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# First-Trimester Lipid Profile and Subsequent Gestational Diabetes Mellitus: A Retrospective Case–Control Study

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## Highlights

### What are the main findings?

- Women who subsequently developed gestational diabetes mellitus had higher first-trimester triglyceride levels and LDL-C/HDL-C ratios and lower HDL-C levels than women without GDM.
- Triglycerides showed the strongest association with subsequent GDM among the evaluated lipid parameters, although their discriminatory performance was modest (AUC = 0.687).

### What are the implications of the main findings?

- First-trimester lipid alterations may provide additional metabolic information for identifying women at increased risk of subsequent GDM.
- Routinely available lipid parameters should not be used as stand-alone predictors of GDM but may warrant evaluation as components of multivariable early-pregnancy risk models.

## Abstract

Background/Objectives: Gestational diabetes mellitus (GDM) is a common metabolic complication of pregnancy, and identifying women at increased risk early in gestation may facilitate closer surveillance and timely preventive strategies. This study aimed to investigate the association between first-trimester maternal lipid profile parameters and subsequent GDM and to evaluate their discriminatory performance for GDM. Methods: This retrospective case–control study included singleton pregnancies followed at İzmir Kâtip Çelebi University Atatürk Training and Research Hospital between January 2015 and December 2019. Serum lipid parameters obtained between 11 + 0 and 13 + 6 weeks of gestation were retrospectively retrieved and compared between women who subsequently developed GDM and those who did not. Associations with GDM were evaluated using binary logistic regression, and discriminatory performance was assessed using receiver operating characteristic (ROC) curve analysis. Results: Of 367 women assessed for eligibility, 336 were included in the final analysis (201 with GDM and 135 controls). Women who developed GDM had higher triglyceride levels (median: 138 vs. 103 mg/dL; $p < 0.001$) and LDL-C/HDL-C ratios (2.339 ± 0.695 vs. 2.174 ± 0.774; $p = 0.042$) and lower HDL-C levels (median: 47 vs. 53 mg/dL; $p = 0.002$). Triglyceride concentration was significantly associated with GDM (OR = 1.010, 95% CI: 1.005–1.014; $p < 0.001$). Triglycerides demonstrated an AUC of 0.687; a cut-off of >125 mg/dL yielded 62.69% sensitivity and 74.81% specificity. Conclusions: First-trimester maternal lipid alterations, particularly higher triglyceride

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levels, were associated with subsequent GDM. However, triglycerides demonstrated only modest discriminatory performance and should not be considered a stand-alone predictor. Routinely available lipid parameters may provide additional information for early GDM risk stratification.

**Keywords:** gestational diabetes mellitus; triglycerides; lipid profile; first trimester; pregnancy; risk stratification

## 1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common metabolic complications of pregnancy and is associated with adverse maternal and neonatal outcomes. Pregnancies complicated by GDM are at increased risk of hypertensive disorders, fetal overgrowth, and other obstetric complications, while affected neonates may experience complications such as hypoglycemia and respiratory morbidity [1,2]. Beyond these immediate pregnancy-related consequences, the identification of women at increased risk of GDM remains clinically important for optimizing antenatal surveillance and metabolic management.

GDM is generally diagnosed in the second or third trimester of pregnancy using glucose-based screening and diagnostic strategies. However, the metabolic alterations contributing to its development begin earlier in gestation. Therefore, considerable interest has focused on identifying routinely available clinical or biochemical parameters measured during early pregnancy that may be associated with the subsequent development of GDM [3]. Such markers could potentially complement established maternal risk factors and contribute to earlier risk stratification rather than replace conventional GDM screening.

Pregnancy is characterized by substantial physiological changes in maternal lipid metabolism. These adaptations are necessary to meet maternal and fetal energy requirements; however, disturbances in lipid metabolism may also accompany the metabolic dysfunction associated with GDM. Previous studies have investigated early-pregnancy concentrations of triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), as well as lipid ratios such as LDL-C/HDL-C, in relation to subsequent GDM [4–10]. Although several studies have reported associations between altered maternal lipid profiles and GDM, the findings have not been entirely consistent across populations and study designs. Differences in maternal characteristics, diagnostic criteria for GDM, timing of lipid measurements, and metabolic status may contribute to this heterogeneity.

The metabolic relevance of lipid measurements in early pregnancy extends beyond their conventional role in cardiovascular risk assessment. Maternal lipid concentrations reflect physiological metabolic adaptations that may also be influenced by pre-existing metabolic risk factors [8]. Alterations in lipid profiles during early gestation have been associated with subsequent GDM, although the magnitude of these associations may vary according to maternal characteristics, including BMI [6,7,10]. Nevertheless, an association with subsequent GDM does not necessarily imply that a lipid parameter can reliably discriminate between women who will and will not develop the condition. Evaluating both the magnitude of the association and its discriminatory performance is therefore important, particularly in populations with pre-existing metabolic risk factors [4,5].

Although previous studies have demonstrated associations between early-pregnancy lipid abnormalities and subsequent GDM, differences in study populations, gestational timing of lipid assessment, and metabolic risk profiles may influence the observed associations and discriminatory performance of individual lipid parameters. In particular, evidence obtained from clinically selected populations undergoing lipid testing because of metabolic

risk factors may provide additional context for interpreting these associations. Therefore, the primary objective of the present study was to compare serum lipid profile parameters measured between 11 + 0 and 13 + 6 weeks of gestation in women who subsequently developed GDM and those who did not. The secondary objective was to assess the associations of these parameters with GDM and evaluate their discriminatory performance. This study was intended to provide additional observational evidence in a clinically selected population rather than to establish a novel association or validate a clinical prediction model.

## 2. Materials and Methods

### *2.1. Study Design and Participants*

This retrospective case–control study was conducted at the Department of Obstetrics and Gynecology, İzmir Kâtip Çelebi University Atatürk Training and Research Hospital, between 1 January 2015 and 31 December 2019.

Women diagnosed with gestational diabetes mellitus (GDM) during the study period were retrospectively identified from the hospital's electronic medical records. Non-GDM controls were selected from the same institution and study period using a non-probability convenience sampling approach. Eligible participants had singleton pregnancies, available serum lipid profile measurements obtained between 11 + 0 and 13 + 6 weeks of gestation, and results of a 75-g oral glucose tolerance test (OGTT) performed at 24–28 weeks of gestation. Women with pregestational diabetes mellitus, multiple pregnancies, other endocrinological or systemic diseases, or elevated fasting blood glucose levels detected at the first antenatal visit were excluded.

During the study period, first-trimester lipid profiling was not routinely performed in all pregnant women at our institution. Instead, lipid measurements were selectively obtained in women with clinical risk factors, including obesity, a family history of diabetes mellitus, previous gestational diabetes mellitus, dyslipidemia, or other metabolic disorders. Consequently, the study population was derived from a clinically selected group of pregnant women with available first-trimester lipid measurements rather than from an unselected obstetric population.

The gestational age interval of 11 + 0 to 13 + 6 weeks was selected to evaluate maternal lipid parameters during a defined first-trimester window, corresponding to the conventional period of first-trimester antenatal screening and preceding the standard diagnostic assessment for GDM at 24–28 weeks of gestation.

The sample size was determined by the availability of eligible patient records during the study period; no a priori sample size calculation or power analysis was performed. A total of 367 women were assessed for eligibility. After the exclusion of 31 women according to the eligibility criteria, 336 participants were included in the final analysis, comprising 201 women with GDM and 135 controls. The unequal group sizes reflected the retrospective case–control sampling procedure rather than the prevalence of GDM in the underlying obstetric population.

### *2.2. Diagnosis of Gestational Diabetes Mellitus*

GDM was diagnosed using the one-step 75-g oral glucose tolerance test (OGTT) according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [11]. The 75-g OGTT was performed at 24–28 weeks of gestation. The diagnostic thresholds were a fasting plasma glucose concentration of ≥92 mg/dL, a 1-h plasma glucose concentration of ≥180 mg/dL, or a 2-h plasma glucose concentration of ≥153 mg/dL. Meeting or exceeding at least one of these thresholds was considered sufficient for the diagnosis of GDM. Women who met the diagnostic criteria were classified as the GDM group, whereas those who did not meet the diagnostic criteria were classified as controls.

### *2.3. Data Collection and Lipid Parameters*

Demographic, clinical, laboratory, and ultrasonographic data were retrospectively retrieved from the hospital's electronic medical records. Serum lipid profile results obtained between 11 + 0 and 13 + 6 weeks of gestation were recorded for each participant. The evaluated lipid parameters included total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and the LDL-C/HDL-C ratio.

During the study period (2015–2019), maternal lipid profile assessments were performed during the first trimester as part of the institutional clinical practice, without routine repeated measurements in the second or third trimester. Consequently, longitudinal lipid profile data were not available for the study population, and changes in lipid parameters throughout pregnancy could not be evaluated. Furthermore, because of the retrospective design, the exact timing of lipid measurements within the specified gestational-age window and the interval between the participants' last meal and blood sampling were not standardized.

At the initial antenatal assessment, elevated fasting blood glucose levels were used as an exclusion criterion. However, individual fasting glucose concentrations were not recorded in the study dataset, as these measurements were used solely for eligibility assessment. Consequently, first-trimester fasting glucose values were unavailable for quantitative comparisons between groups or inclusion as covariates in the regression analysis. In contrast, the results of the 75-g oral glucose tolerance test performed at 24–28 weeks of gestation were used to establish the diagnosis of GDM and classify participants into the GDM and control groups.

Maternal height and weight measurements were not recorded in the study dataset at any time point, including before pregnancy, during the first trimester, or at the time of GDM diagnosis. Therefore, maternal body mass index (BMI) could not be calculated, and adjustment for maternal adiposity was not possible.

Serum lipid profile measurements were performed in the hospital's central biochemistry laboratory using an automated clinical chemistry analyzer (ARCHITECT c16000, Abbott Diagnostics, Abbott Park, IL, USA).

### *2.4. Study Outcomes*

The primary objective was to compare first-trimester serum lipid profile parameters between women who subsequently developed GDM and women who did not.

The secondary objectives were to evaluate the association between lipid parameters and GDM and to assess the discriminatory performance of lipid parameters for subsequent GDM using receiver operating characteristic (ROC) curve analysis.

### *2.5. Statistical Analysis*

Descriptive statistics were presented as number and percentage for categorical variables and as mean ± standard deviation or median with first and third quartiles (Q1–Q3) for continuous variables, as appropriate.

The distribution of continuous variables was assessed using the Shapiro–Wilk test and Q–Q plots, and homogeneity of variances was evaluated using Levene's test. Between-group comparisons were performed using the independent-samples t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed continuous variables.

Binary logistic regression analysis was performed to evaluate the association between first-trimester lipid parameters and subsequent GDM. The initial model included maternal age, total cholesterol, HDL-C, LDL-C, triglycerides, and the LDL-C/HDL-C ratio. Variable

selection was performed using the backward Wald method in SPSS, with the default significance thresholds for variable entry ($p = 0.05$) and removal ($p = 0.10$). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

ROC curve analysis was performed to evaluate the discriminatory performance of lipid parameters for GDM. The area under the ROC curve (AUC), optimal cut-off values, sensitivity and specificity were calculated, as applicable.

All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). A two-sided $p$ value $< 0.05$ was considered statistically significant.

### *2.6. Ethical Considerations*

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the İzmir Kâtip Çelebi Non-Interventional Clinical Studies Institutional Review Board (IRB No. 965/2020). Given the retrospective design of the study and the use of anonymized data, informed consent was not obtained.

## 3. Results

### *3.1. Study Population and Comparison of Lipid Parameters*

A total of 367 pregnant women were assessed for eligibility. Of these, 31 were excluded according to the predefined exclusion criteria, leaving 336 women for the final analysis. The study population comprised 201 women who subsequently developed gestational diabetes mellitus (GDM) and 135 women without GDM (Figure 1).

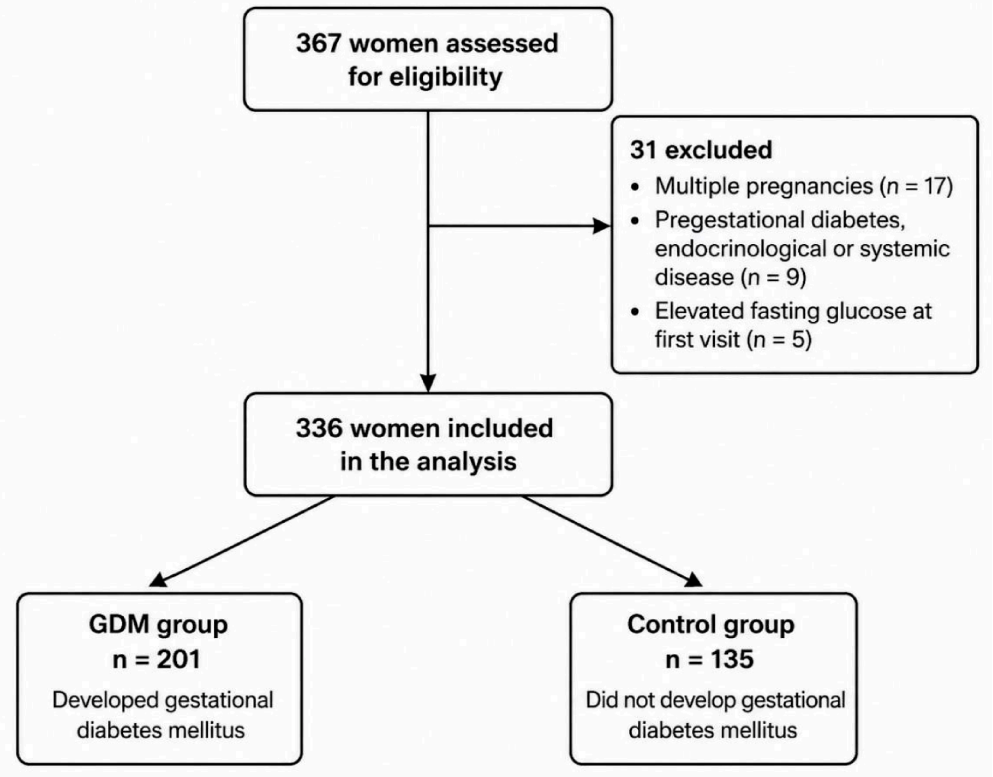


**Figure 1.** Flowchart of participant selection.

Maternal age was comparable between the GDM and control groups (30.6 ± 5.2 vs. 30.7 ± 5.1 years, respectively; $p = 0.832$). Total cholesterol and LDL-C levels also did not differ significantly between the groups (both $p > 0.05$).

In contrast, women who subsequently developed GDM had significantly higher triglyceride concentrations than controls (median [Q1–Q3]: 138.0 [107.5–174.0] vs. 103.0

[77.0–129.0] mg/dL; $p < 0.001$). HDL-C concentrations were significantly lower in the GDM group (47.0 [42.0–56.0] vs. 53.0 [42.0–65.0] mg/dL; $p = 0.002$). The LDL-C/HDL-C ratio was also significantly higher among women who developed GDM (2.339 ± 0.695 vs. 2.174 ± 0.774; $p = 0.042$) (Table 1).

**Table 1.** Comparison of maternal characteristics and first-trimester lipid parameters between the GDM and control groups.

| Data | Groups | | Test Statistics | |
|---|---|---|---|---|
| | **GDM n = 201** | **Control n = 135** | **Test Value** | ***p*-Value** |
| Age (year) x ± sd | 30.6 ± 5.2 | 30.7 ± 5.1 | t = 0.212 | 0.832 |
| Total cholesterol mg/dL M (Q1–Q3) | 186.0 (167.0–206.5) | 185.0 (162.0–219.0) | z = 0.010 | 0.992 |
| HDL-C mg/dL M (Q1–Q3) | 47.0 (42.0–56.0) | 53.0 (42.0–65.0) | z = 3.135 | 0.002 |
| LDL-C mg/dL M (Q1–Q3) | 109.0 (93.0–126.0) | 106.0 (89.0–134.0) | z = 0.426 | 0.670 |
| LDL-C/HDL-C x ± sd | 2.339 ± 0.695 | 2.174 ± 0.774 | t = 2.038 | 0.042 |
| TG mg/dL M (Q1–Q3) | 138.0 (107.5–174.0) | 103.0 (77.0–129.0) | z = 5.730 | <0.001 |

x: mean, sd: standard deviation, M: median, Q1: first quartile value, Q3: third quartile value, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides, z: Mann–Whitney U test, and t: independent two-sample *t*-test.

### *3.2. Logistic Regression Analysis*

Binary logistic regression analysis was initially performed using maternal age, total cholesterol, HDL-C, LDL-C, triglycerides, and the LDL-C/HDL-C ratio as candidate variables. A backward stepwise selection procedure based on the Wald statistic was applied. Following the variable selection procedure, triglyceride concentration was the only variable retained in the final model, whereas maternal age and the other lipid parameters were excluded.

In the final model, triglyceride concentration was significantly associated with subsequent GDM (β = 0.010, SE = 0.002, Wald = 19.261; OR = 1.010 per 1 mg/dL increase, 95% CI: 1.005–1.014; $p < 0.001$). Since maternal age was not retained in the final model, the reported odds ratio represents an unadjusted association rather than an age-adjusted estimate. Furthermore, this association should not be interpreted as independent of unmeasured clinical confounders, particularly maternal adiposity (Table 2).

**Table 2.** Binary logistic regression analysis of factors associated with gestational diabetes mellitus.

| Data | β | SE | Wald | *p* | OR | OR (95% CI) |
|---|---|---|---|---|---|---|
| TG | 0.010 | 0.002 | 19.261 | <0.001 | 1.010 | 1.005–1.014 |

TG: triglyceride; β: regression coefficient; SE: standard error; CI: confidence interval.

### *3.3. Discriminatory Performance of Lipid Parameters*

ROC curve analysis was performed to assess the discriminatory performance of triglyceride concentration and the LDL-C/HDL-C ratio for GDM (Figure 2 and Table 3).

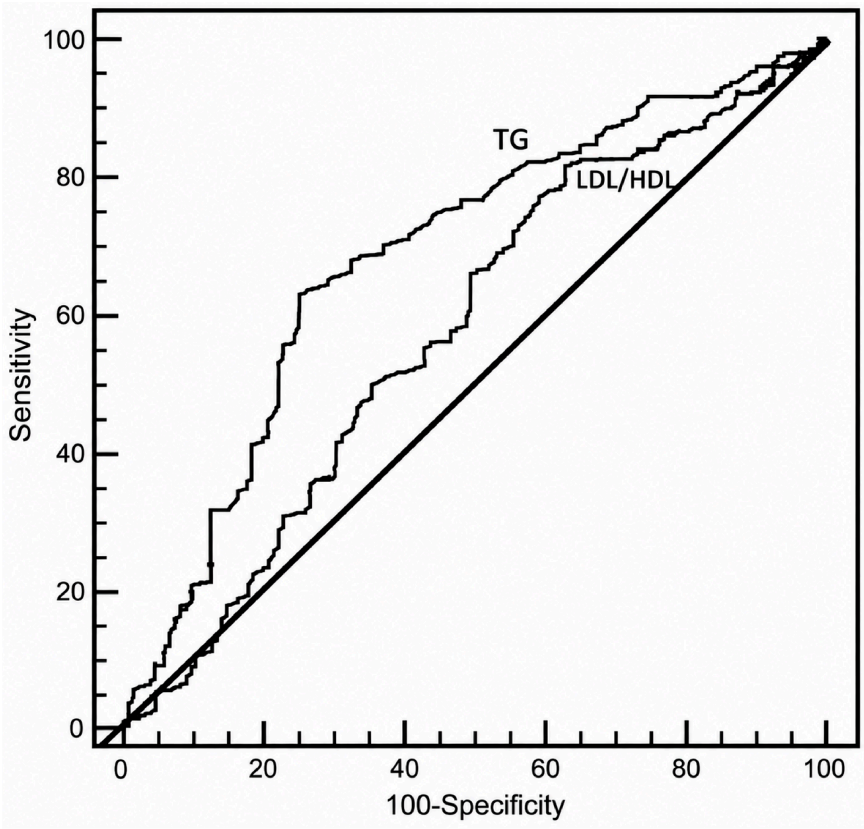


**Figure 2.** Receiver operating characteristic curves for first-trimester triglyceride concentration and the LDL-C/HDL-C ratio for discrimination of subsequent gestational diabetes mellitus.

**Table 3.** Discriminatory performance of first-trimester lipid parameters for subsequent GDM.

| Data | AUC | *p* | Cut Off | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| TG | 0.687 | <0.0001 | >125 mg/dL | 62.69 | 74.81 |
| LDL-C/HDL-C | 0.578 | 0.0159 | >1.76 | 81.59 | 37.04 |

TG: triglyceride; AUC: area under the curve.

Triglycerides demonstrated an AUC of 0.687 ($p < 0.0001$). At the identified cut-off value of >125 mg/dL, the sensitivity was 62.69%, and specificity was 74.81%.

The LDL-C/HDL-C ratio demonstrated a lower discriminatory performance, with an AUC of 0.578 ($p = 0.0159$). At a cut-off value of >1.76, the sensitivity was 81.59%, and specificity was 37.04%.

## 4. Discussion

The principal finding of the present study was that alterations in the maternal lipid profile were already detectable during the first trimester among women who subsequently developed GDM. These women had significantly higher triglyceride concentrations and LDL-C/HDL-C ratios and lower HDL-C concentrations than women who did not develop GDM. Among the evaluated lipid parameters, triglycerides demonstrated the strongest observed association with subsequent GDM and the highest discriminatory performance. However, the absence of adjustment for important maternal characteristics, particularly BMI, prevents determination of whether this association is independent of established GDM risk factors. Furthermore, the observed AUC of 0.687 indicates only modest discrimination, suggesting that triglycerides should not be considered a standalone predictor of GDM.

Our findings regarding triglycerides are consistent with a growing body of evidence linking maternal hypertriglyceridemia with GDM. A large systematic review and meta-analysis including 292 studies and 97,880 women demonstrated significantly higher triglyceride concentrations in women with GDM, with elevated triglyceride levels detectable from the first trimester and persisting throughout pregnancy [12]. Importantly, the magnitude of the difference varied according to maternal age, BMI, geographic region, OGTT procedure, and diagnostic criteria for GDM [12]. More recent trimester-specific meta-analytic evidence has similarly demonstrated significantly elevated triglyceride concentrations in women with GDM across all three trimesters, with prominent lipid abnormalities already evident during early pregnancy [13]. These findings support the observation in our cohort that disturbances in maternal triglyceride metabolism precede the conventional period of GDM diagnosis.

Recent prospective evidence further supports an association between early-pregnancy lipid abnormalities and subsequent GDM. In a large study evaluating lipid profiles and lipid ratios during early and mid-pregnancy, early-pregnancy triglycerides and several lipid-derived indices were positively associated with subsequent GDM even after adjustment for potential confounders [14]. These findings, together with the results of the present study, suggest that alterations in lipid metabolism may be evident before GDM is clinically diagnosed.

The association between triglycerides and GDM is biologically plausible. Normal pregnancy is accompanied by progressive changes in maternal lipid metabolism that facilitate the transfer of metabolic substrates to the developing fetus. Pregnancy-related insulin resistance and hormonal adaptations promote lipolysis and increase circulating free fatty acids and triglycerides. In women predisposed to GDM, inadequate pancreatic β-cell compensation for increasing insulin resistance may coexist with more pronounced metabolic dysregulation [15]. Abnormal lipid metabolism may further contribute to insulin resistance through mechanisms involving increased circulating free fatty acids, impaired insulin signaling, oxidative stress, and inflammatory pathways [15,16]. Thus, dyslipidemia may represent an integrated component of the metabolic phenotype associated with GDM rather than merely a secondary consequence of hyperglycemia.

In addition to higher triglyceride concentrations, women who subsequently developed GDM in our study had significantly lower HDL-C concentrations and higher LDL-C/HDL-C ratios. Previous studies have reported similar alterations [4–10], although findings regarding individual cholesterol fractions have been less consistent than those for triglycerides. Large meta-analyses have generally demonstrated lower HDL-C concentrations in GDM, whereas associations with LDL-C and total cholesterol appear to vary according to gestational period and study population [12,13]. In our cohort, total cholesterol and LDL-C concentrations did not differ significantly between groups, suggesting that triglyceride-related alterations may be more prominent than changes in absolute cholesterol concentrations during early pregnancy.

From a pathophysiological perspective, alterations in HDL-C concentrations and the LDL-C/HDL-C ratio may reflect the metabolic disturbances associated with insulin resistance during pregnancy [15,17]. Increased adipose tissue lipolysis and hepatic production of triglyceride-rich lipoproteins may promote lipid exchange between lipoprotein particles and accelerate HDL-C catabolism, contributing to lower circulating HDL-C concentrations [18]. Furthermore, HDL-C particles participate in reverse cholesterol transport and exert antioxidant and anti-inflammatory effects, which may be relevant to metabolic homeostasis. Although LDL-C concentrations did not differ significantly between groups in our study, insulin resistance may be associated with changes in LDL-C particle composition and size without substantial alterations in total LDL-C concentrations [17,18]. Therefore,

an elevated LDL-C/HDL-C ratio may reflect a relative imbalance between atherogenic and protective lipoprotein fractions [17]. However, these mechanisms were not directly evaluated in the present study, and the observed associations should not be interpreted as evidence of causality.

The LDL-C/HDL-C ratio was significantly higher in women who developed GDM; however, its discriminatory performance was limited, with an AUC of 0.578. Although its relatively high sensitivity at the identified cut-off may appear favorable, the low specificity substantially limits its potential clinical utility when used alone. Triglycerides performed better, with an AUC of 0.687 and a specificity of 74.81% at a cut-off of >125 mg/dL, but their overall discriminatory ability remained modest. These findings emphasize the distinction between a statistically significant association and clinically useful prediction.

The interpretation of ROC-derived thresholds also requires consideration of the underlying study design. Although sensitivity and specificity describe discrimination at a selected cut-off, they do not establish the clinical usefulness of a biomarker in routine antenatal care. In particular, the case–control sampling approach used in this study does not provide a representative estimate of GDM prevalence, limiting the applicability of prevalence-dependent predictive values [19]. Furthermore, selecting and evaluating a threshold within the same dataset may result in optimistic estimates of performance. Independent validation in prospectively recruited obstetric populations is therefore necessary before any triglyceride threshold can be considered for clinical decision-making [20].

Although the LDL-C/HDL-C ratio was evaluated as an indicator of the balance between atherogenic and antiatherogenic cholesterol fractions, the TG/HDL-C ratio, which has been widely investigated as a surrogate marker of insulin resistance, was not assessed in the present study. Future studies should evaluate the comparative performance of these lipid-derived indices in relation to GDM.

Recent studies have increasingly explored multivariable and machine learning-based approaches to risk assessment in obstetric populations. Temur et al. [21] investigated gestational diabetes mellitus using artificial neural network and physics-informed neural network models incorporating periodontal health indices and hematological inflammatory markers, highlighting the potential value of integrating information from multiple biological domains. In a related methodological application, Özsan et al. [22] developed an artificial neural network model incorporating hematological, periodontal, and behavioral parameters for the classification of preterm prelabor rupture of membranes. Although the latter study addressed a different obstetric outcome, both investigations illustrate the growing interest in multidomain modeling approaches. In contrast, our study focused on routinely available first-trimester lipid parameters and demonstrated modest discriminatory performance for triglycerides (AUC = 0.687). These findings suggest that triglyceride measurements may provide complementary metabolic information, but their incremental value beyond established maternal risk factors and other biomarkers requires evaluation in appropriately adjusted, externally validated multivariable models.

From a clinical perspective, the potential value of lipid parameters lies in their accessibility rather than in their use as stand-alone screening tests. Serum lipid measurements are inexpensive and widely available, and first-trimester lipid values may provide additional metabolic information when interpreted alongside established maternal risk factors. Future prediction models could investigate whether triglycerides or lipid-derived ratios provide incremental discriminatory value beyond readily available characteristics such as maternal age, pre-pregnancy BMI, family history of diabetes, previous GDM, and early-pregnancy glucose measurements. Such models would require prospective development and appropriate internal and external validation before clinical implementation.

An additional consideration is that the clinical interpretation of early-pregnancy triglyceride concentrations depends on the population in which they are measured. In an unselected obstetric population, the distribution of metabolic risk factors may differ substantially from that of women undergoing lipid testing because of obesity, dyslipidemia, or other metabolic risk factors. Consequently, the discriminatory performance of a triglyceride threshold may vary across clinical settings. The cut-off identified in our analysis should therefore be regarded as an exploratory, sample-derived finding rather than a clinically validated decision limit.

Moreover, triglyceride concentrations reflect several overlapping metabolic processes rather than a pathway specific to GDM. Insulin resistance, hepatic lipoprotein production, adipose tissue metabolism, and recent dietary intake may all influence circulating triglyceride levels [15,16,18]. Their association with subsequent GDM may therefore reflect a broader metabolic phenotype associated with susceptibility to glucose intolerance. Distinguishing these mechanisms would require prospective studies incorporating standardized fasting measurements, maternal anthropometric characteristics, glucose and insulin indices, and repeated lipid assessments throughout pregnancy. Such investigations could clarify whether early-pregnancy triglycerides provide clinically meaningful information beyond established risk factors and improve the discriminatory performance of multivariable GDM risk models.

The present study has several limitations. First, its retrospective, single-center case–control design limits causal inference and may reduce the generalizability of the findings. Furthermore, the selective measurement of first-trimester lipid profiles introduces potential selection bias. Lipid testing was primarily performed in women with clinical risk factors, including obesity, a family history of diabetes mellitus, previous gestational diabetes mellitus, dyslipidemia, or other metabolic disorders. Therefore, the study population may have had a higher baseline metabolic risk than the general obstetric population. In addition, the proportion of GDM cases in the analytical sample does not reflect the prevalence of GDM in the underlying obstetric population because cases and controls were selected separately. These factors underscore the need for validation in independent, representative cohorts.

Second, several potentially important confounding variables were unavailable for analysis. Although elevated fasting blood glucose levels at the initial antenatal assessment were used as an exclusion criterion, individual fasting glucose concentrations were not recorded in the study dataset and therefore could not be included in statistical analyses. Moreover, maternal height and weight measurements were not recorded in the study dataset at any time point, including before pregnancy, during the first trimester, or at the time of GDM diagnosis. Consequently, maternal body mass index (BMI) could not be calculated, and adjustment for maternal adiposity was not possible. Because obesity is associated with both altered lipid metabolism and an increased risk of GDM, the observed association between first-trimester triglyceride concentrations and subsequent GDM may be partly attributable to unmeasured differences in maternal adiposity or other metabolic characteristics. Additional metabolic parameters, including insulin concentrations, HOMA-IR, and the triglyceride-glucose–BMI (TyG-BMI) index, were not evaluated. Therefore, the observed association cannot be considered independent of these unmeasured confounding factors.

Third, fasting status and the interval between the last meal and blood sampling were not systematically documented. Since triglyceride concentrations are influenced by recent dietary intake, variability in preanalytical conditions may have affected the measured lipid concentrations and contributed to the observed differences between groups.

Fourth, lipid parameters were assessed at a single time point during the first trimester. During the study period, institutional clinical practice did not include routine repeated lipid profile measurements in the second or third trimester. Consequently, longitudinal lipid

data were unavailable, preventing the evaluation of changes in maternal lipid metabolism throughout pregnancy and their potential association with subsequent GDM.

Fifth, formal multicollinearity diagnostics were not performed. Because the initial logistic regression model included potentially correlated lipid parameters and a derived lipid ratio, multicollinearity cannot be excluded. Consequently, the stability of the regression coefficients and the results of the backward variable selection procedure should be interpreted with caution.

Finally, the discriminatory performance of triglycerides was modest, and the identified cut-off value was derived and evaluated within the same study sample without external validation. Therefore, the proposed triglyceride threshold should be considered exploratory rather than a clinically validated screening cut-off. Future prospective, multicenter studies incorporating standardized fasting conditions, comprehensive anthropometric and metabolic assessments, serial lipid measurements at predefined gestational intervals, and independent validation cohorts are needed to confirm these findings and evaluate their potential clinical utility.

Despite these limitations, the study has clinically relevant features. Lipid measurements were obtained during the first trimester, before the conventional period of GDM diagnosis, allowing assessment of metabolic differences that precede the diagnosis of GDM. Furthermore, the study evaluated routinely available laboratory parameters in a relatively large study sample of women with and without GDM using standardized diagnostic criteria.

## 5. Conclusions

First-trimester maternal lipid alterations were associated with the subsequent development of GDM, with triglycerides demonstrating the strongest association among the evaluated lipid parameters. However, the discriminatory performance of triglycerides was modest, indicating that lipid parameters should not be considered stand-alone predictors of GDM. Given their widespread availability and low cost, first-trimester lipid measurements may provide additional metabolic information for early risk stratification. Prospective studies incorporating established maternal risk factors and appropriate external validation are needed to determine whether lipid parameters provide incremental value in multivariable GDM prediction models.

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**Informed Consent Statement:** Informed consent was not obtained due to the retrospective nature of the study and the use of anonymized data.

**Data Availability Statement:** The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

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## Abbreviations

The following abbreviations are used in this manuscript:

| Abbreviation | Definition |
|---|---|
| GDM | Gestational diabetes mellitus |
| OGTT | Oral glucose tolerance test |
| IADPSG | International Association of Diabetes and Pregnancy Study Groups |
| HDL-C | High-density lipoprotein cholesterol |
| LDL-C | Low-density lipoprotein cholesterol |
| TC | Total cholesterol |
| TG | Triglycerides |
| ROC | Receiver operating characteristic |
| AUC | Area under the receiver operating characteristic curve |
| OR | Odds ratio |
| CI | Confidence interval |
| SD | Standard deviation |
| Q1 | First quartile |
| Q3 | Third quartile |
| IRB | Institutional Review Board |

## References

1. Hod, M.; Kapur, A.; Sacks, D.A.; Hadar, E.; Agarwal, M.; Di Renzo, G.C.; Roura, L.C.; McIntyre, H.D.; Morris, J.L.; Divakar, H. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. *Int. J. Gynaecol. Obstet.* **2015**, *131*, S173–S211. [CrossRef]
2. American Diabetes Association. 14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2020. *Diabetes Care* **2020**, *43*, S183–S192. [CrossRef]
3. Talasaz, Z.H.; Sadeghi, R.; Askari, F.; Dadgar, S.; Vatanchi, A. First trimesters Pregnancy-Associated Plasma Protein-A levels value to predict gestational diabetes mellitus: A systematic review and meta-analysis of the literature. *Taiwan. J. Obstet. Gynecol.* **2018**, *57*, 181–189. [CrossRef]
4. Savvidou, M.; Nelson, S.M.; Makgoba, M.; Messow, C.M.; Sattar, N.; Nicolaides, K. First-trimester prediction of gestational diabetes mellitus: Examining the potential of combining maternal characteristics and laboratory measures. *Diabetes* **2010**, *59*, 3017–3022. [CrossRef]
5. Correa, P.J.; Venegas, P.; Palmeiro, Y.; Albers, D.; Rice, G.; Roa, J.; Cortez, J.; Monckeberg, M.; Schepeler, M.; Osorio, E.; et al. First trimester prediction of gestational diabetes mellitus using plasma biomarkers: A case-control study. *J. Perinat. Med.* **2019**, *47*, 161–168. [CrossRef]
6. Wang, C.; Zhu, W.; Wei, Y.; Su, R.; Feng, H.; Lin, L.; Yang, H. The predictive effects of early pregnancy lipid profiles and fasting glucose on the risk of gestational diabetes mellitus stratified by body mass index. *J. Diabetes Res.* **2016**, *2016*, 3013567. [CrossRef]
7. Li, G.; Kong, L.; Zhang, L.; Fan, L.; Su, Y.; Rose, J.C.; Zhang, W. Early pregnancy maternal lipid profiles and the risk of gestational diabetes mellitus stratified for body mass index. *Reprod. Sci.* **2015**, *22*, 712–717. [CrossRef]
8. Emet, T.; Üstüner, I.; Güven, S.G.; Balık, G.; Ural, Ü.M.; Tekin, Y.B.; Şentürk, Ş.; Şahin, F.K.; Avşar, A.F. Plasma lipids and lipoproteins during pregnancy and related pregnancy outcomes. *Arch. Gynecol. Obstet.* **2013**, *288*, 49–55. [CrossRef]
9. Rizzo, M.; Berneis, K.; Altinova, A.E.; Toruner, F.B.; Akturk, M.; Ayvaz, G.; Rini, G.B.; Spinas, G.A.; Arslan, M. Atherogenic lipoprotein phenotype and LDL size and subclasses in women with gestational diabetes. *Diabet. Med.* **2008**, *25*, 1406–1411. [CrossRef]
10. Enquobahrie, D.A.; Williams, M.A.; Qiu, C.; Luthy, D.A. Early pregnancy lipid concentrations and the risk of gestational diabetes mellitus. *Diabetes Res. Clin. Pract.* **2005**, *70*, 134–142. [CrossRef]
11. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* **2010**, *33*, 676–682. [CrossRef]
12. Hu, J.; Gillies, C.L.; Lin, S.; Stewart, Z.A.; Melford, S.E.; Abrams, K.R.; Baker, P.N.; Khunti, K.; Tan, B.K. Association of maternal lipid profile and gestational diabetes mellitus: A systematic review and meta-analysis of 292 studies and 97,880 women. *eClinicalMedicine* **2021**, *34*, 100830. [CrossRef]
13. Milincic, M.; Cirkovic, A.; Ivanovic, K.; Dugalic, S.; Gojnic Dugalic, M. Trimester-specific serum lipid profiles in gestational diabetes mellitus: A systematic review, meta-analysis, and meta-regression. *Medicina* **2025**, *61*, 1290. [CrossRef]

14. Xu, X.; Luo, S.; Lin, J.; Zhou, J.; Zheng, L.; Yang, L.; Zhang, Z.; Dong, Y.; Ma, M.; Li, H.; et al. Association between maternal lipid profiles and lipid ratios in early to middle pregnancy as well as their dynamic changes and gestational diabetes mellitus. *BMC Pregnancy Childbirth* **2024**, *24*, 510. [CrossRef]
15. Hivert, M.-F.; Backman, H.; Benhalima, K.; Catalano, P.; Desoye, G.; Immanuel, J.; McKinlay, C.J.D.; Meek, C.L.; Nolan, C.J.; Ram, U.; et al. Pathophysiology from preconception, during pregnancy, and beyond. *Lancet* **2024**, *404*, 158–174. [CrossRef]
16. Wang, Y.; Pan, X.F.; Pan, A. Lipidomics in gestational diabetes mellitus. *Curr. Opin. Lipidol.* **2023**, *34*, 1–11. [CrossRef]
17. Cibickova, L.; Schovanek, J.; Karasek, D. Changes in serum lipid levels during pregnancy in women with gestational diabetes. A narrative review. *Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub.* **2021**, *165*, 8–12. [CrossRef]
18. Hirano, T. Pathophysiology of diabetic dyslipidemia. *J. Atheroscler. Thromb.* **2018**, *25*, 771–782. [CrossRef]
19. Brenner, H.; Gefeller, O. Variation of sensitivity, specificity, likelihood ratios and predictive values with disease prevalence. *Stat. Med.* **1997**, *16*, 981–991. [CrossRef]
20. Steyerberg, E.W.; Harrell, F.E. Prediction models need appropriate internal, internal–external, and external validation. *J. Clin. Epidemiol.* **2016**, *69*, 245–247. [CrossRef]
21. Temur, İ.; Özsan, M.; Temur, K.T.; Çolak, A.B. A Hybrid and Comparative Machine Learning Framework for Predicting Gestational Diabetes Mellitus via a Prospective Case-Control Design: A Pilot Study Integrating Periodontal Health and Hematological Inflammatory Markers. *Metabolites* **2026**, *16*, 617. [CrossRef]
22. Özsan, M.; Temur, İ.; Temur, K.T.; Çolak, A.B. Classification Model of Preterm Prelabor Rupture of Membranes Risk Using an Artificial Neural Network Model Based on Hematological, Dental, and Periodontal Markers. *BMC Oral Health* **2026**, *26*, 1641. [CrossRef]

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