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Original Research

Serum Family With Sequence Similarity 19 Member A5 Combined With 25-Hydroxyvitamin D Predicts Preeclampsia in Gestational Diabetes Mellitus: A Prospective Cohort Study

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Abstract

Background: Preeclampsia frequently coexists with gestational diabetes mellitus and increases adverse maternal outcomes, yet reliable early biomarkers remain limited. This study aims to evaluate the predictive value of serum family with sequence similarity 19 member A5 (FAM19A5) and 25-hydroxyvitamin D [25-(OH)D] for preeclampsia (PE) in women with gestational diabetes mellitus (GDM). **Methods:** In this prospective cohort study, 352 GDM women receiving regular prenatal care at the First Affiliated Hospital of Hebei North University Hospital between June 2023 and January 2025 were enrolled. Based on the subsequent development of PE, participants were stratified into a PE group (n = 110) and a non-PE group (n = 242). Serum FAM19A5 levels were measured by enzyme-linked immunosorbent assay (ELISA) and 25-(OH)D by chemiluminescence immunoassay (CLIA), and clinical and laboratory parameters were collected. Multivariable logistic regression was used to identify independent determinants of PE, and receiver operating characteristic (ROC) curves were constructed to assess predictive performance. **Results:** FAM19A5 and 25-(OH)D levels were significantly reduced in PE patients relative to controls ($p < 0.001$) and showed a moderate positive correlation (r = 0.389). Multivariable analysis identified both FAM19A5 (odds ratio [OR] = 0.990, 95% confidence interval [CI] 0.988–0.993) and 25-(OH)D (OR = 0.878, 95% CI 0.842–0.915) as independent protective factors against PE. The area under the curve (AUC) for FAM19A5 alone was 0.817 and for 25-(OH)D alone was 0.788; combined use increased the AUC to 0.855 with a specificity of 85.12%. **Conclusions:** Lower serum FAM19A5 and 25-(OH)D levels are independently associated with increased PE risk in women with GDM; their combined measurement may serve as an early predictive biomarker for PE.

Keywords: gestational diabetes mellitus; preeclampsia; family with sequence similarity 19 member A5; 25-hydroxyvitamin D

1. Introduction

Preeclampsia (PE) is a major obstetric complication in pregnancies complicated by gestational diabetes mellitus (GDM), and the coexistence of both conditions significantly increases the risk of adverse maternal outcomes [1,2]. Early identification of women with GDM who are at highest risk for PE is therefore essential to improve pregnancy outcomes.

Family with sequence similarity 19 member A5 (FAM19A5) is a recently recognized adipokine. Circulating FAM19A5 levels correlate inversely with body mass index (BMI), fasting insulin (FINS), fasting glucose, and glycated hemoglobin (HbA1c), and its expression is downregulated in obesity and non-alcoholic fatty liver disease, suggesting a potential protective role in metabolic regulation [3,4,5]. FAM19A5 also suppresses vascular smooth-muscle cell (VSMC) migration and proliferation via the sphingosine-1-phosphate receptor 2 (S1PR2) pathway, thereby preserving a vasodilatory and anti-remodeling phenotype; reduced expression promotes VSMC hyperactivation, exaggerated contractility, and neointimal thickening, indicating a key role in vascular homeostasis [6]. Whether FAM19A5 contributes to PE development among women with GDM remains unknown.

25-hydroxyvitamin D [25-(OH)D] represents the principal circulating metabolite of vitamin D and modulates immune function, calcium-phosphorus balance, and skeletal health [7,8,9]. In GDM, vitamin D supplementation lowers homeostasis model assessment of insulin resistance (HOMA-IR) and improves glycemic control, thereby reducing adverse pregnancy outcomes [10]. Moreover, accumulating evidence demonstrates that circulating 25-(OH)D levels are consistently lower in PE than in normotensive pregnancies, and adequate vitamin D supplementation during gestation decreases PE incidence [11,12,13,14]. However, data specifically linking maternal 25-(OH)D status to PE risk in GDM cohorts remain limited.

We therefore investigated the associations of serum FAM19A5 and 25-(OH)D levels with PE in women with GDM, with the aim of identifying novel biomarkers for early prediction and targeted intervention.

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2. Materials and Methods

2.1 Study Population

This prospective observational study was designed to investigate the risk of PE in patients with GDM. The sample size was estimated based on the area under the receiver operating characteristic (ROC) curve (AUC) for each biomarker independently using PASS 2021 (NCSS, LLC, Kaysville, UT, USA). Assuming a null AUC of 0.50 (no discriminatory ability), an expected AUC of 0.70, a two-sided type I error (alpha) of 0.05, and a statistical power of 80%, the minimum required total sample size was 90 subjects per biomarker (22 with PE and 68 without PE), based on the reported incidence of PE in patients with GDM [15]. The final enrolled cohort (n = 352) exceeded this requirement, ensuring adequate statistical power and precision for AUC estimation.

From June 2023 to January 2025, 352 women with GDM admitted to the First Affiliated Hospital of Hebei North University were enrolled and classified into a PE group (n = 110) and a non-PE group (n = 242); the participant flow diagram is presented in Fig. 1. Inclusion criteria were as follows: (1) a confirmed diagnosis of GDM [16], established by a 75-g oral glucose tolerance test (OGTT) performed at 24–28 weeks of gestation at our hospital, with diagnosis confirmed if any single threshold was met: fasting plasma glucose (FPG) level ≥5.1 mmol/L, a 1-h glucose level ≥10.0 mmol/L, or a 2-h glucose level ≥8.5 mmol/L. (2) No history or clinical manifestations of PE prior to GDM diagnosis. (3) Singleton, naturally conceived pregnancy. (4) Normal fetal and placental development with a normal amniotic fluid index. (5) Absence of post-term pregnancy, with planned regular prenatal care and delivery at our hospital. (6) No use of medications affecting glucose or vitamin D metabolism within the preceding 4 weeks. (7) Complete clinical and laboratory data available. Exclusion criteria: (1) Multiple gestation. (2) Pre-existing diabetes; (3) Concurrent pregnancy complications, including gestational hypertension, abnormal amniotic fluid, placental abruption, or fetal growth restriction. (4) *De novo* postpartum PE, defined as new-onset hypertension and proteinuria between 48 h and 6 weeks postpartum in women without clinical manifestations of PE prior to delivery. (5) Chronic hypertension, renal disease, hepatic disease, autoimmune disease, or infectious disease. (6) Cognitive impairment or psychiatric disorders precluding study participation. (7) Severe dysfunction of vital organs, including the heart, lungs, liver, or kidneys. (8) Uncontrolled thyroid dysfunction. (9) Use of calcium or vitamin D supplements, multivitamin preparations, or fortified foods within the preceding 4 weeks. (10) Treatment with active vitamin D metabolites or analogs within the preceding 3 months.

2.2 Follow-up and Group Allocation

All enrolled GDM patients were prospectively followed from the date of diagnosis until 48 h postpartum. During the follow-up period, prenatal visits were conducted every 2–4 weeks to monitor blood pressure, urinary protein, and clinical symptoms. The diagnosis of PE was independently determined by two or more obstetricians, with departmental consultation conducted when necessary.

PE was diagnosed according to the following criteria [17]: diagnosed from ≥20 weeks of gestation until delivery, with seated blood pressure ≥140/90 mmHg, plus at least one of the following: urine protein-to-creatinine ratio ≥30 mg/mmol, random urine protein (1+), or 24-hour urinary protein ≥0.3 g; or without proteinuria but with hematologic, neurologic, gastrointestinal, or other major organ abnormalities, or uteroplacental dysfunction. Based on follow-up outcomes, participants were categorized into two groups: the PE group (n = 110), comprising GDM patients who developed new-onset PE between 20 weeks of gestation and delivery; and the non-PE group (n = 242), comprising GDM patients who did not develop PE throughout the follow-up period until 48 h postpartum. New-onset PE occurring between 48 h and 6 weeks postpartum (postpartum PE) was excluded from the predefined study endpoint. The flowchart of patient enrollment and group allocation is presented in Fig. 1.

2.3 Data Acquisition

Clinical data were extracted from the medical records of enrolled participants, including age, pre-pregnancy BMI, gestational age at GDM diagnosis, pre-pregnancy smoking history (defined as habitual smoking of ≥1 cigarette per day for >6 months before pregnancy), pre-pregnancy alcohol use history (defined as habitual alcohol consumption of ≥1 occasions per week with ≥10 g of alcohol per occasion for >6 months before pregnancy), place of residence, gravidity, parity, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at GDM diagnosis, glucose and lipid metabolism-related indicators including FPG, 1-h postprandial glucose (1-h PG), 2-h postprandial glucose (2-h PG), HbA1c, FINS, HOMA-IR (calculated as HOMA-IR = FINS (mU/L) × FPG (mmol/L) / 22.5) [18], total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). Additional parameters included uric acid (UA), creatinine (Cr), and complete blood count indices comprising hemoglobin (Hb), white blood cell count (WBC), and platelet count (PLT).

2.4 Determination of Serum FAM19A5 and 25-(OH)D Levels

All enrolled GDM patients underwent fasting venous blood collection within 24 h of GDM diagnosis (the following morning). Considering that participants had already undergone multiple blood draws on the day of GDM diagnosis, study samples were uniformly collected the following morning between 8:00 and 10:00 AM after a fast of 8–12 h, in order to minimize repeated venipuncture

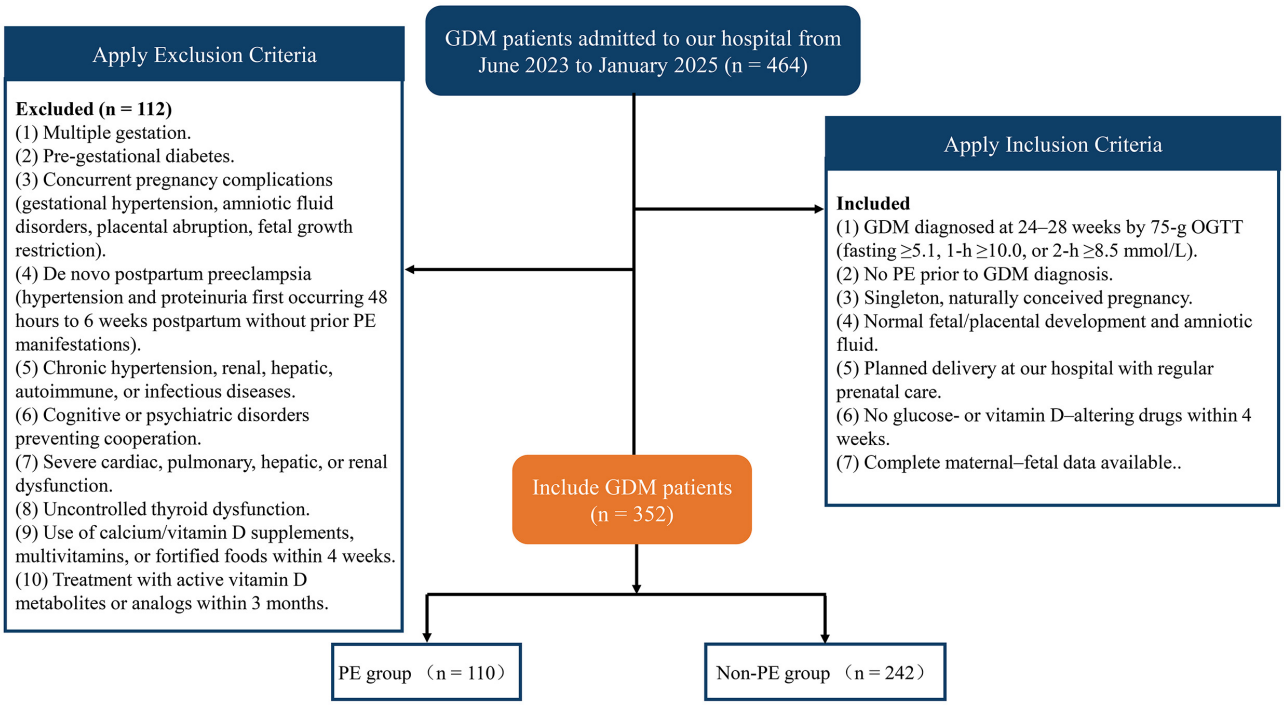


Fig. 1. Flowchart of patient enrollment and group allocation. GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PE, preeclampsia; BP, blood pressure.

and ensure a standardized fasting state. After collection, samples were allowed to stand at room temperature for 30 minutes and then centrifuged at 1000 ×g for 15 minutes at 4 °C. The resulting supernatant was aliquoted and stored at –80 °C until analysis. All samples were subjected to a single freeze-thaw cycle to prevent protein degradation. Prior to analysis, serum samples and all reagents were equilibrated to room temperature (21–26 °C). Serum FAM19A5 concentrations were determined by a sandwich enzyme-linked immunosorbent assay (ELISA) kit (Catalog Number: ml104974; Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China), with all procedures performed strictly according to the manufacturer's instructions. Serum 25-(OH)D levels were measured by chemiluminescence immunoassay (CLIA) on the ADVIA Centaur XP Immunoassay System (Siemens Healthineers, Erlangen, Germany). Both biomarkers were assayed in the same batch in duplicate, and all analyses were completed within 2 h of sample thawing. Intra- and inter-assay coefficients of variation (CVs) were both <10%. Samples were randomly ordered using unique identification numbers, and laboratory personnel remained blinded to clinical group assignments throughout the analytical process.

2.5 Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA), and graphs were prepared in GraphPad Prism 9.5 (GraphPad Software, Boston, MA, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables following a normal distribution are summarized as mean ± standard deviation (SD) and compared between the two groups using the independent samples *t*-test. Non-normally distributed continuous variables were expressed as median with interquartile range [M (P_{25}, P_{75})] and compared between the two groups using the Mann–Whitney U test. Categorical variables were expressed as frequencies (n) and percentages (%) and compared using the chi-square (χ^2) test. The association between serum FAM19A5 and 25-(OH)D was assessed using Pearson correlation analysis. ROC curves were constructed to evaluate the predictive value of serum levels of FAM19A5 and 25-(OH)D, both individually and in combination, for the development of PE in patients with GDM. The predicted probability derived from multivariable logistic regression was used as the test variable in the combined model, and an ROC curve was plotted to assess its predictive performance. DeLong's test was employed to compare the AUCs of the combined model with those of each individual biomarker. Bootstrap internal validation (1000 iterations) was performed to correct for optimism. Multivariable logistic regression was performed to identify factors associated with PE in patients with GDM. Variable inclusion criteria: Variables with $p < 0.05$ on univariate analysis were entered into the multivariable model; the primary exposures of interest, FAM19A5 and 25-(OH)D, were forced into the model regardless of their univariate *p*-values, based on the study hypothesis. The variance inflation factor (VIF) was

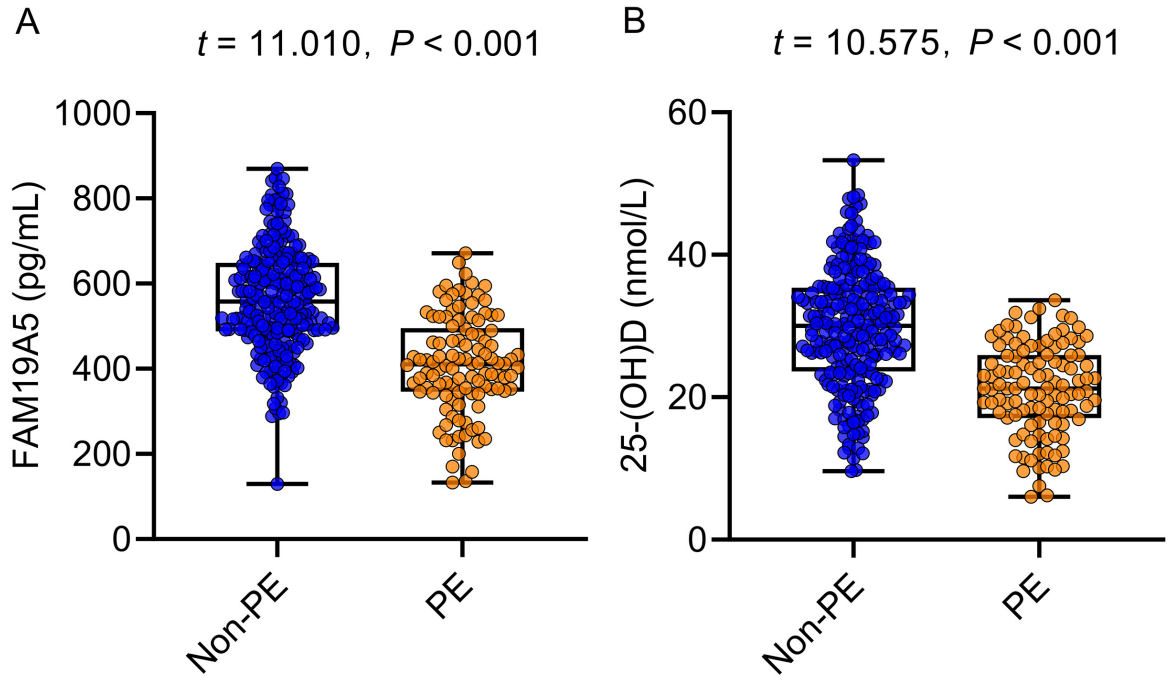


Fig. 2. Comparison of serum FAM19A5 and 25-(OH)D levels between the two groups. (A) Comparison of serum FAM19A5 levels between the non-PE and PE groups. (B) Comparison of serum 25-(OH)D levels between the non-PE and PE groups. FAM19A5, family with sequence similarity 19 member A5; 25-(OH)D, 25-hydroxyvitamin D.

calculated for all covariates to assess multicollinearity, with VIF <5 indicating no substantial collinearity. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Comparison of Clinical Characteristics

Compared with the non-PE group, the PE group exhibited significantly higher pre-pregnancy BMI, SBP, DBP, FPG, HbA1c, HOMA-IR, TC, TG, UA, and Cr, and significantly lower HDL-C ($p < 0.05$). No significant differences were observed between the two groups in the remaining baseline parameters ($p > 0.05$).

3.2 Serum FAM19A5 and 25-(OH)D Levels

Compared with non-PE controls, the PE group displayed markedly lower circulating FAM19A5 and 25-(OH)D concentrations ($p < 0.001$; Fig. 2).

3.3 Correlation Between Serum FAM19A5 and 25-(OH)D Levels

Pearson analysis revealed a significant direct association between circulating FAM19A5 and 25-(OH)D concentrations (r = 0.389, $p < 0.001$; Fig. 3).

3.4 Multivariable Logistic Regression Analysis of Factors Associated With PE in Women With GDM

During multivariable model construction, SBP and DBP were excluded from the multivariable logistic regression analysis. Although these measurements were obtained at the time of GDM diagnosis (24 to 28 weeks of gestation), predating the clinical diagnostic window for PE, elevated blood pressure (≥140/90 mmHg) constitutes a core diagnostic criterion for PE. Their inclusion risked structural overlap between predictor variables and the outcome definition; exclusion therefore ensured accurate assessment of the independent predictive values of FAM19A5 and 25-(OH)D.

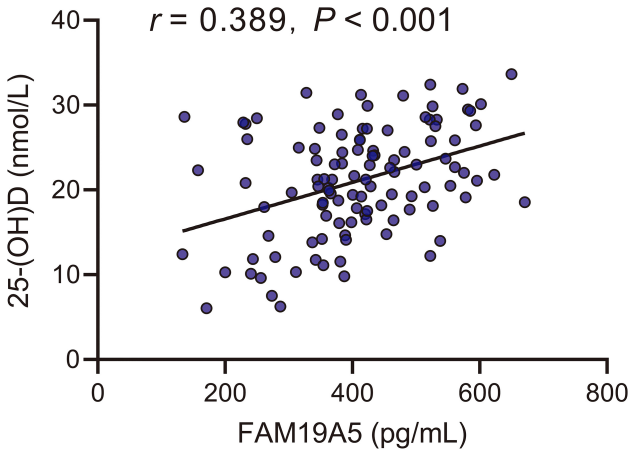


Fig. 3. Correlation between serum FAM19A5 levels and 25-(OH)D levels. 25-(OH)D, 25-hydroxyvitamin D.

Multivariable logistic regression analysis was performed with PE occurrence in patients with GDM as the dependent variable (yes = 1, no = 0). Independent variables

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Table 1. Comparison of clinical characteristics between the PE and non-PE groups.

Variable	Non-PE (n = 242)	PE (n = 110)	$t/Z/\chi^2$	p-value
Age [M (P_{25}, P_{75}), years]	29 (26, 32)	30 (27, 33)	–1.369#	0.171
Pre-pregnancy BMI (mean ± SD, kg/m^2)	22.39 ± 3.12	24.28 ± 3.85	–4.882*	<0.001
Gestational week at GDM diagnosis [M (P_{25}, P_{75}), weeks]	26 (25, 27)	26 (25, 27)	–0.556#	0.578
Pre-pregnancy smoking history [n (%)]	26 (10.74)	15 (13.64)	0.615^	0.433
Pre-pregnancy alcohol consumption history [n (%)]	43 (17.77)	23 (20.91)	0.490^	0.484
Residence (n/%)			0.368^	0.544
Urban	106 (43.80)	52 (47.27)		
Rural	136 (56.20)	58 (52.73)		
Gravidity (n/%)			1.369^	0.242
1	77 (31.82)	42 (38.18)		
≥2	165 (68.18)	68 (61.82)		
Parity (n/%)			0.795^	0.373
0	113 (46.69)	57 (51.82)		
≥1	129 (53.31)	53 (48.18)		
SBP [M (P_{25}, P_{75}), mmHg]	110 (102, 120)	156 (145, 162)	–14.846#	<0.001
DBP [M (P_{25}, P_{75}), mmHg]	71 (66, 76)	96 (90, 102)	–14.407#	<0.001
FPG [M (P_{25}, P_{75}), mmol/L]	4.90 (4.60, 5.20)	5.40 (4.90, 5.70)	–5.910#	<0.001
1-h PG (mean ± SD, mmol/L)	9.84 ± 1.58	10.16 ± 1.35	–1.840*	0.067
2-h PG (mean ± SD, mmol/L)	8.25 ± 1.32	8.42 ± 1.26	–1.120*	0.263
HbA1c [M (P_{25}, P_{75}), %]	5.40 (5.10, 5.60)	5.60 (5.30, 6.00)	–5.061#	<0.001
HOMA-IR [M (P_{25}, P_{75})]	2.20 (2.00, 2.50)	3.20 (2.90, 3.40)	–13.603#	<0.001
TC (mean ± SD, mmol/L)	5.25 ± 1.16	5.86 ± 1.22	–4.500*	<0.001
TG [M (P_{25}, P_{75}), mmol/L]	2.18 (2.05, 2.34)	3.16 (2.92, 3.35)	–14.700#	<0.001
LDL-C (mean ± SD, mmol/L)	2.62 ± 0.69	2.68 ± 0.72	–0.746*	0.456
HDL-C [M (P_{25}, P_{75}), mmol/L]	1.41 (1.12, 1.74)	1.22 (0.96, 1.48)	–4.013#	<0.001
UA [M (P_{25}, P_{75}), µmol/L]	221.00 (207.75, 234.25)	344.50 (329.00, 362.00)	–15.042#	<0.001
Cr [M (P_{25}, P_{75}), µmol/L]	68.25 (64.48, 72.10)	98.90 (93.60, 104.28)	–15.028#	<0.001
Hb (mean ± SD, g/L)	130.12 ± 21.15	128.85 ± 20.68	0.526*	0.599
WBC (mean ± SD, ×10^9/L)	10.74 ± 2.10	11.02 ± 2.17	–1.150*	0.251
PLT (mean ± SD, ×10^9/L)	228.21 ± 31.15	223.68 ± 34.21	1.223*	0.222

Note: * indicates t value, # indicates Z value, ^ indicates χ^2 value.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 1-h PG, 1-h plasma glucose; 2-h PG, 2-h plasma glucose; HbA1c, glycated hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; Cr, creatinine; Hb, hemoglobin; WBC, white blood cell count; PLT, platelet count.

included all parameters that reached statistical significance ($p < 0.05$) in Table 1 (pre-pregnancy BMI, FPG, HbA1c, HOMA-IR, TC, TG, HDL-C, UA, and Cr), as well as serum FAM19A5 and 25-(OH)D levels. The results identified elevated pre-pregnancy BMI, FPG, HbA1c, HOMA-IR, TC, TG, UA, and Cr as independent risk factors for PE development in GDM patients, whereas elevated HDL-C, serum FAM19A5, and 25-(OH)D levels were each independently associated with a reduced risk of PE ($p < 0.05$). The VIF for all variables was <5, indicating no significant multicollinearity (Table 2).

3.5 Serum FAM19A5 and 25-(OH)D for Predicting PE Risk in Patients With GDM

ROC curve analysis revealed AUCs of 0.817, 0.788, and 0.855 for serum FAM19A5, 25-(OH)D, and their combination, respectively, in predicting PE in patients with GDM, with the combined model demonstrating higher specificity than either individual marker. DeLong's test confirmed that the differences in AUC between the combined model and FAM19A5 or 25-(OH)D alone were statistically significant (Z = 4.143 and 2.441, respectively; $p < 0.05$) (Table 3, Fig. 4). Bootstrap internal validation (1000 iterations) yielded an optimism-corrected AUC of 0.839 (95% confidence interval [CI]: 0.793–0.885) for the combined model, reflecting a 0.016 decrease from the original AUC of 0.855 and an optimism estimate of 1.9%, indicative of acceptable model stability.

4. Discussion

In the present study, among 352 pregnant women with GDM, serum FAM19A5 and 25-(OH)D levels were signifi-

Table 2. Multivariable logistic regression of factors associated with PE in women with GDM.

Variable	β	S.E.	Wald	*p*-value	OR	95% CI	VIF
Pre-pregnancy BMI	0.164	0.036	21.037	<0.001	1.179	1.099–1.265	1.073
FPG	1.477	0.262	31.727	<0.001	4.382	2.620–7.327	1.145
HbA1c	1.475	0.295	24.979	<0.001	4.369	2.451–7.791	1.118
HOMA-IR	0.154	0.046	11.312	0.001	1.166	1.066–1.276	2.322
TC	0.360	0.143	6.328	0.012	1.433	1.083–1.896	1.079
TG	0.425	0.141	9.101	0.003	1.530	1.161–2.017	3.224
HDL-C	–1.017	0.265	14.768	<0.001	0.362	0.215–0.608	1.098
UA	0.247	0.079	9.820	0.002	1.281	1.097–1.495	2.301
Cr	0.718	0.203	12.488	<0.001	2.049	1.387–3.051	2.751
FAM19A5	–0.010	0.001	48.797	<0.001	0.990	0.988–0.993	1.364
25-(OH)D	–0.130	0.021	37.178	<0.001	0.878	0.842–0.915	1.298

Note: β, regression coefficient; S.E., standard error; Wald, Wald statistic; OR, odds ratio; CI, confidence interval; VIF, variance inflation factor.

Table 3. Diagnostic performance of serum FAM19A5 and 25-(OH)D for predicting PE in women with GDM.

Variable	AUC	95% CI	Cutoff	Sensitivity (%)	Specificity (%)
FAM19A5	0.817	0.771–0.863	467.10 pg/mL	71.82	79.75
25-(OH)D	0.788	0.742–0.835	26.02 nmol/L	76.36	69.01
FAM19A5+25-(OH)D	0.855	0.814–0.896	-	71.82	85.12

Note: AUC, area under the curve; Cutoff, cutoff value.

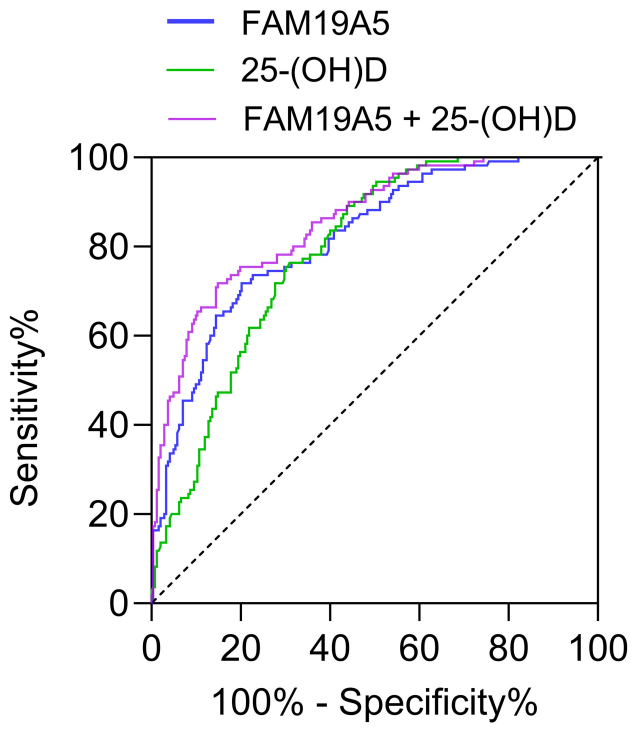


Fig. 4. ROC curves of serum FAM19A5 and 25-(OH)D for predicting PE in women with GDM. ROC, receiver operating characteristic.

cantly lower in the PE group than in the non-PE group. Multivariable logistic regression confirmed that higher serum FAM19A5 and 25-(OH)D levels were independently associated with a reduced risk of PE in women with GDM. ROC analysis further demonstrated that the combination of FAM19A5 and 25-(OH)D yielded an AUC of 0.855 for PE prediction, which was significantly superior to that of either biomarker alone, suggesting that this combined panel may serve as a potential early predictive biomarker for PE in women with GDM.

In this study, serum levels of FAM19A5 and 25-(OH)D were significantly decreased in the PE group, suggesting that reductions in both markers may be associated with an increased risk of PE in patients with GDM. The potential underlying mechanisms are further described. Serum FAM19A5 is significantly decreased in obese individuals and is negatively correlated with HOMA-IR, indicating a potential role in improving insulin sensitivity. Its decline may further exacerbate pre-existing insulin resistance in patients with GDM, perpetuating hyperglycemia, hyperinsulinemia, and lipid metabolism dysregulation. This, in turn, may promote the accumulation of free fatty acids and Advanced Glycation End-products (AGEs), activate systemic oxidative stress and inflammatory responses, induce vascular endothelial dysfunction, and contribute to impaired placental vascular remodeling [19,20]. Furthermore, FAM19A5 can inhibit VSMC proliferation and migration via paracrine signaling. Reduced FAM19A5 levels may therefore lead to excessive VSMC proliferation and migration into the intima, resulting in arterial wall thickening and lumen narrowing in systemic small arteries and uterine spiral arteries, reducing placental perfusion, and thereby further increasing the risk of PE [3,4,6,21]. Additionally, reduced 25-(OH)D may further impair insulin secretion by attenuating calcium signal-

ing, thereby aggravating insulin resistance and glucose dysmetabolism and compromising vascular endothelial function [22,23]. Moreover, decreased 25-(OH)D may weaken immune tolerance, inhibit trophoblast invasion and angiogenesis, and intensify oxidative stress and systemic inflammation, collectively contributing to impaired placental perfusion and endothelial dysfunction that drive progression from GDM to PE [24]. This study also identified a positive correlation between 25-(OH)D and FAM19A5, suggesting that reductions in both markers may synergistically amplify insulin resistance, vascular injury, and impaired placental vascular remodeling, jointly driving progression from GDM to PE. Furthermore, ROC curve analysis demonstrated that FAM19A5 and 25-(OH)D, both individually and in combination, exhibited predictive value for PE development in patients with GDM. Accordingly, simultaneous clinical monitoring of serum 25-(OH)D and FAM19A5 levels may represent a novel strategy for the early identification of patients with GDM at risk of progression to PE, potentially enabling timely intervention and reducing the risk of PE.

Multivariable logistic regression further confirmed that elevated pre-pregnancy BMI, glucolipid metabolic disturbances (increased FPG, HbA1c, HOMA-IR, TC, and TG), and elevated UA and Cr levels were independent risk factors for PE development in patients with GDM, whereas higher HDL-C was independently protective, consistent with previous reports [15,25,26,27]. Therefore, in patients with GDM presenting with the aforementioned metabolic abnormalities or early renal dysfunction, intensified integrated management of blood pressure, glucose, and lipid levels, along with close monitoring of PE-related target organ injury markers, is warranted to minimize the risk of PE onset. In the present study, serum FAM19A5 and 25-(OH)D levels were measured within 24 h of GDM diagnosis (at 24–28 weeks of gestation), a time point clearly preceding the clinical diagnosis of PE. Thus, biomarker assessment occurred prior to the occurrence of the outcome event, satisfying the temporal precedence requirement of a prospective predictive study.

Limitations

This study has several limitations. First, this was a single-center study, with all samples collected exclusively from the First Affiliated Hospital of Hebei North University, which may have introduced selection bias. Second, the sample size was limited; although a total of 352 patients with GDM were enrolled, only 110 were in the PE group, potentially restricting statistical power. Third, external validation was not performed, and the absence of an independent validation cohort means that the generalizability of these findings requires further confirmation. Fourth, as an observational study, we were unable to determine whether decreased FAM19A5 and 25-(OH)D levels directly cause PE; thus, the causal relationship remains unclear. Moreover, the influence of residual confounding cannot be entirely excluded. Although adjustment was made for known clinical and metabolic covariates to the extent possible, unmeasured or imprecisely measured confounders—such as dietary patterns, physical activity levels, sun exposure duration, vitamin D supplementation, and genetic background—may still have affected the results. These factors may be associated with both FAM19A5 and 25-(OH)D levels and the occurrence of PE, potentially influencing the observed correlations. Therefore, all findings from this study should be interpreted as statistical associations rather than causal inference. Fifth, blood samples in this study were collected at the time of GDM diagnosis (gestational weeks 24–28), which is later than the critical window for spiral artery remodeling in the first trimester. Consequently, the predictive value of FAM19A5 and 25-(OH)D during the first trimester could not be assessed, and the present findings do not support their clinical application as early-pregnancy screening tools for PE. Therefore, future prospective cohort studies are warranted, incorporating baseline blood sample collection during the first trimester and longitudinal follow-up through delivery, to clarify the predictive efficacy of these two biomarkers in early pregnancy and to identify the optimal window for intervention. Finally, dietary intake, sunlight exposure duration, and vitamin D supplementation were not accounted for as potential confounders in this study, which may have influenced the results to some degree.

5. Conclusions

In conclusion, this prospective cohort study demonstrated that lower serum FAM19A5 and 25-(OH)D levels in women with GDM were independently associated with the subsequent development of PE. Reduced levels of both markers were associated with an increased risk of PE in GDM patients, and their combination demonstrated superior predictive performance compared with either marker alone, suggesting potential utility as combined biomarkers for the early prediction of PE in this population. Future multicenter prospective studies with large sample sizes are warranted to validate the generalizability and reproducibility of these findings. In parallel, further investigation into the specific mechanisms by which FAM19A5 and 25-(OH)D contribute to the pathogenesis of PE in the setting of GDM may identify more precise targets for clinical intervention, ultimately improving maternal and neonatal outcomes.

Availability of Data and Materials

All data in this study are available from the corresponding author on reasonable request.

Author Contributions

JC: guarantor of integrity of the entire study, study concepts, study design, definition of intellectual content,

funding acquisition, project administration. JW: literature research, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, writing—review & editing. YG: manuscript preparation, manuscript editing, manuscript review, statistical analysis, writing—original draft. All authors critically revised the manuscript for important intellectual content and approved the final version. All authors agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (Approval Number: K2023435) and adheres to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants, ensuring their autonomy and understanding of the study. Furthermore, measures were implemented to maintain the confidentiality and anonymity of the participants throughout the research process.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Kimi (developed by Moonshot AI), version 3.2.16 in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG49749.

References

[1] Noonan SB, Brennecke SP, Jones GD. Predicting Preeclampsia in Gestational Diabetes Mellitus Using the sFlt-1/PlGF Ratio. The Journal of Clinical Endocrinology and Metabolism. 2025; 110: e3343–e3352. https://doi.org/10.1210/clinem/dgaf069

[2] Tang WZ, Kang ZM, Zhao YF, Cai QY, Deng BN, Zhou ZJ, et al. Perinatal adverse outcomes in twin pregnancies with preeclampsia complicated by distinct gestational diabetes subtypes. Acta Diabetologica. 2025; 62: 1233–1246. https://doi.org/10.1007/s00592-025-02444-z

[3] Wesołek-Leszczyńska A, Pastusiak K, Bogdański P, Szulińska M. Can Adipokine FAM19A5 Be a Biomarker of Metabolic Disorders? Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2024; 17: 1651–1666. https://doi.org/10.2147/DMSO.S460226

[4] Wesolek A, Skoracka K, Skrypnik K, Suliburska J, Bogdanski P, Szulinska M, et al. Assessment of progranulin and FAM19A5 protein blood levels in patients with metabolic syndrome. Journal of Physiology and Pharmacology: an Official Journal of the Polish Physiological Society. 2022; 73: 10.26402/jpp.2022.1.13. https://doi.org/10.26402/jpp.2022.1.13

[5] Yari FA, Shabani P, Karami S, Sarmadi N, Poustchi H, Bandegi AR. Circulating levels of FAM19A5 are inversely associated with subclinical atherosclerosis in non-alcoholic fatty liver disease. BMC Endocrine Disorders. 2021; 21: 153. https://doi.org/10.1186/s12902-021-00820-8

[6] Wang Y, Chen D, Zhang Y, Wang P, Zheng C, Zhang S, et al. Novel Adipokine, FAM19A5, Inhibits Neointima Formation After Injury Through Sphingosine-1-Phosphate Receptor 2. Circulation. 2018; 138: 48–63. https://doi.org/10.1161/CIRCULATIONAHA.117.032398

[7] Wimalawansa SJ. Infections and Autoimmunity-The Immune System and Vitamin D: A Systematic Review. Nutrients. 2023; 15: 3842. https://doi.org/10.3390/nu15173842

[8] Ren Q, Liang J, Su Y, Tian R, Wu J, Ge S, et al. A Causal Effect of Serum 25(OH)D Level on Appendicular Muscle Mass: Evidence From NHANES Data and Mendelian Randomization Analyses. Journal of Cachexia, Sarcopenia and Muscle. 2025; 16: e13778. https://doi.org/10.1002/jcsm.13778

[9] Wimalawansa SJ. Physiology of Vitamin D-Focusing on Disease Prevention. Nutrients. 2024; 16: 1666. https://doi.org/10.3390/nu16111666

[10] Li DY, Wang L, Li L, Zhou S, Tan J, Tang C, et al. Maternal vitamin D status and risk of gestational diabetes mellitus in twin pregnancies: a longitudinal twin pregnancies birth cohort study. Nutrition Journal. 2024; 23: 41. https://doi.org/10.1186/s12937-024-00944-2

[11] Wojczakowski W, Dłuski D, Futyma K. Vitamin D and calcium status in preeclampsia and pregnancy-induced hypertension. Biomolecules & Biomedicine. 2025; 26: 612–618. https://doi.org/10.17305/bb.2025.13081

[12] Shahid S, Ladak A, Fatima SS, Zaidi FA, Farhat S. Association of vitamin D levels with preeclampsia. JPMA. the Journal of the Pakistan Medical Association. 2020; 70: 2390–2393. https://doi.org/10.47391/JPMA.414

[13] Rouhani P, Mokhtari E, Lotfi K, Saneei P. The association between circulating 25-hydroxyvitamin D levels and preeclampsia: a systematic review and dose-response meta-analysis of epidemiologic studies with GRADE assessment. Nutrition Reviews. 2023; 81: 1267–1289. https://doi.org/10.1093/nutrit/nuad006

[14] Moghib K, Ghanm TI, Abunamoos A, Rajabi M, Moawad SM, Mohsen A, et al. Efficacy of vitamin D supplementation on the incidence of preeclampsia: a systematic review and meta-analysis. BMC Pregnancy and Childbirth. 2024; 24: 852. https://doi.org/10.1186/s12884-024-07081-y

[15] Chatzakis C, Sotiriadis A, Demertzidou E, Eleftheriades A, Dinas K, Vlahos N, et al. Prevalence of preeclampsia and uterine arteries resistance in the different phenotypes of gestational diabetes mellitus. Diabetes Research and Clinical Practice. 2023; 195: 110222. https://doi.org/10.1016/j.diabres.2022.110222

[16] Sert UY, Ozgu-Erdinc AS. Gestational Diabetes Mellitus Screening and Diagnosis. Advances in Experimental Medicine and Biology. 2021; 1307: 231–255. https://doi.org/10.1007/5584_2020_512

[17] Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study

of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension. 2022; 27: 148–169. https://doi.org/10.1016/j.preghy.2021.09.008

[18] Tahapary DL, Pratisthita LB, Fitri NA, Marcella C, Wafa S, Kurniawan F, et al. Challenges in the diagnosis of insulin resistance: Focusing on the role of HOMA-IR and Tryglyceride/glucose index. Diabetes & Metabolic Syndrome. 2022; 16: 102581. https://doi.org/10.1016/j.dsx.2022.102581

[19] Xie K, Liu L, Yin C, Li M, Wang L, Lv W, et al. Follistatin-Like 1 and Family with Sequence Similarity to 19 Member A5 Levels Are Decreased in Obese Children and Associated with Glucose Metabolism. Annals of Nutrition & Metabolism. 2022; 78: 213–221. https://doi.org/10.1159/000524624

[20] Liu H, Ning F, Lash GE. Contribution of vascular smooth muscle cell apoptosis to spiral artery remodeling in early human pregnancy. Placenta. 2022; 120: 10–17. https://doi.org/10.1016/j.placenta.2022.02.005

[21] Nieves-Colón MA, Badillo Rivera KM, Sandoval K, Villanueva Dávalos V, Enriquez Lencinas LE, Mendoza-Revilla J, et al. Clotting factor genes are associated with preeclampsia in high-altitude pregnant women in the Peruvian Andes. American Journal of Human Genetics. 2022; 109: 1117–1139. https://doi.org/10.1016/j.ajhg.2022.04.014

[22] Tarfeen N, Nisa KU, Ahmad MB, Waza AA, Ganai BA. Metabolic and Genetic Association of Vitamin D with Calcium Signaling and Insulin Resistance. Indian Journal of Clinical Biochemistry: IJCB. 2023; 38: 407–417. https://doi.org/10.1007/s12291-022-01105-0

[23] Lei X, Zhou Q, Wang Y, Fu S, Li Z, Chen Q. Serum and supplemental vitamin D levels and insulin resistance in T2DM populations: a meta-analysis and systematic review. Scientific Reports. 2023; 13: 12343. https://doi.org/10.1038/s41598-023-39469-9

[24] Zheng S, Dong S, Shen H, Xu P, Shu C. Role of vitamin D in the pathogenesis of early-onset preeclampsia: a narrative review. Frontiers in Nutrition. 2025; 12: 1598691. https://doi.org/10.3389/fnut.2025.1598691

[25] Nicolì F, Citro F, Battini L, Aragona M, De Gennaro G, Marchetti P, et al. Prevalence and predictive risk factors of hypertensive disorders in pregnant women at high risk for gestational diabetes. The PREeclampsia in DIabetiC gestaTION (PREDICTION) study. Journal of Endocrinological Investigation. 2025; 48: 1033–1040. https://doi.org/10.1007/s40618-024-02520-1

[26] de Carvalho LS, de Oliveira AAD, Grabovski TCM, Renzo CC, Ribeiro E Silva R, Loz SH, et al. Maternal prepregnancy obesity and gestational diabetes influence on adverse perinatal outcomes. Archives of Endocrinology and Metabolism. 2023; 67: e000605. https://doi.org/10.20945/2359-3997000000605

[27] Aziz F, Khan MF, Moiz A. Gestational diabetes mellitus, hypertension, and dyslipidemia as the risk factors of preeclampsia. Scientific Reports. 2024; 14: 6182. https://doi.org/10.1038/s41598-024-56790-z