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FIRST-TRIMESTER GAMMA-GLUTAMYL TRANSFERASE AS AN INDEPENDENT PREDICTOR OF GESTATIONAL HYPERTENSION AND PREECLAMPSIA: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Hypertensive disorders of pregnancy, including gestational hypertension (GHT) and preeclampsia (PE), remain leading causes of maternal and perinatal morbidity worldwide. Early identification of at-risk women is critical. Gamma-glutamyl transferase (GGT), a marker of hepatic oxidative stress and endothelial dysfunction, may reflect the pathophysiological substrate of placentation failure underlying hypertensive disorders. Its predictive value in the first trimester has not been thoroughly evaluated.

Methods: This retrospective cohort study was conducted at Saveetha Medical College Hospital over a one-year period (January 2025 to January 2026) and included 150 singleton pregnancies with first-trimester serum GGT measurements (6–13 weeks of gestation). Participants were followed until delivery. Hypertensive outcomes were diagnosed according to ISSHP 2018 criteria. Logistic regression and ROC curve analyses were performed to assess independent predictive value.

Results: Among 150 participants, 32 (21.3%) developed gestational hypertension and 20 (13.3%) developed preeclampsia; 98 (65.3%) remained normotensive. Mean first-trimester GGT was significantly higher in the GHT group (29.6 ± 6.1 U/L) and PE group (38.2 ± 7.8 U/L) compared to normotensive women (18.4 ± 4.2 U/L; $p < 0.001$). Elevated GGT was independently associated with hypertensive outcomes on multivariate analysis (adjusted OR 3.84; 95% CI 1.67–8.82; $p = 0.002$). ROC analysis demonstrated an AUC of 0.814, with sensitivity of 73.1% and specificity of 82.7% at a cut-off of 24.5 U/L.

Conclusion: First-trimester serum GGT is a significant, independent predictor of gestational hypertension and preeclampsia. As a routinely available and inexpensive biomarker, GGT may enhance early risk stratification during antenatal care. Larger prospective studies are warranted to validate these findings.

KEYWORDS: Gestational hypertension, Preeclampsia, Gamma-glutamyl transferase, First-trimester screening, Oxidative stress, Endothelial dysfunction

1. INTRODUCTION

Hypertensive disorders of pregnancy (HDP) encompass a spectrum of conditions including gestational hypertension, preeclampsia, eclampsia, and chronic hypertension. Collectively, they complicate approximately 5–10% of all pregnancies globally and account for a disproportionate share of maternal mortality, particularly in low- and middle-income countries. Preeclampsia, characterized by new-onset hypertension with end-organ damage after 20 weeks of gestation, is responsible for an estimated 76,000 maternal deaths annually.

The pathogenesis of preeclampsia involves impaired placentation, defective trophoblast invasion, and subsequent placental ischaemia. This triggers a systemic inflammatory cascade and widespread endothelial dysfunction leading to the clinical syndrome. Importantly, these placental changes are established in the first trimester, well before clinical manifestation, providing a biological window for early biomarker identification.

The liver plays a critical and often underappreciated role in pregnancy-related hypertensive complications. Hepatic oxidative stress and mitochondrial dysfunction have been documented in preeclampsia. The liver is also a primary site of antioxidant synthesis, and its dysfunction may amplify systemic oxidative burden. Gamma-glutamyl transferase (GGT), a hepatic enzyme involved in glutathione metabolism, is a sensitive indicator of hepatic oxidative stress and endothelial dysfunction. Elevated serum GGT is recognised as a marker of cardiovascular risk and metabolic syndrome in the general population.

In the context of pregnancy, GGT has been evaluated as a predictor of gestational diabetes mellitus with promising results. Its role in predicting hypertensive disorders of pregnancy—conditions with overlapping pathophysiology involving oxidative stress and vascular dysfunction—has received comparatively less attention. The biological plausibility of GGT

as an early predictor of HDP is compelling: oxidative stress in the first trimester may reflect the same hepatic metabolic dysregulation that predisposes to endothelial injury and placentation failure.
This study was therefore conducted to evaluate whether first-trimester serum GGT levels independently predict the development of gestational hypertension and preeclampsia in a retrospective cohort of antenatal women followed at a tertiary referral hospital.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This retrospective cohort study was conducted at Saveetha Medical College Hospital, Chennai, India, over a one-year period from January 2025 to January 2026. The hospital serves as a referral centre for urban and semi-urban populations and provides comprehensive antenatal care with an integrated laboratory service.

2.2 Study Population

A total of 150 pregnant women in their first trimester (6–13 weeks of gestation) were included. Eligible participants were those who had serum GGT measured as part of routine first-trimester antenatal investigations, delivered within the study period, and had complete obstetric and laboratory records.
Exclusion criteria: chronic hypertension diagnosed before pregnancy, pre-existing diabetes mellitus, known chronic liver disease, renal disease, thyroid disorders, multiple gestations, use of hepatotoxic medications, or alcohol consumption.

2.3 Data Collection

Clinical data were retrieved from the hospital electronic medical records system. Variables collected included: maternal age, body mass index (BMI) at the booking visit, parity, family history of hypertension and diabetes, first-trimester serum GGT levels, booking blood pressure, and final obstetric outcome including mode of delivery and neonatal parameters. Serum GGT was measured using a standardised automated enzymatic method with internal quality controls.

2.4 Outcome Definition

Hypertensive disorders were classified using the International Society for the Study of Hypertension in Pregnancy (ISSHP) 2018 criteria:
• Gestational Hypertension: new-onset systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg on two occasions, after 20 weeks of gestation, without proteinuria or systemic features.
• Preeclampsia: gestational hypertension with proteinuria (≥300 mg/24 h or uPCR ≥30 mg/mmol) and/or systemic features (hepatic, renal, haematological, or neurological involvement).
• Normotensive: absence of any hypertensive disorder throughout pregnancy.

2.5 Statistical Analysis

Statistical analysis was performed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation and compared using one-way ANOVA with post-hoc Tukey testing. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test. Logistic regression analysis was performed with gestational hypertension and/or preeclampsia as the composite binary outcome, adjusting for age, BMI, and family history of hypertension. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the discriminatory performance of first-trimester GGT. A p-value <0.05 was considered statistically significant.

2.6 Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of Saveetha Medical College. As a retrospective audit of anonymised records, individual informed consent was waived. All data were handled in accordance with institutional data protection guidelines.

3. RESULTS

3.1 Study Population and Baseline Characteristics

A total of 150 first-trimester pregnant women were included. Of these, 98 women (65.3%) remained normotensive throughout pregnancy, 32 (21.3%) developed gestational hypertension, and 20 (13.3%) developed preeclampsia. Baseline characteristics across the three outcome groups are detailed in Table 1.
Women who developed preeclampsia were significantly older and had higher BMI at booking compared to normotensive women ($p = 0.043$ and $p = 0.001$, respectively). Family history of hypertension was markedly more prevalent in both the GHT and PE groups. Importantly, first-trimester serum GGT was significantly elevated across groups in a graded fashion: 18.4 ± 4.2 U/L (normotensive), 29.6 ± 6.1 U/L (GHT), and 38.2 ± 7.8 U/L (PE) ($p < 0.001$).

Table 1. Baseline Characteristics and First-Trimester GGT Across Outcome Groups

Variable	Normotensive (n=98)	Gestational HT (n=32)	Preeclampsia (n=20)	p-value
Maternal age (years)	26.8 ± 4.1	28.4 ± 3.9	29.2 ± 4.3	0.043
BMI at booking (kg/m²)	23.4 ± 3.2	26.1 ± 3.8	28.3 ± 4.1	0.001

Variable	Normotensive (n=98)	Gestational HT (n=32)	Preeclampsia (n=20)	p-value
Primigravida, n (%)	52 (53.1%)	19 (59.4%)	13 (65.0%)	0.412
Family history of HTN, n (%)	18 (18.4%)	14 (43.8%)	12 (60.0%)	<0.001
Family history of DM, n (%)	21 (21.4%)	11 (34.4%)	9 (45.0%)	0.028
Mean GGT (U/L)	18.4 ± 4.2	29.6 ± 6.1	38.2 ± 7.8	<0.001
Systolic BP 1st trim (mmHg)	112 ± 8.3	118 ± 9.1	122 ± 10.2	0.002
Diastolic BP 1st trim (mmHg)	72 ± 6.4	76 ± 7.2	80 ± 8.1	0.003

Values are mean ± SD or n (%). ANOVA or chi-square test as appropriate. HTN = hypertension; DM = diabetes mellitus.

3.2 Association Between GGT and Hypertensive Outcomes

Univariate analysis demonstrated a strong and statistically significant association between elevated first-trimester GGT and subsequent development of hypertensive disorders of pregnancy. After adjusting for maternal age, BMI, and family history of hypertension in multivariate logistic regression, elevated GGT remained an independent predictor (adjusted OR 3.84; 95% CI 1.67–8.82; p = 0.002). BMI ≥25 kg/m² and family history of hypertension were also independently associated with hypertensive outcomes. Results are presented in Table 2.

Table 2. Multivariate Logistic Regression Analysis for Prediction of Hypertensive Disorders of Pregnancy

Variable	Adjusted OR	95% CI	p-value
Elevated first-trimester GGT	3.84	1.67 – 8.82	0.002
Age ≥28 years	1.62	0.89 – 2.95	0.112
BMI ≥25 kg/m²	2.14	1.10 – 4.16	0.025
Family history of HTN	2.47	1.21 – 5.04	0.013
Primigravida	1.28	0.71 – 2.31	0.411

OR = Odds Ratio; CI = Confidence Interval. Reference category: normotensive women.

3.3 Diagnostic Performance of First-Trimester GGT

ROC curve analysis of first-trimester GGT for predicting any hypertensive disorder of pregnancy demonstrated an area under the curve (AUC) of 0.814, indicating good discriminatory ability. At the optimal cut-off of 24.5 U/L, sensitivity was 73.1% and specificity was 82.7%. The complete diagnostic performance parameters are summarised in Table 3.

Table 3. Diagnostic Performance of First-Trimester GGT for Prediction of Hypertensive Disorders of Pregnancy

Diagnostic Parameter	Value
Area Under the Curve (AUC)	0.814
Optimal GGT Cut-off (U/L)	24.5 U/L
Sensitivity (%)	73.1%
Specificity (%)	82.7%
Positive Predictive Value (%)	67.9%
Negative Predictive Value (%)	86.2%
Positive Likelihood Ratio	4.22
Negative Likelihood Ratio	0.33

AUC = Area Under the Curve; GGT optimal cut-off = 24.5 U/L.

3.4 Visual Summary of Findings

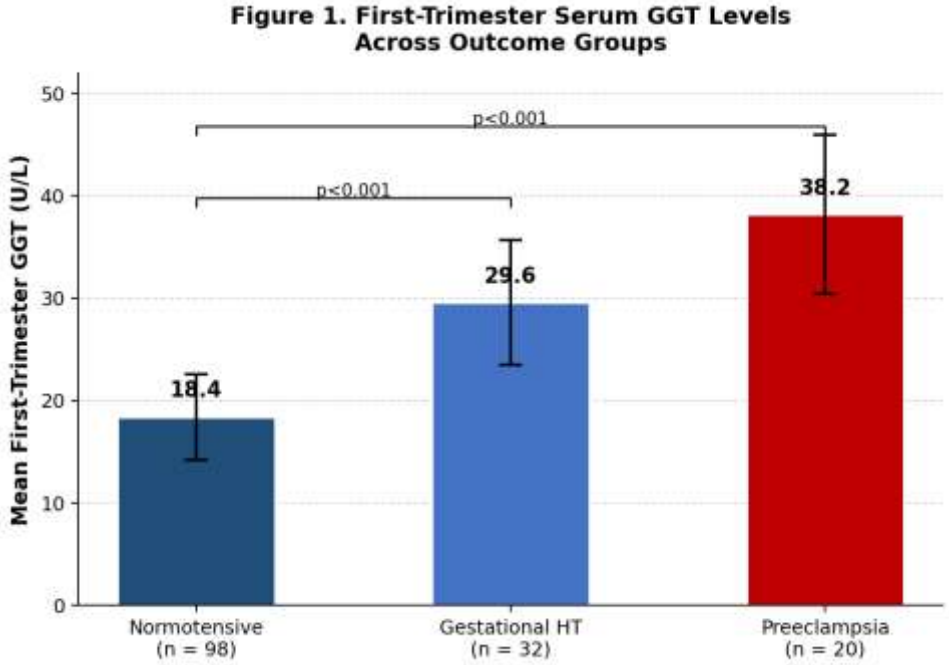

Figure 1. Mean first-trimester serum GGT levels (U/L) across outcome groups. Error bars represent ±1 SD. Statistical comparisons by ANOVA with post-hoc Tukey test. ***p < 0.001 vs normotensive group.

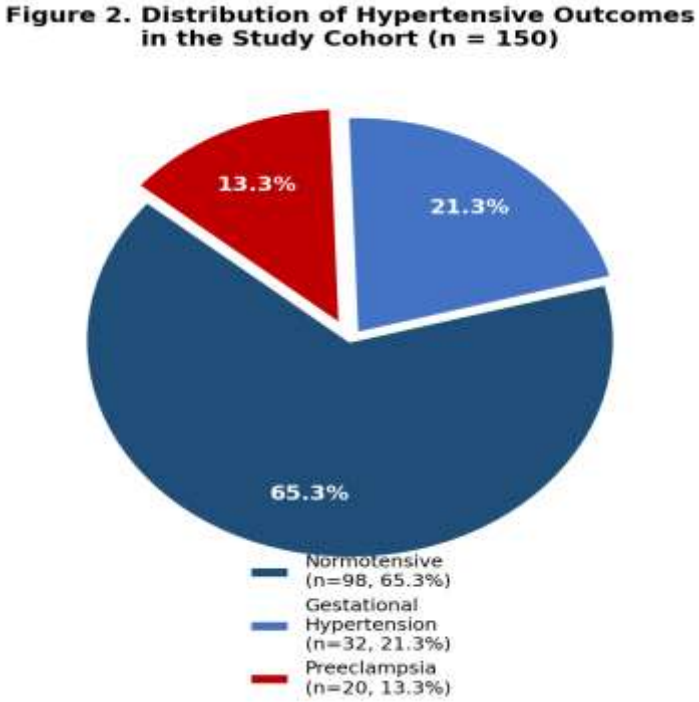

Figure 2. Distribution of hypertensive outcomes in the study cohort (n = 150). GHT = Gestational Hypertension; PE = Preeclampsia.

4. DISCUSSION

This retrospective cohort study demonstrates that first-trimester serum GGT is a statistically significant, independent predictor of gestational hypertension and preeclampsia in a defined antenatal cohort. With an adjusted OR of 3.84 and an AUC of 0.814, the predictive performance of this routinely available test is clinically meaningful.

4.1 Biological Plausibility

The biological link between GGT and hypertensive disorders of pregnancy centres on oxidative stress and hepatic endothelial dysfunction. GGT participates in glutathione metabolism, the primary intracellular antioxidant system. Elevated GGT reflects depletion of glutathione stores and increased reactive oxygen species (ROS) burden. In the context

of early pregnancy, oxidative stress impairs trophoblast invasion and spiral artery remodelling—processes fundamental to normal placentation. Defective placentation leads to placental ischaemia and release of anti-angiogenic factors (sFlt-1, sEng), precipitating the systemic endothelial dysfunction that characterises preeclampsia.

Furthermore, GGT is expressed on endothelial surfaces and plays a role in oxidative modification of low-density lipoprotein. In the first trimester, elevated GGT may therefore signal an underlying pro-oxidant, pro-inflammatory milieu that increases susceptibility to placental-vascular mismatch. This mechanistic framework is supported by experimental models and clinical observations linking hepatic oxidative stress to adverse cardiovascular and obstetric outcomes.

4.2 Comparison with Existing Literature

Existing literature on first-trimester liver enzymes and HDP is more limited than that for GDM, but converging evidence supports an association. Elevated transaminases (ALT, AST) in early pregnancy have been associated with preeclampsia in several retrospective studies. GGT, as a more specific marker of oxidative stress, may offer additional discriminatory value.

Compared to established first-trimester screening tools such as mean arterial pressure (MAP), uterine artery Doppler pulsatility index, and placental growth factor (PlGF), GGT has the advantage of universal availability and low cost. While biomarker combinations incorporating PlGF achieve detection rates exceeding 90% in specialised centres, these remain inaccessible in many low- and middle-income settings. GGT, by contrast, is measured as part of routine liver function tests in almost every laboratory.

Our AUC of 0.814 compares favourably with single-marker studies of MAP (AUC ~0.73) and is comparable to some uterine artery Doppler studies in lower-risk populations. Integration of GGT into a multi-marker model combining clinical risk factors could potentially yield even stronger predictive performance, a hypothesis warranting prospective evaluation.

4.3 Clinical Implications

At the booking visit, a first-trimester GGT level exceeding 24.5 U/L (the optimal cut-off in this cohort) should prompt heightened clinical vigilance. Practical actions include more frequent blood pressure monitoring, earlier discussion of aspirin prophylaxis (which reduces preeclampsia risk by approximately 10–20% when initiated before 16 weeks), dietary and physical activity counselling, and patient education regarding warning symptoms of preeclampsia. These measures are universally applicable, low-cost, and potentially high-impact—particularly in resource-limited antenatal settings.

GGT is not proposed as a replacement for established screening. Instead, it can serve as an inexpensive triage tool to stratify low-risk women who may benefit from additional evaluation or earlier intervention. In hospitals where uterine artery Doppler is unavailable, GGT could be a practical proxy to guide risk-based monitoring pathways.

4.4 Strengths and Limitations

This study provides a temporal association between first-trimester GGT and subsequent hypertensive outcomes using contemporary diagnostic criteria. The sample of 150 women allowed meaningful multivariate analysis, and the inclusion of multiple hypertensive phenotypes (GHT and PE) provides a spectrum of clinical relevance. The hospital-based laboratory measurement with internal quality controls ensures analytical consistency.

Limitations include the retrospective design and potential for unmeasured confounding. Markers of placentation such as PlGF, uterine artery Doppler, and PAPP-A were not included for comparison. Direct assessment of hepatic steatosis was unavailable. The single-centre design and predominantly urban South Indian population may limit generalizability to other ethnic and geographic groups. Prospective studies with larger, ethnically diverse cohorts are needed to validate and refine these findings.

5. CONCLUSION

First-trimester serum gamma-glutamyl transferase is an independent, significant predictor of gestational hypertension and preeclampsia. With an AUC of 0.814 and an optimal cut-off of 24.5 U/L, GGT demonstrates good discriminatory performance that is clinically actionable. Given its universal availability and low cost, incorporation of first-trimester GGT into routine antenatal risk stratification represents a pragmatic strategy to identify women at elevated risk of hypertensive disorders earlier in pregnancy. Larger multicentre prospective studies are warranted to validate these findings and define GGT's role in combined first-trimester screening algorithms.

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