Original Article

DOI: 10.7860/JCDR/2026/89569.24123

Comparison of sFlt-1/PlGF Ratio in Gestational Diabetes and Normoglycaemic Pregnancies with Early-onset Preeclampsia: A Cross-sectional Study

Biochemistry Section

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ABSTRACT

Introduction: Preeclampsia involves disrupted angiogenic balance, marked by elevated soluble Fms-Like Tyrosine kinase-1(sFlt-1) and reduced Placental Growth Factor (PlGF) levels. Preeclampsia is associated with angiogenic imbalance, and Gestational Diabetes Mellitus (GDM) may further influence this disruption, necessitating evaluation of combined diabetic and angiogenic effects.

Aim: To compare the maternal sFlt-1/PlGF ratio between GDM and normoglycaemic pregnancies with Early-Onset Preeclampsia (EO-PE).

Materials and Methods: The present cross-sectional study was conducted at the Department of Biochemistry at KAHER Jawaharlal Nehru Medical College and KLE Dr. Prabhakar Kore Hospital & Medical Research Centre, Belagavi, Karnataka, India from July 2024 to July 2025 study included 100 pregnant women {50 GDM and 50 normoglycaemic (non GDM)} with preeclampsia between 20 and 33 weeks of gestation. Serum sFlt-1 and PlGF levels were measured, and their ratio was calculated. Data normality was assessed using the Shapiro-Wilk test. Group comparisons were performed using the Mann-Whitney U test, and correlations were analysed using Spearman's correlation test. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, Version 25.0.

Results: The mean age of participants was comparable between the groups, with the GDM group having a mean age of (29.92±3.26) years and the non GDM group having a mean age of (29.26±2.81) years. The newborn gender distribution in the GDM group included 28 (56%) males and 22 (44%) females, while the normoglycaemic group included 26 (52%) males and 24 (48%) females. The sFlt-1/PlGF ratio was significantly higher in the GDM group {median: 109.8; Interquartile Range (IQR): 96.7-132.9} compared to normoglycaemic pregnancies (median: 56.8; IQR: 52.9-62.5) ($p<0.001$). Significant differences were also observed in Body Mass Index (BMI), fasting glucose, Glycated Haemoglobin (HbA1c), sFlt-1, and PlGF levels ($p<0.001$). The ratio showed strong positive correlations with fasting glucose ($r=0.807$) and HbA1c ($r=0.838$).

Conclusion: Elevated sFlt-1/ PlGF ratio in GDM compared to normoglycaemic pregnancies reflects early angiogenic imbalance and suggests greater angiogenic imbalance in GDM-associated EO-PE.

Keywords: Angiogenesis, Blood glucose, Hypertension, Placental growth factor, Soluble fms-like tyrosine kinase-1

INTRODUCTION

Preeclampsia is a complex multisystem disorder of pregnancy characterised by new-onset hypertension, endothelial dysfunction, and placental insufficiency occurring after 20 weeks of gestation [1]. It affects approximately 2-8% of pregnancies worldwide and contributes significantly to maternal and perinatal morbidity and mortality [1].

The underlying pathophysiology of preeclampsia is primarily attributed to abnormal placentation, leading to impaired uteroplacental perfusion, hypoxia, and the release of circulating factors that disrupt maternal endothelial function [1]. Among these factors, angiogenic imbalance plays a central role, characterised by increased anti-angiogenic factors such as sFlt-1 and decreased pro-angiogenic factors like PlGF, leading to endothelial dysfunction and impaired placental vascular development [1-3]. PlGF a pro-angiogenic molecule, is essential for normal placental vascular development, whereas sFlt-1 acts as an anti-angiogenic factor by binding and neutralising circulating vascular endothelial growth factor and PlGF [1,2].

An increase in sFlt-1 levels along with reduced PlGF results in an anti-angiogenic state, which is a hallmark of preeclampsia. The sFlt-1/PlGF ratio has therefore emerged as a reliable biomarker reflecting this imbalance and is widely used for the prediction and diagnosis of preeclampsia [2,3]. Clinical studies have demonstrated that elevated sFlt-1/PlGF ratios are associated with adverse pregnancy outcomes and threshold values such as >85 are linked with an increased risk of preeclampsia and related complications [4].

The GDM, a common metabolic disorder of pregnancy, has also been associated with endothelial dysfunction and an increased risk of preeclampsia [5]. Emerging evidence suggests that pregnancies complicated by GDM may exhibit alterations in angiogenic factors [6], potentially influencing the sFlt-1/PlGF ratio and reflecting early vascular changes [7].

EO-PE, occurring before 34 weeks of gestation, represents a severe form of the disease and is strongly associated with defective placentation, impaired uteroplacental perfusion, and adverse maternal and foetal outcomes [8-10]. Furthermore, meta-analytical evidence indicates that the sFlt-1/PlGF ratio has superior diagnostic and predictive performance compared to individual angiogenic markers alone [11].

Unlike previous studies [11-13] that assessed angiogenic markers independently, the present study evaluates the sFlt-1/PlGF ratio specifically in GDM-associated EO-PE. This provides additional insight into the combined impact of diabetic and angiogenic dysregulation which may contribute to improve early risk stratification.

Therefore, the present study was conducted to compare maternal sFlt-1/PlGF ratio between GDM and normoglycaemic preeclampsic pregnancies, thereby assessing its association with angiogenic imbalance in pregnancies complicated by EO-PE correlating with clinical and biochemical parameters.

MATERIALS AND METHODS

The present cross-sectional study was conducted at the Department of Biochemistry at KAHERs Jawaharlal Nehru Medical College and KLE Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka, India, from July 2024 to July 2025. Study was commenced after obtaining approval from the Institutional Ethics Committee (IEC No: MDC/JNMCIEC/153). Written informed consent was obtained from all participants prior to enrolment.

Inclusion criteria: The inclusion criteria comprised pregnant women aged ≥18 years between 20 and 33 weeks+6 days of gestation, diagnosed with preeclampsia, with or without GDM, and willing to provide informed consent. Fasting plasma glucose ≥92 mg/dL in pregnancy was considered diagnostic of GDM as per International Association of Diabetes and Pregnancy Study Groups/World Health Organisation (IADPSG/WHO) criteria [14] if less than 92, they were included in non GDM group. Preeclampsia was diagnosed based on the criteria defined by the American College of Obstetricians and Gynaecologists [9]: characterised by a Systolic Blood Pressure (SBP) ≥140 mmHg or Diastolic Blood Pressure (DBP) ≥90 mmHg, measured on two occasions at least four hours apart after 20 weeks of gestation in a previously normotensive woman, along with the presence of proteinuria. Proteinuria was defined as ≥300 mg of protein in a 24-hour urine sample or a urine dipstick reading of ≥2+ as a point-of-care test.

Exclusion criteria: Any history of pre-existing diabetes mellitus, chronic hypertension prior to pregnancy, renal, hepatic, or cardiovascular disorders, multiple pregnancies (twins or more), and any systemic illness that could affect angiogenic markers were excluded.

Sample size calculation: Sample size was calculated for comparison between two independent groups using standard statistical methods. Assuming a two-sided significance level (α) of 0.05, a study power (1-β) of 80%, an expected mean difference of 20 units between the groups, and a pooled standard deviation of 36 units, the minimum required sample size was estimated to be 51 participants per group. Therefore, 50 participants were included in each group, resulting in a total sample size of 100 participants [13].

Participants were selected using a convenience sampling method and screened for eligibility based on clinical history, biochemical investigations, and standard diagnostic criteria. A total of 100 pregnant women between 20 and 33 weeks of gestation (50 in each group) with preeclampsia were enrolled in the study and categorised into two groups: Group 1 included pregnant women diagnosed with GDM with preeclampsia, and Group 2 comprised normoglycaemic pregnant women with preeclampsia and no history of diabetes or GDM.

Study Procedure

Venous blood samples were collected from all participants under aseptic conditions using standard phlebotomy techniques. Fasting venous blood samples were collected after an overnight fast of 8-10 hours. Approximately, 3-5 mL of venous blood was collected into fluoride (grey) vacutainer tubes. The samples were centrifuged at 3000 rpm for 10 minutes to obtain plasma, which was used for glucose estimation. Fasting serum glucose was estimated using the hexokinase method. For measuring HbA1c another 1-2 mL blood was collected in Ethylene Diamine Tetraacetic Acid (EDTA) (lavender) vacutainer and HbA1c was measured using high-performance liquid chromatography. In suspected cases of preeclampsia, approximately 3-5 mL random venous blood was collected in serum separator (yellow) vacutainer tube which is later centrifuged at 3000 rpm for 10 minutes to obtain serum, for estimating sFlt-1 and PlGF.

Biochemical analysis: Serum levels of sFlt-1 and PlGF were measured using the Electrochemiluminescence Immunoassay (ECLIA) method on suspecting preeclampsia. The assays were performed using Elecsys sFlt-1 and Elecsys PlGF immunoassay kits on a Cobas e 801 immunoassay autoanalyser (Roche Diagnostics, Mannheim, Germany) [15]. The assay is based on a sandwich immunoassay principle, where antigen-antibody binding generates a chemiluminescent signal proportional to the concentration of the analyte [15]. The sFlt-1/PlGF ratio was calculated for each participant using the measured values. The blood glucose was analysed using Cobas c 503 autoanalyser whereas HbA1c was estimated using Bio rad D-10. The sFlt-1/PlGF ratio was interpreted according to established clinical guidelines. For pregnancies between 20 and 33+6 weeks, a ratio of <38 was considered to rule out preeclampsia within one week, while a ratio of >85 indicated a high likelihood of preeclampsia [4,16].

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS version 25.0. Data normality was assessed using the Shapiro-Wilk test. Continuous variables were expressed as median (IQR). Categorical variables (e.g., gender) were compared using the chi-square test. Group comparisons were performed using the Mann-Whitney U test and correlations were analysed using Spearman's test. A p-value <0.05 was considered statistically significant.

RESULTS

The mean age of participants was comparable between the groups, with the GDM group having a mean age of (29.92±3.26) years and the non GDM group having a mean age of (29.26±2.81) years. The newborn gender distribution in the GDM group included 28 (56%) males and 22 (44%) females, while the normoglycaemic group included 26 (52%) males and 24 (48%) females. The GDM group showed significantly higher BMI, fasting glucose, HbA1c, sFlt-1, PlGF, and sFlt-1/PlGF ratio compared to the normoglycaemic group (p<0.001). Birth weight was significantly lower in the GDM group, while no significant differences were observed in age, gender gestational age, or blood pressure [Table/Fig-1].

Variables		Group (GDM) median (Q1, Q3)	Group (non GDM) median (Q1, Q3)	p-value
Age (years)		30 (27, 33)	29 (27, 32)	0.277
Gender	Male	28 (56%)	26 (52%)	0.841
	Female	22 (44%)	24 (48%)	
BMI (kg/m²)		27.7 (26.4, 29.6)	24.1 (23.4, 24.9)	0.001*
Gestational age (weeks)		31.6 (31, 32.1)	31.6 (31, 32)	0.785
Fasting glucose (mg/dL)		107.5 (100, 112)	86 (83, 88)	0.001*
HbA1c (%)		6.25 (6, 6.7)	5.3 (5.2, 5.4)	0.001*
sFlt-1 (pg/mL)		44401 (38196.5, 50475)	9075 (8800, 10500)	0.001*
PlGF (pg/mL)		395 (375, 410)	165 (160, 180)	0.001*
sFlt-1/PlGF ratio		109.8 (96.7, 132.9)	56.8 (52.9, 62.5)	0.001*
Neonatal birth weight (g)		3180 (2850, 3350)	3350 (3250, 3450)	0.001*
Baseline SBP (mmHg)		152 (145, 160)	150 (146, 155)	0.095
Baseline DBP (mmHg)		100 (95, 105)	97 (94, 102)	0.132
4-hour SBP (mmHg)		152.5 (142, 162)	150 (146, 154)	0.144
4-hour DBP (mmHg)		96 (91, 105)	96 (93, 101)	0.964

[Table/Fig-1]: Comparison of clinical and biochemical parameters between gestational diabetic and normoglycaemic pregnant women.
Gender distribution was compared using the chi-square test. *p<0.05 considered statistically significant (Mann–Whitney U test). GDM: Gestational diabetes mellitus; BMI: Body mass index; sFlt-1: soluble fms-like tyrosine kinase; PlGF: Placental growth factor; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

In present study, the sFlt-1/PlGF ratio showed significant positive correlations with BMI, fasting glucose, HbA1c, sFlt-1, SBP and

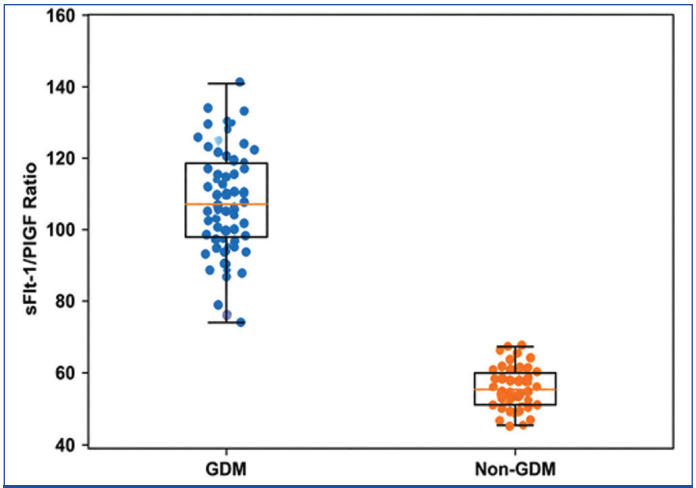
PlGF, and a negative correlation with birth weight. No significant correlation was observed with age, gestational age or blood pressure parameters [Table/Fig-2].

Variables	Correlation Coefficient	p-value
Age	0.19	0.058
BMI	0.793	0.001*
Gestational age	0.104	0.302
Fasting glucose	0.807	0.001*
HbA1c	0.838	0.001*
Birth Weight	-0.318	0.001*
Baseline SBP	0.254	0.011
Baseline DBP	0.156	0.122
4-hour SBP	0.083	0.414
4-hour DBP	-0.063	0.53

[Table/Fig-2]: Correlation of sFlt-1/PlGF Ratio with clinical and biochemical variables.
*p<0.05 considered statistically significant (Spearman's correlation test).

The IQR is wider in the GDM group, indicating greater variability in the ratio values. In contrast, the control group shows a relatively narrower distribution with lower median values.

The overlaid individual data points further highlight the clear separation between the two groups, with minimal overlap, supporting the statistically significant difference observed in the sFlt-1/PlGF ratio (p<0.001) [Table/Fig-3].



[Table/Fig-3]: Boxplot with overlaid individual data points illustrating the distribution of maternal sFlt-1/PlGF ratio in GDM and Non-GDM preeclamptic pregnancies. The median value is higher in the GDM group compared to non- GDM. The box represents the Interquartile Range (IQR) (25^{th}-75^{th} percentile), the central line indicates the median, and the overlaid points represent individual observations, demonstrating the distribution and variability within each group.

DISCUSSION

The present study demonstrates a significant elevation of the maternal sFlt-1/PlGF ratio in pregnancies complicated by GDM compared to normoglycaemic pregnancies. Similar findings have been reported by Nuzzo AM et al., who observed altered angiogenic profiles in GDM pregnancies [13]. These findings indicate a clear alteration in angiogenic balance and suggest the presence of endothelial and placental dysfunction in GDM.

The sFlt-1/PlGF ratio represents the balance between anti-angiogenic and pro-angiogenic pathways. sFlt-1 reduces the bioavailability of PlGFs, thereby impairing normal vascular development, while PlGF promotes placental angiogenesis. An increased ratio reflects a shift toward an anti-angiogenic state, which is a key feature of placental dysfunction in preeclampsia. These mechanistic insights are consistent with studies by Verlohren S et al., Zeisler H et al., and Hurrell A et al., which emphasised angiogenic imbalance and the clinical utility of angiogenic biomarkers in hypertensive disorders of pregnancy [4,17,18].

In the present study, metabolic parameters such as BMI, fasting glucose, and HbA1c were significantly higher in the GDM group, reflecting increased insulin resistance. Comparable findings have been documented in previous studies evaluating metabolic dysfunction and angiogenic dysregulation in GDM pregnancies [19,20]. The strong positive correlation observed between the sFlt-1/PlGF ratio and glycaemic parameters suggests that worsening glucose control may contribute to angiogenic imbalance. Similar associations have been reported in studies demonstrating that hyperglycaemia and insulin resistance can promote endothelial dysfunction through oxidative stress and inflammatory pathways and are associated with an increased risk of preeclampsia [21].

The observed elevation of sFlt-1 levels and significant alterations in PlGF levels in the GDM group indicate disruption of normal angiogenic signalling. These findings agree with previous studies that reported altered angiogenic marker profiles in GDM pregnancies [20], suggesting that metabolic disturbances may contribute to placental vascular dysfunction. However, some studies have reported variable PlGF levels in GDM, indicating that the relationship between metabolic status and pro-angiogenic factors may be influenced by disease severity, glycaemic control, and timing of assessment [12,18].

Importantly, the sFlt-1/PlGF ratio was significantly elevated in the GDM group. Similar observations were reported by Zeisler H et al., and Stepan H et al., who demonstrated that elevated sFlt-1/PlGF ratios can serve as indicators of angiogenic imbalance and predictors of preeclampsia severity [17,22]. Thus, the present study supports the concept that GDM pregnancies may exhibit early or preclinical features of angiogenic dysregulation.

Interestingly, no significant differences were observed in blood pressure parameters between the groups. Similar findings have been noted in prospective studies where angiogenic marker alterations were identified before the appearance of overt hypertension or clinical preeclampsia [4]. This suggests that angiogenic alterations may precede clinical manifestations of hypertension, supporting the concept of a preclinical phase of vascular dysfunction.

Overall, the findings of this study suggest that GDM is associated not only with metabolic disturbances but also with significant alterations in angiogenic regulation. These results are largely consistent with previous evidence [13,20-22] and support the concept of shared pathophysiological pathways between GDM and preeclampsia. The elevated sFlt-1/PlGF ratio observed in this study highlights its potential utility as an early biomarker for identifying pregnancies at increased risk of adverse outcomes.

A key strength of the present study is the inclusion of a well-defined cohort of pregnant women with EO-PE, allowing focused evaluation of angiogenic imbalance in a clinically relevant high-risk group. Additionally, the use of standardised ECLIA for measurement of sFlt-1 and PlGF ensures analytical reliability, and appropriate group stratification based on established diagnostic criteria enhances the validity of the findings.

Limitation(s)

The present study has certain limitations. It was conducted at a single tertiary care centre with a relatively small sample size, which may limit generalisability. The study followed a cross-sectional design hence serial follow-up measurements of angiogenic markers throughout pregnancy were not performed. Additionally, potential confounding factors such as treatment status and severity of disease were not analysed.

CONCLUSION(S)

The maternal sFlt-1/PlGF ratio was significantly higher in pregnant women with GDM and EO-PE compared with normoglycaemic women with EO-PE. This finding suggests greater angiogenic imbalance and endothelial dysfunction in GDM-associated

preeclampsia. Furthermore, the significant positive correlations of the sFlt-1/PlGF ratio with fasting glucose, HbA1c, and BMI indicate a close association between metabolic dysregulation and angiogenic imbalance.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 09, 2026
- Manual Googling: Jun 08, 2026
- iThenticate Software: Jun 10, 2026 (7%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 04, 2026**
Date of Peer Review: **Apr 25, 2026**
Date of Acceptance: **Jun 12, 2026**
Date of Publishing: **Aug 01, 2026**