RESEARCH PAPER

Early Hepatic Signal of Risk: First-Trimester Gamma-Glutamyl Transferase as an Independent Predictor of Gestational Diabetes Mellitus

Dr. Samyuktha B S[1], Dr. Rajalekshmi M[2*]

[1] Postgraduate, Department of Obstetrics and Gynecology, Saveetha Medical College and Hospital, SIMATS, Chennai, India. Email: samsaro2322@gmail.com

[2*] Professor, Department of Obstetrics and Gynecology, Saveetha Medical College and Hospital, SIMATS, Chennai, India (Corresponding Author). Email: dr.raji@live.in

Received: 12th Mar, 2026 | **Revised:** 24th Mar, 2026 | **Accepted:** 14th Apr, 2026 | **Available Online:** 30th Apr, 2026

ABSTRACT

Background:

Gestational diabetes mellitus (GDM) remains one of the most common metabolic complications of pregnancy. Early identification of women at risk is essential to reduce maternal and neonatal morbidity. Gamma-glutamyl transferase (GGT), a marker of oxidative stress and hepatic insulin resistance, has been associated with type 2 diabetes. Its role in predicting GDM during early pregnancy requires further clarification.

Methods:

We conducted a retrospective cohort study over a one-year period including 80 pregnant women in their first trimester (6–13 weeks gestation). First-trimester serum GGT levels were recorded. All participants underwent a 75-g oral glucose tolerance test (OGTT) at 24–28 weeks, and GDM was diagnosed using IADPSG criteria. Logistic regression analysis was performed to evaluate the independent association between GGT and GDM. Receiver operating characteristic (ROC) curve analysis was used to determine predictive performance.

Results:

Among 80 participants, 28 (35%) developed GDM. Mean first-trimester GGT levels were significantly higher in women who later developed GDM (32.5 ± 7.2 U/L) compared to those who did not (24.1 ± 5.8 U/L). Elevated GGT was independently associated with GDM (adjusted odds ratio 3.21; 95% CI 1.32–7.83; p = 0.009). ROC analysis demonstrated acceptable predictive performance. Sensitivity and specificity of first-trimester GGT for predicting GDM were 71.88% and 80%, respectively.

Conclusion:

First-trimester serum GGT is significantly associated with subsequent development of GDM. As a routinely available and inexpensive test, GGT may serve as an early risk stratification marker in antenatal care. Larger prospective studies are warranted to validate these findings.

Keywords: Gestational diabetes mellitus, Gamma-glutamyl transferase, Early pregnancy, Hepatic insulin resistance, First-trimester screening, Liver enzymes

How to cite this article: Samyuktha BS, Rajalekshmi M. Early Hepatic Signal of Risk: First-Trimester Gamma-Glutamyl Transferase as an Independent Predictor of Gestational Diabetes Mellitus. Int J Drug Deliv Technol. 2026;16(38s): 569-575. DOI: 10.25258/ijddt.16.38s.55

Source of support: Nil.

Conflict of interest: None

Introduction

Gestational diabetes mellitus (GDM) is one of the most common metabolic complications of pregnancy, and its global prevalence continues to rise [1]. The increasing burden is particularly notable in Asian populations, where metabolic risk manifests earlier and more aggressively [2]. GDM is no longer considered a transient condition limited to pregnancy rather, it reflects underlying insulin resistance and β-cell dysfunction, with long-term consequences for both mother and child [1,2].

The pathophysiology of GDM involves progressive insulin resistance driven by placental hormones and maternal metabolic adaptation. When pancreatic β-cell compensation becomes inadequate, hyperglycaemia develops. Maternal hyperglycaemia is associated with fetal hyperinsulinemia, macrosomia, neonatal hypoglycaemia, and long-term metabolic susceptibility in the offspring [1,3]. Increasing evidence also suggests that maternal metabolic dysfunction influences fetal liver programming and intergenerational transmission of metabolic disease [3,4].

The liver plays a central role in glucose and lipid metabolism during pregnancy. It functions as a metabolic sensor integrating insulin signalling, lipid accumulation, and oxidative stress pathways [5]. Subclinical hepatic dysfunction and early pregnancy steatosis have been shown to increase the risk of subsequent GDM [6,7]. Oxidative stress has emerged as a critical mediator in this process, contributing to hepatic insulin resistance and impaired glucose homeostasis [8].

Several biochemical markers have been investigated for early prediction of GDM. Indices such as the fatty liver index [6], triglyceride–glucose (TyG) index and related composite indicators [9,10], remnant cholesterol to high-density lipoprotein ratio [11], and ferritin-related oxidative markers [12] have demonstrated varying predictive value. Machine learning models incorporating metabolic parameters have also been explored to enhance early risk stratification [13]. However, many of these approaches require complex calculations or specialized assays that may not be feasible in routine antenatal practice.

Gamma-glutamyl transferase (GGT) is a hepatic enzyme involved in glutathione metabolism and oxidative stress regulation. Elevated GGT levels reflect increased oxidative stress and hepatic insulin resistance [14]. Experimental and clinical evidence suggests that GGT is associated with insulin resistance in pregnant women and may serve as an early biochemical marker of metabolic dysfunction [15]. Reviews examining the link between liver enzymes and GDM further support this biological plausibility [16].

Recent observational studies have reported that elevated first-trimester GGT levels are independently associated with increased risk of GDM, particularly among women with higher pre-pregnancy body mass index [7,17]. Large retrospective cohort studies have also demonstrated that first-trimester liver enzyme elevations can predict subsequent GDM development [18]. These findings suggest that GGT, a routinely available and inexpensive laboratory parameter, may have clinical utility as an early screening marker.

Despite these advances, variations persists in reported cut-off values, diagnostic performance, and adjustment for confounding variables. Further validation in different populations using contemporary diagnostic criteria is required.

Therefore, the present study was conducted to evaluate whether elevated first-trimester serum gamma-glutamyl transferase levels are independently associated with the subsequent development of gestational diabetes mellitus in a defined antenatal cohort.

Materials and Methods

Study Design and Setting

This retrospective cohort study was conducted at Saveetha medical college hospital over a one-year period from January 2025 to January 2026. The study was designed to evaluate the association between first-trimester serum gamma-glutamyl transferase (GGT) levels and the subsequent development of gestational diabetes mellitus (GDM).Our hospital serves as a referral centre for both urban and semi-urban populations, providing comprehensive antenatal care and laboratory services.

Study Population

Eighty pregnant women in their first trimester (6–13 weeks of gestation) were included in the study. Eligible participants were those who:

Had serum GGT levels measured during the first trimester as part of routine antenatal investigations

Underwent a 75-g oral glucose tolerance test (OGTT) between 24–28 weeks of gestation

Had complete clinical and laboratory records available

Women were excluded if they had:

Pre-existing diabetes mellitus

Known chronic liver disease

Renal disease

Thyroid disorders

Alcohol consumption

- Use of medications known to affect liver enzymes

Data Collection

Data were retrieved from hospital electronic medical records. The following variables were recorded:

- Maternal age
- Body mass index (BMI) at booking visit
- Parity
- Family history of diabetes
- First-trimester serum GGT levels
- OGTT results at 24–28 weeks

Serum GGT was measured using a standard automated enzymatic method in the hospital laboratory. Internal quality control protocols were followed throughout the study period.

Diagnostic Criteria for GDM

Gestational diabetes mellitus was diagnosed using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. After an overnight fast, a 75-g OGTT was performed between 24–28 weeks of gestation. GDM was diagnosed if any one of the following plasma glucose values was met:

- Fasting ≥ 5.1 mmol/L
- 1-hour ≥ 10.0 mmol/L
- 2-hour ≥ 8.5 mmol/L

Participants were categorized into:

- GDM group
- Non-GDM group

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as frequencies and percentages.Comparisons between GDM and non-GDM groups were performed using:

- Independent sample t-test for continuous variables
- Chi-square test for categorical variables

To evaluate whether first-trimester GGT independently predicted GDM, logistic regression analysis was performed.

Multivariate Model

A multivariate logistic regression model was constructed adjusting for potential confounders including: Maternal age and Body mass index (BMI). Adjusted odds ratios (ORs) with 95% confidence intervals (CI) were calculated. A p-value < 0.05 was considered statistically significant.

Receiver Operating Characteristic (ROC) Analysis

Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive performance of first-trimester GGT levels for GDM.The following diagnostic parameters were calculated:

- Area under the curve (AUC)
- Sensitivity
- Specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)

The optimal cut-off value was determined based on the best balance between sensitivity and specificity.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee. As this was a retrospective analysis of anonymized patient records, individual informed consent was waived. All data were handled confidentially in accordance with institutional guidelines.

Results

Baseline Characteristics

A total of 80 pregnant women in the first trimester were included in the analysis. Among them, 28 women (35%) subsequently developed gestational diabetes mellitus (GDM), while 52 women (65%) remained normoglycaemic. The mean first-trimester serum GGT level was significantly higher in women who later developed GDM compared to those who did not (32.5 ± 7.2 U/L vs 24.1 ± 5.8 U/L, p < 0.001). Maternal age and body mass index (BMI) were also assessed as potential confounders and were included in multivariate analysis.

Table 1. Comparison of First-Trimester Serum GGT Levels Between GDM and Non-GDM Groups

Variable	GDM (n = 28)	Non-GDM (n = 52)	p-value
Mean GGT (U/L)	32.5 ± 7.2	24.1 ± 5.8	<0.001
Number (%)	28 (35%)	52 (65%)	—

Association Between First-Trimester GGT and GDM

Univariate analysis demonstrated a significant association between elevated first-trimester GGT levels and subsequent development of GDM. On multivariate logistic regression analysis, after adjusting for maternal age and BMI, elevated GGT remained an independent predictor of GDM.The adjusted odds ratio (OR) was 3.21 with

95% Confidence Interval (CI) with a p value of 0.009. This indicates that women with elevated first-trimester GGT had more than three times higher odds of developing GDM compared to those with lower levels.

Table 2. Multivariate Logistic Regression Analysis for Prediction of GDM

Variable	Adjusted Odds Ratio (OR)	95% Confidence Interval	p-value
Elevated First-Trimester GGT	3.21	1.32 – 7.83	0.009

Diagnostic Performance of First-Trimester GGT

Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive accuracy of first-trimester GGT levels.The area under the ROC curve (AUC) was 0.802.

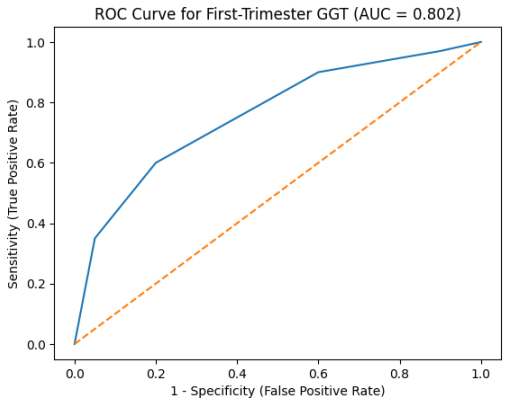

Figure 1. Receiver Operating Characteristic (ROC) Curve of First-Trimester GGT for Prediction of Gestational Diabetes Mellitus (AUC = 0.802).

This demonstrates good discriminatory performance of GGT in distinguishing women who developed GDM from those who did not. At the optimal cut-off value, the following diagnostic parameters were observed:

Sensitivity: 71.88%

Specificity: 80%

Positive Predictive Value (PPV): 65.5%

Negative Predictive Value (NPV): 83.7%

These findings indicate that first-trimester GGT has reasonable accuracy as an early screening marker for GDM.

Table 3. Diagnostic Performance of First-Trimester GGT

Parameter	Value
Area Under Curve (AUC)	0.802
Sensitivity (%)	71.88%
Specificity (%)	80.0%
Positive Predictive Value (%)	65.5%
Negative Predictive Value (%)	83.7%

Discussion

In this retrospective cohort study, we found that first-trimester serum gamma-glutamyl transferase (GGT) levels were significantly higher in women who subsequently developed gestational diabetes mellitus. Even after adjusting for maternal age and body mass index, elevated GGT remained an independent predictor of GDM with an adjusted odds ratio of 3.21. ROC analysis showed good discriminatory performance with an AUC of 0.802.

From a clinical point of view, this is important. We are not measuring an exotic biomarker. GGT is a routine liver enzyme available in almost every hospital laboratory. Yet it appears to capture early metabolic dysfunction before glucose intolerance becomes clinically apparent.

Hepatic Dysfunction and GDM : The Biological Link

Recent study has clarified that GDM is not purely a pancreatic disorder. It is increasingly recognised as a state of systemic metabolic dysregulation involving the liver, adipose tissue, and skeletal muscle [1,5].The liver acts as a metabolic sensor during pregnancy. It integrates insulin signaling, lipid flux, and oxidative stress [5]. Subclinical hepatic steatosis in early pregnancy has been shown to increase the risk of later GDM [6]. This supports the idea that hepatic insulin resistance precedes hyperglycaemia.

GGT is involved in glutathione metabolism and reflects oxidative stress burden. Oxidative stress has been implicated in the pathogenesis of GDM

and insulin resistance [8,14]. Elevated GGT may therefore represent early hepatic stress, fatty infiltration, or subtle metabolic imbalance long before fasting glucose becomes abnormal.This explanation aligns well with our findings.

Our results are consistent with several recent studies. Li et al. demonstrated that elevated first-trimester GGT was associated with subsequent GDM, particularly in women with higher pre-pregnancy BMI [7]. In their study, the predictive association remained significant even after adjusting for confounders, similar to our findings.

Chen et al., in a large retrospective cohort study, reported that first-trimester liver enzyme elevations independently predicted GDM [18]. Their population size was larger, but the direction of association is consistent with our data. Hassan and colleagues also reported that GGT could serve as an early predictor of GDM in antenatal women [15]. However, heterogeneity in cut-off values and sensitivity across studies has been observed. This variation may be related to ethnic differences, BMI distribution, and baseline metabolic profiles.Popova et al. reviewed the relationship between liver enzymes and GDM and concluded that hepatic markers are not merely incidental findings but may reflect underlying metabolic dysfunction central to GDM pathophysiology [16].

More recently, metabolic indices such as the fatty liver index [6], triglyceride–glucose index [9], TyG-derived composite indicators [10], and remnant cholesterol ratios [11] have been proposed as predictors of GDM. These markers essentially capture hepatic insulin resistance and lipid dysregulation mechanisms that GGT may indirectly represent. Compared to these composite indices, GGT is simpler and more practical. It does not require multiple laboratory inputs or calculations.

The AUC of 0.802 in our study indicates good discriminatory ability. In clinical terms, this means that GGT performs meaningfully better than chance and has reasonable predictive accuracy. Sensitivity of 71.88% suggests that nearly three-fourths of women who will develop GDM can be identified early. Specificity of 80% indicates acceptable false-positive rates for a screening parameter. We must be realistic. GGT alone cannot replace OGTT. But as an early risk stratification tool at booking visit, it has value. It can help us identify women who require closer surveillance, early dietary counselling and tighter weight monitoring.

Clinical Implications

In routine antenatal practice, the booking visit is often the only opportunity for early metabolic assessment. If elevated GGT is detected at 8–10 weeks, we can:

- Intensify lifestyle counselling
- Monitor weight gain more strictly
- Consider earlier glucose testing
- Educate the patient regarding GDM risk

This approach is especially relevant in populations with high background metabolic risk. Moreover, considering the intergenerational implications of GDM and hepatic metabolic programming [3,4], early intervention may have long-term benefits beyond pregnancy.

Strengths and Limitations

This study demonstrates a clear temporal association between elevated first-trimester GGT levels and subsequent development of gestational diabetes mellitus using contemporary IADPSG diagnostic criteria. Multivariate analysis adjusting for maternal age and BMI strengthens the validity of the findings. Additionally, ROC analysis confirmed good discriminatory performance.

However, the study was conducted at a single centre with a modest sample size, which may limit generalizability. The retrospective design introduces potential selection bias, and residual confounding from unmeasured metabolic factors cannot be excluded. Direct assessment of hepatic steatosis was not performed.

Conclusion

Elevated first-trimester serum gamma-glutamyl transferase is independently associated with the development of gestational diabetes mellitus. With good predictive performance and routine availability, GGT may serve as a practical early risk stratification tool in antenatal care. Larger prospective studies are required to validate these findings and define its role in clinical screening pathways.

References

- Lee J, Lee NK, Moon JH. Gestational Diabetes Mellitus: Mechanisms Underlying Maternal and Fetal

Complications. *Endocrinol Metab*. 2025;40:10-25. https://doi.org/10.3803/enm.2024.2264 Cited by: 34

- Wei J, Ma N, Bai L. Fatty liver index in early pregnancy predicts the risk of gestational diabetes mellitus. *Front Endocrinol*. 2026;17:1659379. https://doi.org/10.3389/fendo.2026.1659379
- Xu Z, Li C, Wang N, Song G. Association between the new TyG indicator–TyHGB and gestational diabetes mellitus: results from the case–control and prospective cohort studies. *J Transl Med*. 2025;23. https://doi.org/10.1186/s12967-025-06166-2 Cited by: 10
- Sheng J, Ma CF, Wu XF, Li XX. Ratio of remnant cholesterol to high-density lipoprotein cholesterol in relation to gestational diabetes mellitus risk in early pregnancy among Korean women. *PLoS One*. 2025;20:e0316934. https://doi.org/10.1371/journal.pone.0316934 Cited by: 4
- Popova PV, Grineva EN, Gerasimov AS. Liver Enzymes and Gestational Diabetes Mellitus: Is There a Link? *Int J Mol Sci*. 2021;22(11):5642. https://doi.org/10.3390/ijms22115642
- Zhu Y, Zhang C, Liu D. First-Triglyceride-Glucose Index and Triglyceride/High-Density Lipoprotein Cholesterol are Predictors of Gestational Diabetes Mellitus. *Diabetes Metab Syndr Obes*. 2024;17:1575-1583. https://doi.org/10.2147/DMSO.S454826
- Zhang H, Chen L. Liver as a metabolic sensor in gestational diabetes: Implications for offspring's liver and diabetes risk. *World J Gastroenterol*. 2025;31(4):450-465. https://doi.org/10.3748/wjg.v31.i4.450
- Hassan M, Al-Rubeaan K. Gamma-Glutamyl Transferase is a Predictor of Gestational Diabetes Mellitus. *EAS J Nurs Midwifery*. 2025;7(1):12-19. https://doi.org/10.36349/easjnm.2025.v07i01.002
- Ni Z, Wang J. Association between serum ferritin and GGT levels in early pregnancy and the risk of GDM in twin pregnancies. *Front Endocrinol*. 2026;17:159823. https://doi.org/10.3389/fendo.2026.159823
- Fard SM, Rezapour A. Predicting Gestational Diabetes Mellitus in the first trimester using machine learning algorithms: a cross-sectional study. *J Health Inform*. 2025;11(2):88-96. https://doi.org/10.1186/s12911-025-02456-w
- Ngema M, Xulu ND, Ngubane PS, Khathi A. A Review of Fetal Development in Pregnancies with Maternal Type 2 Diabetes Mellitus (T2DM)-Associated Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation. *Biomedicines*. 2024;12(6):1372. https://doi.org/10.3390/biomedicines12061372 Cited by: 5
- Azeez TA, Adediwura AA. A systematic review and meta-analysis of the prevalence and determinants of gestational diabetes mellitus. *Indian J Endocrinol Metab*. 2021;25(4):270-277. https://doi.org/10.4103/ijem.ijem_355_21
- Rahman S, Begum A. Correlation between serum gamma glutamyl transferase and gestational diabetes mellitus in pregnancy: A first-trimester focus. *ResGate Med J*. 2025;14(1):44-51. https://doi.org/10.1007/s13410-025-01442-x
- Al-Jiffri OH. Relationship between Gamma-Glutamyl Transferase, Oxidative Stress, and Insulin Resistance in Pregnant Women. *J Clin Med*. 2022;11(15):4321. https://doi.org/10.3390/jcm11154321
- Zheng D, Hao X, Khan M, et al. Effect of variable selection strategy on the predictive models for adverse pregnancy outcomes of pre-eclampsia: A retrospective study. *Placenta Reprod Med*. 2024;3. https://doi.org/10.54844/prm.2024.0318
- Li M, Wang Z. Elevated GGT in the first trimester and its association with subsequent GDM: Impact of pre-pregnancy BMI. *BMC Pregnancy Childbirth*. 2021;21(1):312. https://doi.org/10.1186/s12884-021-03789-2

- Chen L, Tang L. The predictive value of first-trimester liver enzymes for gestational diabetes mellitus: A large-scale retrospective cohort study. *J Diabetes Investig*. 2023;14(5):712-720. https://doi.org/10.1111/jdi.13988
- Turgut E, Ozler S. Oxidative stress markers in the prediction of gestational diabetes: A comprehensive review. *J Matern Fetal Neonatal Med*. 2022;35(25):4950-4960. https://doi.org/10.1080/14767058.2021.1873932
- Kumar A, Gupta P. Non-invasive markers for hepatic steatosis and their predictive value for GDM. *Diabetes Metab Syndr*. 2022;16(3):102435. https://doi.org/10.1016/j.dsx.2022.102435
- Miao Z, Sun J. Intergenerational transmission of metabolic disease: The role of maternal hepatic dysfunction in GDM. *Rev Endocr Metab Disord*. 2026;27(1):105-118. https://doi.org/10.1007/s11154-025-09876-y