


Evaluating Maternal Serum SHH Levels in the First Trimester as a Potential Biomarker for Predicting Preeclampsia

Caifeng Deng^{1,*}, Si Zhang^{2,*}, Chanyu Li¹, Zhiling Yang¹, Qin Guo³, Yanmian Cheng⁴ 

¹Department of Gynecology and Obstetrics, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan, People's Republic of China;

²Department of Emergency Medicine, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan, People's Republic of China;

³Department of Orthopedics, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan, People's Republic of China; ⁴Department of Infectious Diseases, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yanmian Cheng, Department of Infectious Diseases, The First Affiliated Hospital of Chengdu Medical College, No. 278, The Middle Section of Baoguang Avenue, Xindu District, Chengdu, Sichuan, 610500, People's Republic of China, Email 18215577119@163.com; Qin Guo, Department of Orthopedics, The First Affiliated Hospital of Chengdu Medical College, No. 278, The Middle Section of Baoguang Avenue, Xindu District, Chengdu, Sichuan, 610500, People's Republic of China, Email 513497978@qq.com

Objective: To determine whether first-trimester maternal serum Sonic Hedgehog (SHH) predicts subsequent preeclampsia and to compare its predictive performance with soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF).

Materials and Methods: In a prospective cohort study, women with singleton pregnancies were enrolled at 8–13 weeks' gestation, clinical data were recorded, and fasting serum was collected. SHH, sFlt-1, and PlGF were quantified by ELISA in triplicate with coefficients of variation <10%. Associations between SHH and subsequent preeclampsia were tested using multivariable logistic regression with adjusted confounders; discriminative ability was evaluated by ROC analysis and stratified for early-onset (≤ 34 weeks) and late-onset (> 34 weeks) preeclampsia.

Results: Among 2532 enrolled pregnancies, 271 developed preeclampsia and 2261 remained normotensive. First-trimester SHH concentrations were significantly lower in pregnancies that later developed preeclampsia, with the greatest decrement in early-onset disease. Compared to the highest SHH tertile, adjusted odds of preeclampsia were higher in the middle (OR 2.64; 95% CI 1.334–5.38) and lowest tertiles (OR 5.21; 95% CI 3.15–8.42). SHH achieved an AUC of 0.86 (95% CI 0.62–0.91), with 81.46% sensitivity and 76.58% specificity at 58.26 ng/mL; sFlt-1 and PlGF yielded AUCs of 0.71 and 0.62, respectively. Performance was strongest for early-onset preeclampsia with an AUC of 0.93 (95% CI 0.67–0.97); sensitivity 87.73%; specificity 82.43% at 62.37 ng/mL, and modest for late-onset preeclampsia with an AUC of 0.75 (95% CI 0.54–0.86); sensitivity 73.42%; specificity 68.24% at 55.78 ng/mL.

Conclusion: Lower maternal serum SHH level in the first trimester is independently associated with later development of preeclampsia and provides clinically significant early prediction, particularly for early-onset disease. Incorporating SHH into first-trimester multiparametric screening alongside maternal factors and angiogenic markers may improve risk stratification and enable earlier prophylaxis and individualized antenatal surveillance.

Keywords: Sonic Hedgehog protein, first-trimester, biomarker, preeclampsia, extravillous trophoblast

Introduction

Pre-eclampsia is a serious hypertensive disorder of pregnancy, defined by the new onset of hypertension after 20 weeks of gestation, and it remains a leading global cause of maternal and perinatal morbidity and mortality.^{1,2} It affects approximately 2–8% of pregnancies and is associated with fetal growth restriction, placental abruption, preterm birth, and maternal cardiovascular complications.^{3–5} Early prediction and diagnosis remain challenging; however, timely identification of women at increased risk enables intensified antenatal surveillance and prophylactic interventions that can mitigate adverse outcomes for both mothers and fetuses.^{6,7} Current clinical approaches rely largely on maternal

history combined with biophysical assessments, yet these approaches have limited predictive performance in early gestation, especially in the first trimester. Therefore, the discovery of robust first-trimester biomarkers has emerged as a promising strategy to facilitate earlier and more accurate prediction of preeclampsia.

Previous studies have linked the pathogenesis of preeclampsia to the shallow placental implantation and inadequate remodeling of the spiral arteries in the uterus.^{8–10} Successful placentation is a complex process dependent on highly orchestrated trophoblast biology. Villous cytotrophoblasts differentiate into either syncytiotrophoblasts or invasive extravillous trophoblasts.¹¹ Extravillous trophoblasts can remodel the uterine spiral arteries into the high-capacity, low-resistance vessels necessary to support fetal growth.¹² Inadequate extravillous trophoblast invasion and spiral artery transformation lead to uteroplacental malperfusion.¹³ This state provokes the release of anti-angiogenic and inflammatory factors into the maternal circulation, ultimately causing the maternal syndrome of hypertension and multi-organ dysfunction associated with preeclampsia.^{8,14} Consequently, molecules that regulate essential trophoblast functions, such as proliferation, differentiation, and invasion, are promising candidate biomarkers for the early prediction of preeclampsia.

SHH protein is the ligand that binds to the receptor Patched 1, leading to the activation of the Sonic Hedgehog signaling pathway.¹⁵ The Sonic Hedgehog signaling pathway is critical for normal placentation and plays a key role in regulating these essential trophoblast functions.^{16,17} Emerging evidence suggests that the placental Sonic Hedgehog signaling pathway is dysregulated in preeclampsia, with decreased levels of Sonic Hedgehog signaling pathway components observed in preeclamptic placentas.¹⁸ This dysregulation is thought to impair the trophoblast functions necessary for adequate uterine artery remodeling.¹⁹

Given that the process of placentation mainly occurs in the first trimester of pregnancy, we hypothesize that serum levels of SHH protein may be altered in the first trimester of pregnant women who develop preeclampsia later. This study aims to evaluate the predictive value of maternal serum SHH concentrations in the first trimester for the subsequent development of preeclampsia. Validation of SHH as an early predictive biomarker could identify women at high risk of preeclampsia, enabling intensified surveillance and timely preventive interventions to reduce adverse pregnancy outcomes.

Materials and Methods

Study Population

Ethical approval for this prospective, observational study was obtained from the Ethics Committee of The First Affiliated Hospital of Chengdu Medical College, and all participants provided written informed consent. Between January 2020 and December 2023, A total of 2942 pregnant individuals attending the obstetric outpatient clinic for routine antenatal visits in their first trimester of 8–13 weeks of gestation were screened. Eligibility required a singleton pregnancy, ultrasound confirmation of gestational age, and signed consent. Individuals with a history of hypertension, liver or kidney disease, diabetes mellitus, or cardiovascular disease were excluded. Enrolled participants were followed through delivery; those who miscarried or transferred antenatal care to other hospitals during follow-up were subsequently excluded. The final cohort comprised 2532 participants. The patient enrollment diagram was showed in [Figure 1](#).

Clinical Data Collection

At the initial obstetric outpatient visit for routine antenatal care, demographic and clinical information were recorded, including maternal age, smoking status, body mass index (BMI), parity, prior medical conditions, and blood pressure. Gestational age at enrollment was verified by ultrasonography. Preeclampsia was diagnosed according to the criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP).²⁰

Laboratory Data Collection

During the first trimester of 8–13 weeks of gestation, peripheral venous blood was obtained after an overnight fast. Blood samples were centrifuged at 2000 g for 10 minutes to isolate serum, which was then aliquoted and stored at –80 °C until analysis. Routine laboratory tests, including fasting glucose, lipid profile, serum creatinine, liver function panels, and

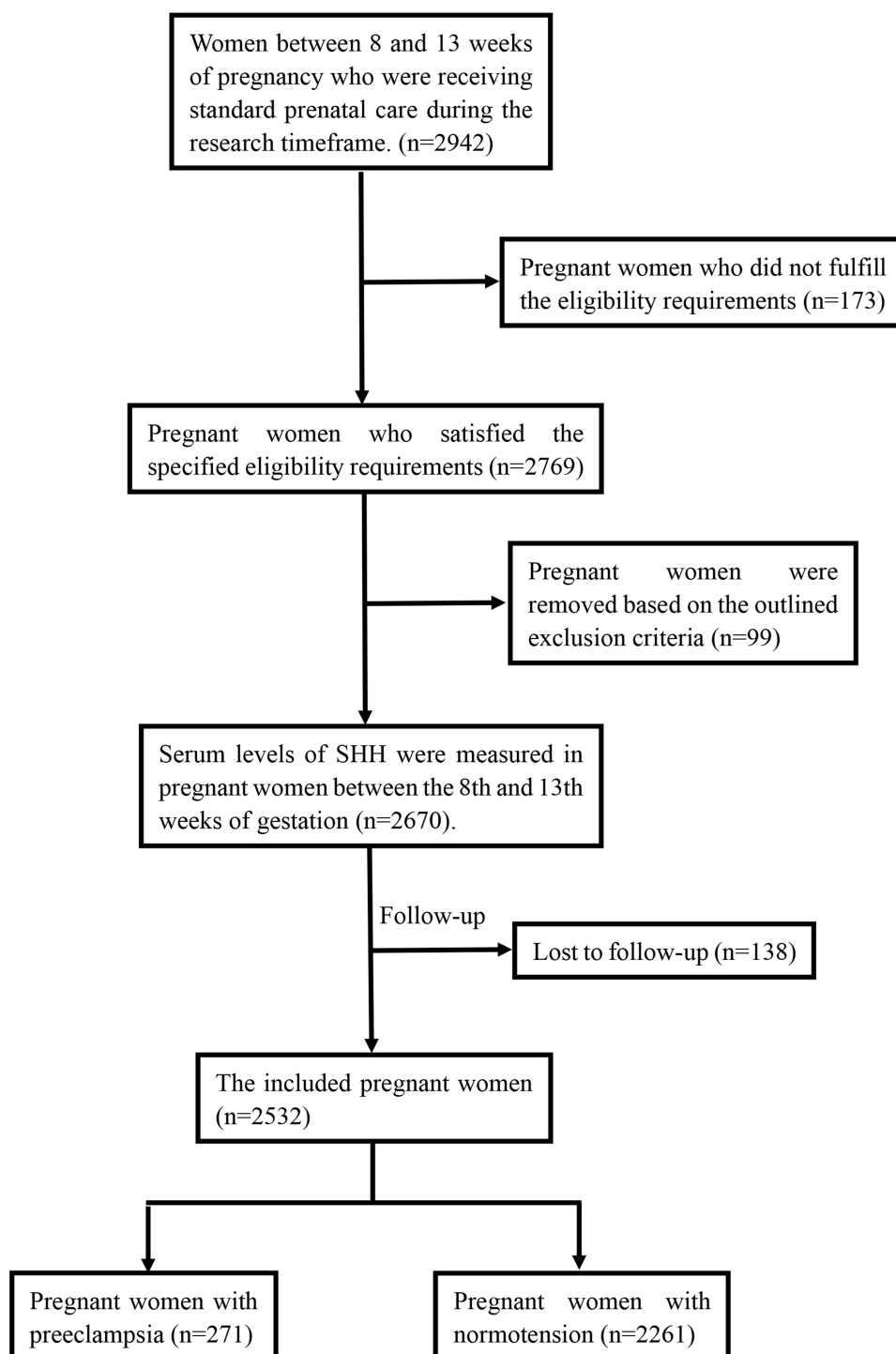


Figure 1 The patient enrollment diagram.

complete blood counts, were performed on automated analyzers according to standardized protocols in the Clinical Laboratory of the First Affiliated Hospital of Chengdu Medical College.

Quantification of Serum SHH, sFlt-1, and PIGF

Maternal serum concentrations of SHH, sFlt-1, and PIGF were assessed at 8–13 weeks of gestation using commercial ELISA kits (SHH: ab 100639, Abcam Co. Ltd., Shanghai, China; sFlt-1: DVR100C, R&D Systems, Minneapolis, MN,

USA; PIGF: DPG00, R&D Systems, Minneapolis, MN, USA). All assays were performed strictly following the protocols of the manufacturers. In brief, diluted serum samples were dispensed into the manufacturer's antibody-coated wells and incubated at room temperature for 2 hours. After thorough washing, horseradish peroxidase-conjugated detection antibodies were added for a 1-hour incubation. Plates were then washed, substrate solution was applied, and reactions proceeded in the dark for 30 minutes before being stopped. Optical density was read at 450 nm with a microplate reader (BioTek Instruments, Winooski, VT, USA). Each specimen was analyzed in triplicate, with the mean value used for subsequent analyses. Intra- and inter-assay coefficients of variation were maintained below 10%.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics, version 31.0 (IBM Corp., Armonk, NY, USA). Variables with normal distributions are reported as mean \pm standard deviation, and group differences were assessed with Student's *t*-test. Associations between serum SHH levels and clinical or laboratory measures were evaluated using Pearson's correlation. The relationship between serum SHH levels and subsequent preeclampsia was examined with logistic regression to adjust for potential confounders; adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were reported.

To evaluate the early predictive value of serum SHH levels for preeclampsia, receiver operating characteristic (ROC) curve analysis was performed. The area under the ROC curve (AUC) with its 95% CI quantifies discriminative performance. The optimal threshold value was identified by maximizing Youden's index. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Clinical Parameters of the Study Population

Of the 2532 enrolled pregnancies, 271 developed preeclampsia and 2261 remained normotensive. Statistical analyses revealed that pre-pregnancy BMI, maternal age, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), neonatal birth weight, gestational age at delivery, sFlt-1, and PIGF were significantly different between preeclampsia and normotensive groups (Table 1). In contrast, gestational age at enrollment, systolic and diastolic blood pressure, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), serum uric acid, and creatinine did not show statistical differences between the two groups (Table 1).

Maternal Serum SHH Levels in the First Trimester

First-trimester maternal serum SHH concentrations were significantly lower in individuals who subsequently developed preeclampsia than in those with normotensive pregnancies (Figure 2A). When preeclampsia was subclassified as early-onset (≤ 34 weeks) and late-onset (> 34 weeks) cases, individuals in the early-onset group had significantly lower serum SHH values than individuals in the late-onset group (Figure 2B).

Correlations Between Serum SHH and Clinical Parameters

Pearson correlation analyses investigated the correlations between maternal serum SHH and clinical parameters for the preeclampsia and normotensive groups (Table 2). Negative associations of SHH with pre-pregnancy BMI, maternal age, systolic blood pressure, TGs, TC, sFlt-1, PIGF, and LDL-C were observed in the preeclampsia group (all $P < 0.05$). No significant associations were observed between SHH and other variables, including gestational age at enrollment, diastolic blood pressure, HDL-C, AST, ALT, creatinine, and uric acid, within the preeclampsia group ($p > 0.05$). In addition, maternal SHH was not significantly correlated with any measured clinical parameters in the normotensive group.

Table 1 Baseline Characteristics of the Study Population (n=2532)

Characteristics	Preeclampsia (n=271)	Normotension (n=2261)	p-value
Pre-pregnancy BMI (kg/m ²)	28.47±4.56	24.42±2.51	0.001
Maternal age (years)	25±3.75	22±2.64	0.002
Gestational age at enrollment (weeks)	11.34±1.22	12.56±1.45	0.316
SBP (mm/Hg)	122.51 ± 8.34	121.43 ± 10.27	0.142
DBP (mm/Hg)	71.27 ± 3.21	72.36 ± 4.21	0.312
ALT (U/L)	28±2.74	29±2.34	0.294
AST (U/L)	29±4.35	32±2.17	0.324
TC (mmol/L)	5.93±0.45	6.12±0.62	0.413
LDL-C (mmol/L)	6.54±0.28	4.25±0.31	0.003
TG (mmol/L)	3.27±0.32	2.24±0.17	0.006
HDL-C (mmol/L)	3.38±0.25	3.24±0.37	0.412
Uric acid (μmol/L)	324±16.21	331±15.23	0.317
Creatinine (μmol/L)	64±3.51	68±3.41	0.271
Neonatal birth weight (g)	3217±321	3731±432	0.023
Gestational age at delivery (weeks)	36±3.41	38±126	0.014
sFlt-1 (ng/mL)	91±6.31	67±6.31	0.001
PIGF (ng/mL)	23.27±3.25	36.27±4.21	0.002

Notes: Independent samples t-test was used for statistical analyses. A $P < 0.05$ was considered statistically significant and marked in bold text.

Abbreviations: BMI, body mass index in pregnancy; TC, total cholesterol; TGs, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; sFlt-1, soluble fms-like tyrosine kinase 1; PIGF, placental growth factor; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Association of Serum SHH with Risk of Preeclampsia

The relationship between maternal serum SHH and the risk of preeclampsia was examined using multivariable logistic regression models with adjustment for potential confounders including maternal age, pre-pregnancy BMI, history of preeclampsia, and levels of TC, TG, HDL-C, LDL-C, sFlt-1, and PIGF. SHH concentrations were partitioned into tertiles

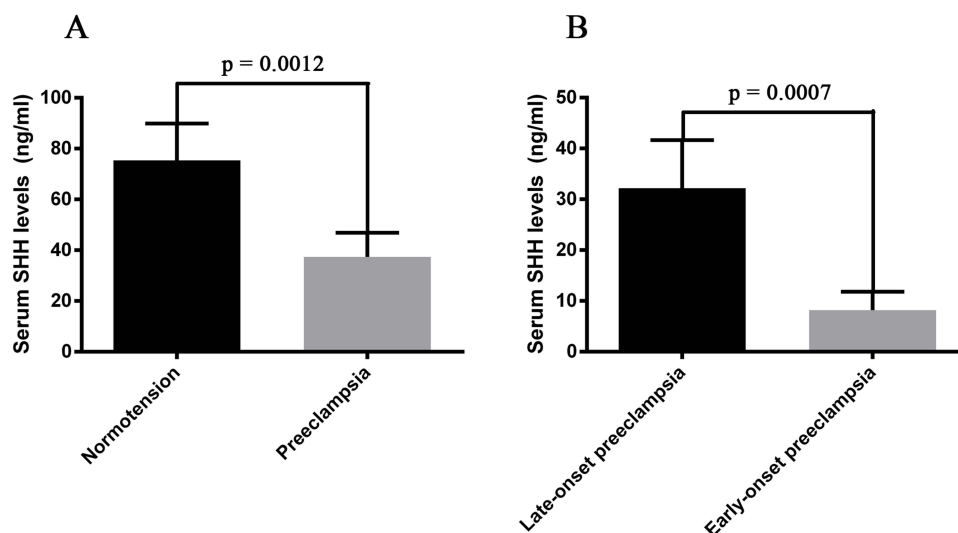


Figure 2 Maternal serum SHH levels in the first trimester. **(A)** First-trimester maternal serum SHH concentrations were significantly lower in individuals who subsequently developed preeclampsia than in those with normotensive pregnancies. **(B)** Individuals in the early-onset preeclampsia group had significantly lower serum SHH values than individuals in the late-onset preeclampsia group. Statistical analyses were conducted using IBM SPSS Statistics, and group differences were assessed with Student's t-test. A $P < 0.05$ was considered statistically significant.

Table 2 Correlations Between Serum SHH and Clinical Parameters in the Two Groups

Variable	Serum SHH			
	Preeclampsia (n=271)		Normotension (n=2261)	
	r	p value	r	p value
Pre-pregnancy BMI (kg/m ²)	-0.612	<0.0001	-0.071	0.417
Maternal age (years)	-0.727	0.003	-0.124	0.381
Gestational age at enrollment (weeks)	0.142	0.371	0.187	0.484
SBP (mm/Hg)	-0.634	0.004	-0.192	0.617
DBP (mm/Hg)	0.072	0.412	-0.112	0.213
TC (mmol/L)	-0.532	0.003	-0.206	0.136
TGs (mmol/L)	0.617	0.001	0.193	0.321
LDL-C (mmol/L)	-0.626	0.005	0.127	0.341
HDL-C (mmol/L)	0.071	0.471	0.169	0.125
AST (U/L)	-0.126	0.262	-0.131	0.142
ALT (U/L)	0.149	0.411	0.145	0.516
Creatinine (μmol/L)	0.168	0.231	0.143	0.321
Uric acid (μmol/L)	0.231	0.246	0.176	0.198
sFlt-1 (ng/mL)	-0.718	0.001	-0.122	0.281
PIGF (ng/mL)	0.523	0.002	0.247	0.435

Note: P-values were calculated by partial Spearman correlation analysis. Statistically significant values at $P < 0.05$ are shown in bold.

Abbreviations: BMI, body mass index in pregnancy; TC, total cholesterol; TGs, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; sFlt-1, soluble fms-like tyrosine kinase 1; PIGF, placental growth factor; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3 Association of Serum SHH with Risk of Preeclampsia

Serum SHH Levels (ng/mL)	Preeclampsia, n (%)	Adjusted OR	95% CI	p value
T1: 15.32–35.47	169 (28.42)	5.21	3.15–8.42	0.006
T2: 35.52–61.48	79 (10.15)	2.64	1.33–5.38	0.001
T3: 62.04–91.17	23 (6.23)	1	Reference	–
As a continuous variable	–	-0.647	0.32–0.92	0.002

Notes: P-values were calculated by logistic regression analysis after adjustment for potential confounding factors. Statistically significant values at $P < 0.05$ are shown in bold.

based on their distribution. Across these tertiles, the prevalence of preeclampsia increased progressively from 6.23% to 28.42%, representing a more than fourfold difference when the highest tertile was compared to the lowest tertile (Table 3). Using the highest tertile as reference, women in the lowest and middle tertiles exhibited greater odds of preeclampsia, with adjusted ORs of 5.21 (95% CI, 3.15–8.42) and 2.64 (95% CI, 1.33–5.38), respectively (Table 3). When modeled as a continuous variable, lower SHH levels were associated with an increased risk of preeclampsia (adjusted OR, - 0.647; 95% CI, 0.321–0.928; $p = 0.002$).

Predictive Performance of SHH for Preeclampsia

Receiver operating characteristic (ROC) analysis was used to assess the discriminatory ability of SHH for preeclampsia, with predictive performance compared with the two established markers, PIGF and sFlt-1. SHH demonstrated the highest predictive performance, yielding an AUC of 0.86 (95% CI, 0.62–0.91), surpassing both sFlt-1 and PIGF (Table 4). The corresponding AUCs were 0.71 (95% CI, 0.48–0.83) for sFlt-1 and 0.62 (95% CI, 0.45–0.84) for PIGF. At a cutoff of 58.26 ng/mL, SHH achieved the greatest sensitivity and specificity of 81.46% and 76.58%, respectively (Table 4). Collectively, these findings support SHH as a reliable biomarker for predicting preeclampsia.

Table 4 Predictive Performance of SHH for Preeclampsia

Biomarkers	AUC (95% CI)	Sensitivity	Specificity	Cut-Off Value (ng/mL)	p-value
SHH	0.86 (0.62–0.91)	81.46%	76.58%	58.26	0.002
sFlt-1	0.71 (0.48–0.83)	74.36%	64.28%	42.34	0.001
PIGF	0.62 (0.45–0.84)	65.42%	57.61%	28.75	0.005

Notes: Predictive performances of SHH for preeclampsia were assessed by receiver operating characteristic curve analyses. A $p < 0.05$ was considered statistically significant and marked in bold text.

Table 5 Predictive Performance of SHH for Early-Onset and Late-Onset Preeclampsia

Pre-Eclampsia	AUC (95% CI)	Sensitivity	Specificity	Cut-Off Value (ng/mL)	p-value
Early-onset	0.93 (0.67–0.97)	87.73%	82.43%	62.37	0.001
Late-onset	0.75 (0.54–0.86)	73.42%	68.24%	55.78	0.002

Notes: Predictive performances of SHH for early-onset and late-onset preeclampsia were assessed by receiver operating characteristic curve analyses. A $p < 0.05$ was considered statistically significant and marked in bold text.

We further assessed the predictive performance of SHH for early-onset and late-onset preeclampsia. SHH showed stronger discrimination for early-onset preeclampsia, with an AUC of 0.93 (95% CI, 0.67–0.97; $p = 0.001$), compared with an AUC of 0.75 (95% CI, 0.54–0.86; $p = 0.002$) for late-onset disease (Table 5). For early-onset cases, a cut-off value of 62.37 ng/mL yielded sensitivity and specificity of 87.73% and 82.43%, respectively. For late-onset cases, a cutoff of 55.78 ng/mL produced sensitivity of 73.42% and specificity of 68.24% (Table 5).

Discussion

In this prospective study, first-trimester maternal serum SHH concentrations were significantly lower in pregnancies that later developed preeclampsia, with the greatest decrement observed in early-onset preeclampsia. SHH remained independently associated with preeclampsia after adjustment for conventional maternal factors and angiogenic markers and demonstrated promising discriminative performance in receiver operating characteristic analysis. These findings align with contemporary first-trimester screening paradigms that emphasize placentation biology and support the addition of mechanistically anchored placental biomarkers to improve early risk stratification.

SHH protein is the ligand that binds to the receptor Patched 1, leading to the activation of the Sonic Hedgehog signaling pathway.²¹ Our observations are biologically plausible in light of data implicating Sonic Hedgehog signaling as a regulator of trophoblast lineage specification, migration, and invasion, which are processes central to spiral artery remodeling.^{22–24} Hedgehog signaling is transduced via PTCH1/SMO and GLI transcription factors at the primary cilium of trophoblasts; disruption of ciliary structure or Hedgehog activity impairs motility, tube formation, and trophoblast fusion.^{18,24} Experimental models relevant to preeclampsia suppress Hedgehog pathway components and blunt trophoblast invasiveness, whereas pathway activation restores angiogenic balance and improves pregnancy outcomes; conversely, inhibition of the Hedgehog pathway abrogates these benefits.^{9,16,18,22} Together, these data suggest that reduced maternal SHH in early gestation may reflect insufficient placental Hedgehog signaling, heralding shallow trophoblast invasion and subsequent uteroplacental malperfusion, which are characteristics of preeclampsia.

Circulating markers such as sFlt-1 and PIGF have also been investigated for their predictive utility in preeclampsia.^{25,26} A study in the *New England Journal of Medicine* reported that an sFlt-1/PIGF ratio ≤ 38 reliably excluded development of preeclampsia within 1 week, with a negative predictive value of 99.3% (95% CI, 97.9–99.9%), a sensitivity of 80.0%, and a specificity of 78.3%. In contrast, ratios >38 yielded a positive predictive value of 36.7% (95% CI, 28.4–45.7%) for onset within 4 weeks, with a sensitivity of 66.2% and a specificity of 83.1%.²⁷ Notably, these findings pertain to short-term risk assessment in pregnancies between 24 and 36 weeks' gestation, which may limit their preventive impact earlier in pregnancy. By comparison, our data indicate that SHH can stratify risk as early as the first trimester, enabling clinicians to consider preventive strategies at an earlier stage.

From a clinical perspective, first-trimester identification of women at increased risk of preeclampsia has actionable implications.^{28,29} Risk-stratified care enables timely low-dose aspirin prophylaxis, optimization of maternal comorbidities, and closer surveillance to reduce severe maternal morbidity and iatrogenic prematurity.^{30,31} In our cohort, SHH achieved high sensitivity and specificity at an empirically derived cutoff and showed stronger performance for early-onset preeclampsia, the phenotype most tightly linked to placental pathology and adverse neonatal outcomes.³² These characteristics are precisely those desired in a triage biomarker deployed during the first trimester within competing-risks algorithms that already incorporate maternal factors, mean arterial pressure, uterine artery Doppler indices, and angiogenic proteins. Incorporating SHH into such frameworks may improve calibration and net reclassification beyond single-marker strategies, particularly for early-onset disease, where preventive benefit is greatest.

From a global health perspective, an attractive feature of SHH is that it can be measured on conventional ELISA platforms that are widely available, including in many low- and middle-income settings. In contrast to high-cost proprietary assays (eg, sFlt-1–based tests), first-trimester SHH measurement could provide a more affordable biochemical component of early risk stratification, helping to identify women who require closer antenatal surveillance where access to Doppler ultrasound and angiogenic markers is limited. However, our study did not include a formal cost-effectiveness analysis or implementation evaluation, and further work is needed to confirm the practicality and economic value of SHH-based screening in low-resource environments.

An important strength of our study is that all participants were recruited in the first trimester (8–13 weeks) and followed prospectively until delivery, allowing SHH to be evaluated as an early predictor of incident preeclampsia rather than a concurrent marker. This design ensured that maternal serum SHH was measured well before the onset of clinical disease and that the association we observed reflects true predictive value over the subsequent gestational follow-up, rather than a cross-sectional difference. The ability of low first-trimester SHH levels to identify women who later developed especially early-onset preeclampsia underscores its potential value within first-trimester risk-prediction strategies alongside established placental biomarkers.

The study also has limitations. First, it was conducted at a single center, which may limit generalizability to other populations and care settings; external validation is warranted. Second, despite adjustment for numerous potential confounders, residual confounding cannot be excluded; unmeasured factors, such as genetic susceptibility, socioeconomic conditions, and environmental exposures, may influence both serum SHH concentrations and preeclampsia risk. Finally, assay platform differences and preanalytical variability could affect reproducibility; future work should harmonize protocols and assess interlaboratory performance.

Conclusion

First-trimester maternal serum SHH concentrations were significantly lower in pregnancies that later developed preeclampsia and were an independent, clinically meaningful predictor, particularly for early-onset disease. These findings, consistent with the central role of Hedgehog signaling in trophoblast differentiation and invasion, support SHH as a promising addition to first-trimester screening strategies. With external validation and integration into multiparametric algorithms, SHH-based risk stratification could enable earlier interventions and individualized antenatal surveillance, thereby reducing the burden of preeclampsia for mothers and infants.

Abbreviations

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; sFlt-1, soluble fms-like tyrosine kinase 1; PlGF, placental growth factor; SBP, systolic blood pressure; SHH, Sonic Hedgehog; TC, total cholesterol; TG, triglyceride.

Ethics Approval

Informed consent was obtained from the study participants before the commencement of the study, and the study complies with the Declaration of Helsinki. This study was approved by the Ethics Committee of The First Affiliated Hospital of Chengdu Medical College (No. 23573465).

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Disclosure

The authors declare no conflicts of interest in this work.

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