre in the Beijing area of China. Pregnant women with TG ≥ 2.375 mmol/L in the first trimester were at significantly increased risk for GDM. **(Endokrynol Pol 2024; 75 (2): 192–198)**

Key words: *pregnancy; lipid profile; reference intervals; gestational diabetes mellitus; adverse pregnancy outcomes*

Introduction

Lipids maintain the essential requirements for critical energy and structural cellular components required for embryonic development [1, 2]. During pregnancy, maternal lipid levels undergo normal physiological upregulation to promote foetal growth and development [3]. In addition, multiple studies have demonstrated that aberrant lipid metabolism during pregnancy is linked to several unfavourable pregnancy outcomes, having an impact on the short- and long-term health of the mother and foetus [4–6]. However, there is no uniform standard for normal lipid ranges during pregnancy, both nationally and internationally, which can lead to the inability of clinicians to accurately identify abnormal lipid elevations and provide appropriate interventions promptly. Therefore, it is essential to establish a specific lipid reference interval (RI) during pregnancy.

Gestational diabetes mellitus (GDM) is the most common metabolic disorder in pregnancy, and its prevalence is increasing [7, 8]. Studies have reported that approximately 4–10% of pregnant women suffer from GDM [9], and a meta-analysis has shown that the prevalence of GDM in China is about 14.8% [10]. GDM is also an independent risk factor for the early onset of type 2 diabetes and cardiovascular disease [11]. There is evidence [12] that early exposure in utero to maternal hyperglycaemia already has an impact on foetal growth and development before the period when GDM is traditionally diagnosed (24–28 weeks). A hot area of the current study is how to recognise pregnant women who are at risk of GDM early on, identify their risk factors, and create early preventative

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and treatment plans for them [8, 13]. Few studies have analysed the risk of GDM in lipids in the first trimester of pregnancy.

In this project, we sought out healthy pregnant women and used the indirect Hoffmann technique to establish pregnancy-specific lipid reference intervals (RI) and determine the predictive value of first-trimester lipids for GDM.

Material and methods

Participants (see Figure 1)

This is a single-centre prospective cohort study carried out in the Beijing area of China. Between October 2017 and August 2019, 1588 pregnant patients at Peking University International Hospital were enrolled.

Inclusion criteria: (1) age ≥ 18 years; (2) gestation < 12 weeks; (3) pre-pregnancy weight ≥ 18 and < 28; and (4) regular maternity check-ups and delivery at our hospital. Exclusion criteria: (1) multiple pregnancies; (2) polycystic ovary syndrome (PCOS) co-morbidity; (3) disorders of the liver, kidney, heart, or lungs; (4) pre-pregnancy diabetes; (5) autoimmune diseases; (6) haematological diseases; and (7) tumours.

Meanwhile, 509 healthy pregnant women were screened according to the Clinical and Laboratory Standards Institute (CLSI) guideline C28-A3 [14].

Methods

Basic information (age, gestational week, parity, and medical history) were collected by trained researchers from medical records. Anthropometric assessments, including height and blood pressure, were performed on all subjects. Body mass index (BMI) was calculated by the formula: height (kg)/weight^2 (m^2).

Venous serum samples were collected at weeks 8 and 34 of pregnancy after fasting for 8 h. The following measurements were made: glycated haemoglobin (HbA_{1c}), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). The above tests were performed in the laboratory of the Department of Laboratory Medicine of Peking University International Hospital, which has been accredited by the China National Accreditation Committee.

The diagnostic criteria for GDM in this study were based on the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [15], whereby

an oral glucose tolerance test (OGTT) is done in the fasting state using 75 g of glucose at 24–28 weeks, and GDM is diagnosed if any one of the following cut-offs is met, i.e. fasting ≥ 92 mg/dL (≥ 5.1 mmol/L), one-hour ≥ 180 mg/dL (≥ 10 mmol/L), or 2-hour ≥ 153 mg/dL (≥ 8.5 mmol/L).

The Hoffmann technique [16] is a procedure for RI estimation using routine clinical results. The Hoffmann technique consists of tallying the full set of results into a set of ordered categories representing measurement ranges ("bins"), calculating the cumulative frequencies of the categories and converting them to percentages, and using a normal (Gaussian) probability paper to plot the cumulative percentages (on the y-axis with a Gaussian probability scale) against the measurement values corresponding to the category endpoints (on the x-axis with a linear scale). Hoffmann demonstrated that under these assumptions the result is a plot with 2 regions of approximate linearity corresponding to healthy and diseased subpopulations. By extrapolating the linear region for the healthy individuals to the horizontal lines representing the 2.5th and 97.5th percentiles, the estimated reference interval corresponding to the central 95% of the healthy subpopulation could be read from the x-axis.

Statistical analysis

Data were analysed using SPSS 26.0 software (provided by IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the normality of the data distribution. Normally distributed data were expressed using the mean ± standard deviation (x ± s), non-normally distributed data were expressed using the median (interquartile range), and categorical variables were expressed using absolute numbers and percentages.

We used the Hoffmann technique to estimate the RI of lipid profiles in all pregnant women (n = 1588). Meanwhile, the 95% reference

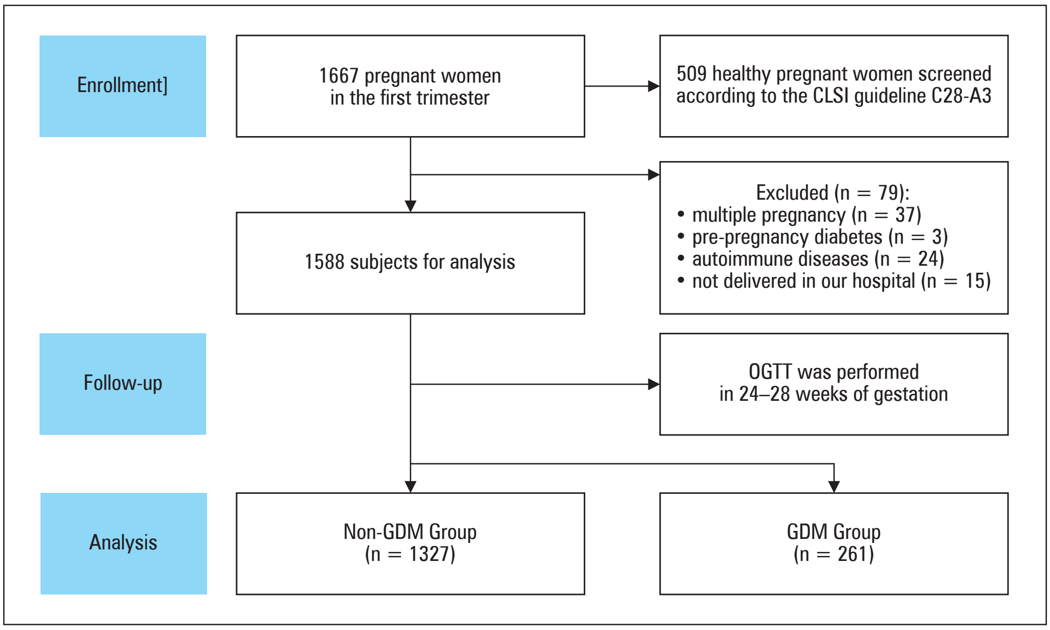

Figure 1. *Flow diagram. GDM — gestational diabetes mellitus. CLSI — Clinical and Laboratory Standards Institute*

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range (P2.5, P97.5) of lipid profiles in healthy pregnant women (n = 509) was estimated using a non-parametric method, using the same subjects in the first and third trimesters. The reference change values (RCV) [17] were calculated to assess the statistical significance of the difference between the Hoffmann technique and the 95% reference range.

We used the Mann-Whitney U test to compare the differences between the 2 groups in the GDM and non-GDM groups.

Count units were compared between the 2 groups using the χ^2 test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariate logistic regression analysis. Differences were considered statistically significant when $p < 0.05$. The receiver operating characteristic (ROC) curves were used to analyse the predictive value of lipids in early pregnancy for GDM, calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) when the Youden index reached its maximum.

Results

Establishment of pregnancy-specific lipid reference intervals in the first and third trimesters

Figure 2 and Table 1 show the distribution of lipid profiles in healthy pregnant women (n = 509) in early and late pregnancy, determined by nonparametric analysis. We can observe a gradual increase in lipid levels as pregnancy progresses, with significant increases in TC, TG, HDL-C, and LDL-C in the third trimester

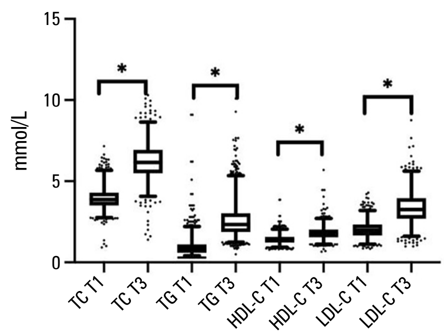

Figure 2. *In the first and third trimesters, the box plots of serum lipid levels in healthy pregnant women. TC — total cholesterol; TG — triglycerides; HDL-C — high-density lipid cholesterol; LDL-C — low-density lipid cholesterol; T1 — first trimester; T2 — third trimester. *p < 0.05*

($p < 0.05$). TC increased approximately 1.5-fold, TG approximately 2.6-fold, and HDL-C and LDL-C approximately 1.4-fold.

We indirectly estimated pregnancy-specific lipid RIs for all pregnant women recruited (n = 1588) using the Hoffmann technique, and no significant differences were observed between the 95% reference range of healthy pregnant women and the RIs calculated using the Hoffmann technique (absolute differences were smaller than RCV) (see Tab. 2).

Associations between lipids in the first trimester and GDM

Table 3 shows the general and biochemical indicators for the first trimester, including 1588 pregnant women. We can see that the number of those diagnosed with GDM in the second trimester was 261 (16.43%). The age of the subjects was significantly higher in the GDM group compared to the non-GDM group. 22.61% of the pregnant women in the GDM group were ≥ 35 years old and 15.37% in the non-GDM group ($\chi^2 = 20.54$, $p < 0.05$). The BMI of pregnant women in the GDM group was higher than in the non-GDM group ($\chi^2 = -7.32$, $p < 0.05$), and there were more overweight and obese pregnant women in the GDM group ($\chi^2 = 47.73$, $p < 0.001$). Furthermore, the proportion of multiple births was significantly higher in the GDM group ($\chi^2 = 7.25$, $p < 0.05$). Systolic blood pressure (SBP) was higher in the GDM group than in the non-GDM group ($p < 0.05$), while diastolic blood pressure (DBP) was not significantly different between the 2 groups. HbA_{1c} and FBG levels were significantly higher in the GDM group compared to the non-GDM group ($p < 0.05$). Regarding the lipid profile, the levels of TC, TG, and LDL-C were higher in the GDM group compared to the non-GDM group ($p < 0.05$), and HDL-C was not statistically different between the 2 groups.

After adjusting for age, body mass index, parity, blood pressure, and HbA1c, we observed a significant positive association between TG levels in the first trimester of pregnancy and GDM. In the first trimester, the risk of GDM is 2.1-fold higher in pregnant women

Table 1. *Serum lipid levels in healthy pregnant women in the first and third trimesters*

	Unit	First trimester Median (P2.5, P97.5)	Third trimester Median (P2.5, P97.5)	p
TC	Mmol/L	3.97 (3.10,6.17)	6.12 (4.57,9.32)	0.02
TG	Mmol/L	0.90 (0.46.2.25)	2.34 (1.69,5.68)	0.03
HDL-C	Mmol/L	1.22 (1.12,2.16)	1.67 (1.22,2.66)	0.04
LDL-C	Mmol/L	2.18 (1.20,3.82)	3.12 (1.96,5.82)	0.02

TC — total cholesterol; TG — triglycerides; HDL-C — high-density lipid cholesterol; LDL-C — low-density lipid cholesterol

Table 2. *Establishment of pregnancy-specific lipid reference intervals in the first and third trimesters*

	First trimester			Third trimester			
	Hoffmann technique	95% reference range	Absolute difference	Hoffmann technique	95% reference range	Absolute difference	RCV
	Mmol/L	Mmol/L	%	Mmol/L	Mmol/L	%	%
TC	3.02,5.83	3.10,6.17	1.30-4.98	4.50,9.17	4.57,9.32	1.33-3.22	10.31
TG	0.48,2.20	0.46,2.25	12.50-5.91	1.53,5.55	1.69,5.68	9.80-2.72	20.79
LDL-C	1.20,3.62	1.20,3.82	3.08-5.26	1.99,5.87	1.96,5.82	2.03-1.03	13.67
HDL-C	1.22,2.16	1.12,2.16	2.97-6.00	1.18,2.61	1.22,2.66	3.36-3.03	13.91

TC — total cholesterol; TG — triglycerides; HDL-C — high-density lipid cholesterol; LDL-C — low-density lipid cholesterol; RCV — reference change value

Table 3. *Comparison of general conditions and biochemical indexes in the first trimester between the gestational diabetes mellitus (GDM) group and the non-GDM group*

Index	GDM group (n = 261)	Non-GDM group (n = 1327)	t (χ^2)	p
Age [years]	31.95 ± 3.79	30.69 ± 3.57	− 5.15	< 0.05
< 25	2 (0.77%)	32 (2.41%)		
25–34	200 (76.62%)	1091(82.22%)		
≥ 35	59 (22.61%)	204 (15.37%)	20.54	< 0.05
BMI [kg/m²]	23.09 ± 3.43	21.63 ± 2.81	−7.32	< 0.05
< 18.5	12 (4.60%)	117 (8.82%)		
18.5–24.9	179 (68.58%)	1060 (79.88%)		
25-29.9	53 (20.31%)	124 (9.34%)		
≥ 30	17 (6.51%)	26 (1.96%)	47.73	< 0.001
Parity			7.25	< 0.05
0	89 (34.09%)	572 (43.11%)		
≥ 1	172 (65.91%)	755 (56.89%)		
SBP [mm Hg]	111.31 ± 10.51	109.58 ± 10.46	−2.44	< 0.05
DBP [mm Hg]	66.18 ± 8.91	66.18 ± 8.78	−0.01	0.98
HbA_{1c} (%)	5.23 ± 0.30	5.01 ± 0.26	−6.78	< 0.05
FBG [mmol/L]	5.01 ± 0.39	4.85 ± 0.35	−6.88	< 0.05
TC [mmol/L]	4.14 ± 0.79	3.91 ± 0.67	−5.01	< 0.05
TG [mmol/L]	1.15 ± 0.80	0.96 ± 0.56	−4.48	< 0.05
LDL-C [mmol/L]	2.16 ± 0.61	2.01 ± 0.53	−3.73	< 0.05
HDL-C [mmol/L]	1.40 ± 0.63	1.41 ± 0.27	0.33	0.16

BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; FBG — fasting blood glucose; HbA_{1c} — glycosylated haemoglobin; TC — total cholesterol; TG — triglycerides; LDL-L — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol

with elevated TG levels compared to those with normal TG levels (95% CI 1.13–3.77, p < 0.05) (Tab. 4).

In the ROC curve, the area under the curve (AUC) for the diagnostic efficacy of TG in GDM in the first 3 months was 0.622 (95% CI: 0.592–0.751). The highest Youden index was found when the TG level was 2.375 mmol/L, with a calculated sensitivity of 73.7%, specificity of 59.3%, PPV of 64.4, and NPV of 69.3% (Fig. 3 and Tab. 5).

Discussion

Previous studies [4, 18] have shown that TC, HDL-C, LDL-C, and TG levels gradually increase as pregnancy progresses; LDL-C levels peak at full term with an increase of approximately 50%; HDL-C levels peak at mid-pregnancy with an increase of 45% compared to pre-pregnancy levels and then decline, but they are still 15% higher at full term compared to

Table 4. *Multivariate logistic regression analyses of lipids in the first trimester and gestational diabetes mellitus (GDM) risk*

	GDM	
	OR (95% CI)	p
TC	1.21 (0.95–1.54)	0.118
TG	2.10 (1.13–3.77)	0.032
LDL	1.20 (0.90–1.62)	0.221

GDM — gestational diabetes mellitus; TC — total cholesterol; TG — triglycerides; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; OR — odds ratio. The multivariate model was adjusted for age, body mass index, parity, blood pressure, and glycosylated haemoglobin (HbA_{1c})

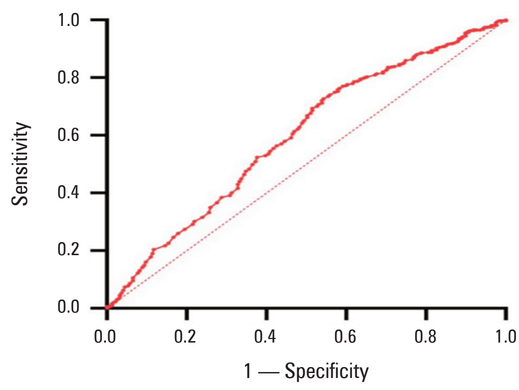

Figure 3. *Receiver operating characteristics (ROC) curve of triglycerides (TG) in the first trimester to predict the risk of gestational diabetes mellitus (GDM)*

pre-pregnancy levels; TG levels increase approximately 2–4-fold during pregnancy and peak in late gestation. Consistent with previous studies, in the present study, it was also found that in pregnant women, blood lipid levels, including TC, TG, HDL-C, and LDL-C, were significantly increased in the third trimester. As the gestational weeks increase, to meet the growth and development of the foetus and maintain pregnancy, sex steroid hormones increase, the intake of various nutrients increases, the accumulation of energy and lipid secretion increases, and pregnant women are in a state of hyperlipidaemia [19]. In the present study, we found the most pronounced increase in TG levels during late pregnancy, which was approximately 2.6-fold. This increase may be due to increased oestrogen levels during pregnancy, increased liver production of very low-density lipoprotein cholesterol, and decreased activity of endothelial lipoprotein lipase. Furthermore, insulin resistance during pregnancy also contributes to elevated triglyceride levels during pregnancy [20]. However, the mechanism of how elevated lipid levels in late pregnancy act on the mother and foetus needs to be further investigated and clarified.

In mid to late pregnancy, the mother's lipid metabolism is altered to accommodate normal foetal growth and development and the needs of pregnancy, and plasma lipid levels are significantly elevated [3]. Abnormal lipid metabolism is associated with the appearance of adverse pregnancy outcomes and seriously affects maternal and infant health [4, 5]. However, there is no national or international consensus on normal maternal lipid levels. As a result, it is difficult for physicians to determine whether the lipid level is at a normal level during a clinical consultation, which can lead to a certain degree of misdiagnosis or underdiagnosis. The traditional and straightforward method of establishing reference values relies on recruiting a sufficient number of healthy individuals of different ages, collecting and testing many specimens, and interpreting the data accurately. However, this method requires a significant investment in human and financial resources, which cannot be achieved by all laboratories. Now, due to the advent of the era of big data, a unique opportunity has been created for clinics to collect different methods for the establishment of reference intervals. The Hoffmann technique is an indirect method of estimating RI that is currently gaining attention in the research field. First proposed in 1963 [16], it does not require the recruitment of healthy subjects and does not require complex computer data processing. In this study, we aimed to calculate the 95% reference range of healthy pregnant women by recruiting them. In parallel, the Hoffmann technique established the pregnancy-specific RI using available laboratory data from a relatively large cohort of patients. The results showed that the lower and upper limits of estimated pregnancy-specific RI were in good agreement with the 5th and 95th centiles of blood lipid levels in healthy

Table 5. *Receiver operating characteristics (ROC) curve values of first-trimester triglycerides (TG) in the diagnosis of gestational diabetes mellitus (GDM)*

	AUC 95% CI	Sensitivity (%)	Specificity (%)	Youden index	Cut-off point [Mmol/L]	PPV (%)	NPV (%)
TG	0.622 (0.592,0.751)	73.7	59.3	0.330	2.375	64.4	69.3

AUC — area under the curve; CI — confidence interval; PPV — positive predictive value; NPV — negative predictive value pregnant women (absolute difference less than RCV). In areas where pregnancy-specific lipid reference ranges for pregnant women have not been established, the Hoffmann technique can be considered to establish appropriate reference ranges.

GDM is one of the most common disease syndromes in pregnancy [21], and its prevalence continues to rise due to epidemiological factors, including increasing rates of obesity in women of childbearing age and rising maternal age. It is estimated that 1 in 7 pregnant women in China will be diagnosed with GDM [10]. Recent data [22] suggest that the effects of exposure to maternal hyperglycaemia in early utero predate the conventional diagnosis of GDM at 24–28 weeks of gestation and that maternal hyperglycaemia can also have lasting adverse effects on child and adolescent metabolism [23, 24]. Globally, screening for GDM is typically conducted 3 months into pregnancy, often resulting in missed opportunities for early intervention. Diagnosing and intervening in GDM early can improve adverse pregnancy outcomes [11, 25], and early prediction of GDM has become a hot topic of research in recent years [25–28].

Previous research has discovered distinct lipid metabolic profiles in women with and without GDM, which suggests that lipid metabolism plays a significant role in the development of diabetes, but the findings are inconsistent. Several studies [29, 30] showed that pregnant women with GDM had an increase in TC, TG, and LDL-C and a decrease in HDL-C with increasing gestational weeks. The results of another meta-analysis [31] showed that women with GDM had inconsistent changes in cholesterol during pregnancy, except for a consistent increase in TG. Another study [32] classified GDM into different subtypes based on the OGTT results and the components of elevated lipids differed between subtypes. The inconsistent results of the above studies may be due to small sample sizes (< 100 in most cases) and differences in measurement platforms, or they may be due to the physiological heterogeneity of GDM. Therefore, larger, multicentre studies in the future are required, as well as more accurate lipidomic analyses. Additionally, few studies have investigated the association of GDM risk with first-trimester lipids, especially in the Chinese population.

In our study, multivariate logistic regression was performed, and after adjusting for confounders (age, body mass index, gestational age, blood pressure, and HbA_{1c}), we found that increased TG in the first trimester was a risk factor for the development of GDM, with a 2.1-fold increased risk of GDM in pregnant women with elevated TG compared to those with normal levels of TG (95% CI: 1.13–3.77, $p < 0.05$). High TG induces increased hormone-sensitive lipase activity, the rate-limiting enzyme of lipolysis 2, and increased lipolysis, leading to increased levels of free fatty acids (FFA). High levels of FFA not only inhibit insulin-stimulated tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 and inhibit insulin signalling at multiple sites, but also inhibit basal and insulin-stimulated tissue glucose uptake, resulting in reduced glucose oxidation and enzymolysis in tissues, causing reduced tissue sensitivity to insulin. Also, FFA can promote liver glucose output, leading to IR in the liver. Diabetes may be influenced by elevated TG levels, but the exact pathway and mechanism need to be further clarified by cellular experiments [33].

We evaluated the predictive capacity performance of the models using the ROC curve, and the AUC of the TG level in the first trimester of the diagnosis of GDM was 0.622 (95% CI: 0.592–0.751). When the TG level was 2.375 mmol/L, the Youden index was highest, and the sensitivity, specificity, PPV, and NPV were 73.7%, 59.3%, 64.4%, and 69.3%, respectively. The findings indicate that TG performed well in terms of prediction and appeared to have potential as a predictor of GDM in the early stages of pregnancy. However, TC is not a standalone risk factor for GDM, and the fact that the combination of TG with other biological indicators can increase the accuracy of prediction is also a focus of future research.

This research has several restrictions. Because blood lipid levels are mostly correlated with ethnicity, this study solely includes pregnant East Asian women. Then, the recommended pregnancy-specific RI did not cover the entire trimester. Finally, the information was gathered from a single centre with a small sample size, and other demographic factors like socioeconomic position and genetic potential, which are also connected to GDM, were not taken into account. Therefore, future studies with multicentre, large samples and multiple parameters are needed.

Conclusion

Our study is a large population-based study that estimated the RI of lipid levels throughout pregnancy in a single centre in the Beijing area of China using the indirect Hoffmann technique, which is consistent with results derived from conventional methods, further demonstrating its merit and validity in a population of pregnant women. In addition, our study prospectively assessed the association between dyslipidaemia and GDM; pregnant women with TG ≥ 2.375 mmol/L in the first trimester were at a significantly increased risk of GDM, providing direct evidence for the predictive value of population-based lipid screening information.

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Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics statement

This study was approved by the Ethics Committee of Peking University International Hospital [2017–021 (BMR)]. All procedures were performed in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Author contributions

D.Z. and X.Z. conceptualised and planned the study; N.Y. and J.S. gathered the data and carried out the study; D.Z., J.S., and X.Z. analysed and evaluated the data; D.Z. produced the first draft of the paper; X.Z. revised it; and X.Z. was primarily in charge of the paper's final content. The final manuscript was read and approved by all writers.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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