The Journal of Obstetrics and Gynecology of India (July-August 2022) 72(4):299–306
https://doi.org/10.1007/s13224-021-01511-z

ORIGINAL ARTICLE

Model for Early Prediction of Preeclampsia: A Nested Case Controlled Study in Indian Women

Sonali Yadav[1,5] · Sukhanshi Khandpur[5] · Yogendra Singh Yadav[2] · Madhu Mati Goel[1] · Urmila Singh[3] · Shankar Madhav Natu[1] · Mahendra Pal S. Negi[4] · Lokendra Kumar Sharma[5] · Swasti Tiwari[5]

Received: 11 November 2020 / Accepted: 1 June 2021 / Published online: 29 June 2021

Abstract

Purpose Preeclampsia (PE) affects 5–7% of the pregnancies worldwide, and is one of the most dreaded disorders of pregnancy contributing to maternal and neonatal mortality. PE is mostly presented in the third trimester of pregnancy. Here, we used serum placental growth factor (PIGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) to develop a model for predicting PE in Indian women in early second trimester.

Methods In this case–control study, a total 1452 healthy pregnant women were recruited. Blood samples were collected at the following gestational weeks (GWs), 12–20 (GW1), 21–28 (GW2) and 29-term (GW3), and post-delivery. Body mass index (BMI) was calculated by anthropometric measurements. Serum sFlt-1, PIGF and VEGF were analyzed by ELISA. A predictive model for PE was developed using multivariable logistic regression analysis.

Results In PE cases, serum PlGF and VEGF levels were significantly lower at each GW, while serum sFlt-1 was lower only at GW1, relative to age-matched controls, ($n = 132$/group). Age-matched comparison between PE cases and controls indicated that sFlt-1 was associated with decreased PE outcome (Odds ratio. OR = 0.988, CI = 0.982–0.993), whereas sFlt-1/PlGF ratio (OR = 1.577, CI = 1.344–1.920) and BMI (OR = 1.334, CI = 1.187–1.520) were associated with increased PE outcome. Logistic regression was used to develop a predictive model for PE at GW1. Using testing dataset, model was externally validated which resulted in 88% accuracy in predicting PE cases at 0.5 probability cutoff.

Conclusion Prediction model using sFlt-1, sFlt-1/PlGF ratio and BMI may be useful to predict PE as early as 12–20 weeks in women with optimal sensitivity and specificity.

Keywords Preeclampsia · Pregnancy · Placenta · PlGF · VEGF · sFlt-1

Swasti Tiwari, Ph.D. is Professor at Department of Molecular Medicine & Biotechnology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, (U.P.) India.

Designations: Sukhanshi Khandpur- Biotatistician (PhD Student); Yogendra Singh Yadav- Assistant Professor; Madhu Mati Goel-Professor; Urmila Singh-Professor; Shankar Madhav Natu-Professor; Mahendra Pal S. Negi- Biostatician; Lokendra Kumar Sharma- Assitant Professor; Swasti Tiwari-Professor. Role for the aurthors: Sonali Yadav—project development, data collection and manuscript writing. Sukhanshi Khandpur and Mahendra Pal S. Negi—data analysis. Yogendra Singh Yadav—data collection. Madhu Mati Goel, Urmila Singh, and Shankar Madhav Natu: project development. KV—data analysis. Lokendra kumar Sharma—manuscript editing. Swasti Tiwari—manuscript writing and data analysis.

✉ Swasti Tiwari
tiwari_pgi@yahoo.com; tiwaris@sgpgi.ac.in

Extended author information available on the last page of the article

Abbreviations

PlGF	Placenta growth factor
VEGF	Vascular endothelial growth factor
PE	Preeclampsia

Introduction

Preeclampsia (PE) is a life threatening disorder of pregnancy characterized by new-onset hypertension (blood pressure ≥ 140/90 mmHg), along with one or more of following: proteinuria, uteroplacental dysfunction and evidence of other maternal organ dysfunction [1, 2]. In 2015, hypertensive disorder of pregnancy and especially preeclampsia, accounted for 14% of the overall global maternal mortality ratio of 216 per 100,000 live births, with highest proportion of deaths in low and middle income middle countries [1, 3]. Worldwide, the incidence of PE ranges between 2 and 10%

of pregnancies, lack of early detection and unavailability of reliable markers for PE makes the situation worse, especially in developing countries [2]. PE is presented mostly in the third trimester of pregnancy. Thus, early prediction of PE would significantly lower the associated morbidity and mortality by timely clinical management.

During pregnancy, angiogenesis is facilitated by angiogenic growth factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). Conversely, soluble fms-like tyrosine kinase-1 (sFlt-1) acts as an antagonist which binds to VEGF and PlGF and inhibits them from activating cognate receptors to promote vascular homeostasis. An imbalance of these factors plays a key role in pathogenesis of preeclampsia and has been used to predict PE [3]. An elevation in sFlt-1 levels and reduced levels of PlGF and VEGF has been reported to contribute to endothelial dysfunction, hypertension and proteinuria in PE cases [3–5]. Besides, recent cohort studies from western countries further suggest the use of sFlt-1/PlGF ratio (a cutoff level ≤ 38 between gestational weeks 26 to 34) for ruling out PE possibility in patients with suspicion of the disease [4, 6]. However, a clear recommendation for cutoff to predict PE in early second trimester in pregnant women without any suspicion/known risk for PE is still lacking. Besides, ethnicity, geographic and social diversity sociodemographic and socioeconomic characteristics of pregnant women are important to be considered for setting up a universal cutoff range for early PE diagnosis [4, 6–9]. In this longitudinal study, serum sFlt-1, PlGF and VEGF levels were estimated in normotensive Indian women, who showed up at antenatal clinics between gestational weeks 12–20. The aim of the study was to determine the time course regulation of circulating anti-angiogenic (sFlt-1), and angiogenic factors (PlGF, VEGF) during the course of pregnancy, and to develop a model for early prediction of preeclampsia with optimal sensitivity and specificity.

Materials and Methods

The nested case–control study was carried out with the approval of the King George's Medical University, Uttar Pradesh ethics committee (XLIII ECM/B-P15). Total 1452 healthy women with singleton pregnancy were included with their written consent. Women with history of essential hypertension, renal disease, epilepsy, diabetes or any other chronic or pre-existing disease were excluded from the study. Women with gestational hypertension, missing specimens or data were also excluded. The gestational age of women, at the time of collection, was determined by ultrasonographic examination.

Among 1452 registered, 132 women were diagnosed with PE according to diagnostic criteria of PE (systolic blood pressure at ≥ 140 mmHg and/or the diastolic blood pressure at ≥ 90 mmHg and accompanied by ≥ 1 of the following new-onset conditions at or after 20 weeks' gestation: (i) proteinuria (i.e., ≥ 30 mg/mol or ≥ 2 + dipstick); (ii) evidence of other maternal organ dysfunction, including: acute kidney injury (creatinine ≥ 90umol/L; 1 mg/dL), liver involvement (elevated transaminases, e.g., alanine aminotransferase or aspartate aminotransferase > 40 IU/L) neurological complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata), or hematological complications (thrombocytopenia–platelet count < 150,000/μL) or (iii) uteroplacental dysfunction such as fetal growth restriction, abnormal umbilical artery, Doppler waveform analysis) [10]. From the rest, age-matched normotensive women ($n = 132$) were selected as control group. Peripheral blood samples were collected from these subjects at different gestational weeks (GWs) categorized as GW1: 12–20 weeks, GW2: 21–28 weeks and GW3: 29 weeks-term and 48 h post-delivery. Serum was separated and stored in multiple aliquots at −80 °C for estimation of sFlt-1, VEGF and PlGF.

Estimation of sFlt1, VEGF and PlGF by Serum ELISA

Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used as per manufacturer's instructions for estimation of sFlt1 (e-Bioscience, USA), PlGF (USCN Life Science Inc., China) and VEGF (Koma Biotech., Korea). The minimal detection limit of assay for sFlt1, PlGF and VEGF was less than 30 pg/ml, 6.8 pg/ml and 16 pg/ml, respectively.

Statistical Analysis

Chi-square tests were used for comparing categorical variables, and Student's t-test/Mann Whitney U test was used for continuous variables wherever applicable. To test the difference in PlGF, VEGF and sFlt-1 between PE cases and controls, the variables under study did not met the assumptions of parametric tests even after testing with transformations; therefore, non-parametric alternative of 2 sample t test was used (*P* value less than 0.05 was considered statistically significant).

Prediction Model

Multivariable logistic regression was performed to predict the occurrence of PE in pregnant women before 20 weeks of their gestation with normal blood pressure. Various maternal parameters from normotensive women were considered as potential predictors and divided in training and validation data set. Finally, sFlt-1, sFlt-1/PlGF ratio and BMI were selected through logistic regression model. The accuracy of

the model was tested by calculating the expected frequency with the observed frequency of the outcome at different levels of predicted probability cutoffs. Receiver operating characteristics (ROC) curve and area under curve (AUC) with 95% C.I. were used to evaluate the performance of the model. All analyses were performed using SPSS and R software (version 3.6.0).

Results

Demographic and Clinical Parameters

The basic characteristics of two groups at enrollment are summarized in Table 1. The characteristics such as height and weight were significantly low in cases than controls. In cases, blood pressure levels were higher than controls both at the time of enrollment as well as at post-delivery. With increasing gestational weeks, we observed a significantly higher rise in blood pressure (SBP and DBP) than controls (Table 2). Further, cases have 21% preterm (< 37 weeks) birth compared to 8% in controls. Besides, a higher percentage of infants (31%) born to cases were small for their GA (< 10 percentile) and had lower infant birth weights than controls (Table 1).

Table 1 Demographic and clinical characteristics of pregnant women enrolled in the study and pregnancy outcomes

Variables	Group 1 (Controls) $N=132$	Group 2 (Cases) $N=132$	*P* value
Age (Mean ± SD)	25.39 ± 0.35	25.58 ± 0.35	0.638
Height (Mean ± SD)	157.32 ± 0.44	149.48 ± 0.49	0.000
Weight (Mean ± SD)	54.21 ± 0.69	56.56 ± 0.68	0.030
BMI (Mean ± SD)*	21.96 ± 0.30	25.42 ± 0.35	0.000
Religion (n, %)			
Hindu	112 (84.8%)	117 (88.6%)	
Muslim	20 (15.2%)	15 (11.4%)	0.364
Socio Economical Status (SES)			
Lower income group	7 (5.3%)	5 (3.8%)	
Middle income group	97 (73.5%)	98 (74.2%)	
Upper income group	28 (21.2%)	29 (22.0%)	0.837
Diet			
Vegetarian	113 (85.6%)	111 (84.1%)	
Non-vegetarian	19 (14.4%)	21 (15.9%)	0.731
Parity			
Primigravida	42 (31.8%)	54 (40.9%)	
Multigravida	90 (68.2%)	78 (59.1%)	0.125
Gestational age at enrollment	16.12 ± 2.47	16.15 ± 2.57	0.952
SBP at enrollment (Mean ± SE)	112.23 ± 1.12	122.11 ± 0.58	0.000
DBP at enrollment (Mean ± SE)	62.17 ± 0.52	74.18 ± 0.46	0.000
Gestational age at delivery	38.30 ± 1.13	37.47 ± 1.31	0.000
SBP at post-delivery (Mean ± SE)	108.39 ± 0.83	120.41 ± 0.53	0.000
DBP at post-delivery (Mean ± SE)	60.70 ± 0.42	77.17 ± 0.45	0.000
Delivery Period (n, %)			
Preterm(< 37 weeks)	8 (6.1%)	28 (21.2%)	
Term(≥ 37 weeks)	124 (93.9%)	104 (78.8%)	0.000
Gestational Age (J)			
AGA (≥ 10 percentile)	127 (96.2%)	101 (76.5%)	
SGA (< 10 percentile)	5 (3.8%)	31 (23.5%)	0.000
Infants birth weight (kg)	2.94 ± 0.03	2.59 ± 0.03	0.000

Abbreviations: *SBP*: Systolic Blood Pressure, *DBP*: Diastolic Blood Pressure, *statistical significance was measured using 2 sample *t* test, and for others, Mann Whitney U test, 2 sample *t* test and χ^2 test were used wherever applicable

Table 2 Median blood pressure during gestational weeks

	Median (IQR)				*P* value
	GW1 (12–20 weeks)	GW2 (21–28 weeks)	GW3 (29 week-term)	Post-delivery	
Control					
SBP	112 (102–124)	115 (106–128)	122 (114–130)	110 (100.50–116)	< 0.001
DBP	62 (58–66)	66 (62–70)	68 (66–72)	60 (58–64)	< 0.001
Cases					
SBP	122 (118–126)	132 (128–136)	146 (142–152)	120 (116–122)	< 0.001
DBP	74 (70–78)	84 (82–88)	94 (92–98)	78 (74–80)	< 0.001

Data are expressed as median (IQR). Friedman ANOVA was used to test for the trend of blood pressure across different weeks of gestation. Abbreviations: *GW*: Gestation Week, *IQR*: Inter Quartile Range

Measurement of PlGF, VEGF and sFlt-1 Levels

Inadequate Rise in PlGFin Cases than Controls During Pregnancy

A progressive rise in the serum PLGF levels was observed with increasing GWs in both cases and controls. The levels of PlGF in controls were 2.48-fold higher in GW2 and peaked to 4.05-fold in GW3 when compared to their levels in GW1 (Table 3). However, in cases, PlGF showed only modest increase in 2.09-fold in GW2 and 2.52-fold in GW3 compared from their GW1 values. Moreover, at each GW, the serum PLGF levels were significantly less in cases as compared to controls. At post-delivery, PlGF levels dropped in both controls and cases, and no significant difference was observed in their final concentrations. Overall, the results indicated that PlGF levels remained low throughout GWs in cases and did not have adequate rise as compared to controls.

Rise in VEGF Levels in Cases than Controls During Pregnancy

Similar to PlGF, basal level of VEGF was significantly lower in cases throughout the GWs and also post-delivery, compared to controls (Table 3). However, contrary to PlGF, the rise in VEGF levels was modestly higher in cases than control. In controls VEGF levels increased initially to 1.55 fold in GW2, and later this rise was reduced and limited to 1.29 fold and 1.21 in GW3 and post-delivery period, respectively. In cases, VEGF levels rose to 1.72 and 1.82 in GW2 and GW3, respectively, and peaked to 2.03 fold post-delivery. These results indicated that although VEGF levels remained low throughout pregnancy similar to PlGF, however, its level increased progressively only in cases till post-delivery.

Table 3 Measurement of PlGF, VEGF and sFlt-1 levels during pregnancy

Markers (pg/ml)	Groups	GW1	GW2	GW3	Post-delivery
PlGF	Control	56.44	140.45 ***(2.48 fold)***	228.90 ***(4.05 fold)***	32.00 (0.56 fold)
	Cases	31.67*	66.37* ***(2.09 fold)***	80.10* ***(2.5 fold)***	32.30 (1.01fold)
VEGF	Control	179.00	278.00 ***(1.55 fold)***	231.50 ***(1.29 Fold)***	218.00 (1.2 fold)
	Cases	90.93*	157.01* ***(1.72 fold)***	166.26* ***(1.82 fold)***	185.28* (2.03)
sFlt-1	Control	302.00	476.00 **(1.57 fold)**	1676.50 **(5.55 fold)**	230.50 (0.76 fold)
	Cases	239.00*	590.00* **(2.46 fold)**	7106.00* **(29.73 fold)**	400.50* (1.67 fold)

Bold, Bolditalics specifies the fold change with respect to GW1

Data are expressed as median. Mann Whitney U test was used for comparison

Higher sFlt-1 Levels in Cases than Controls During Pregnancy

Initially, the basal level of sFlt-1 was significantly lower in cases than control in GW1; a progressive rise in sFlt-1 levels from GW2 to GW3 was observed in both cases and controls, but post-delivery these levels significantly dropped in both groups (Table 3). Controls showed 1.5 and 5.55 fold increase in GW2 and GW3, respectively, from GW1, while most importantly in cases this increase was 5.51 fold in GW2 and peaked at 29.73 fold in GW3. Overall, the sFlt-1 levels were increased significantly during GW2 and GW3 with cases have a greater increase in sFlt-1 levels at GW3 (Table 3).

Prediction Model for Early Detection of Preeclampsia in Normotensive Controls

A prediction model was developed for detecting PE in pregnant women before 20 weeks. A total of 226 out of 264 participants were found normotensive according to the EHS guidelines. Multivariable logistic regression was performed with the aim to study the independent factors to predict the occurrence of PE in pregnant women before 20 weeks of their gestation with normal blood pressure. Therefore, the data were first categorized into training and validation sets. Training set included 70% of randomly selected sample ($n = 159$) from normotensive participants, which were tested for the significant association of each variable (as listed in Table 1) through univariate analysis. These variables were than tested for multi-colinearity and associations, and found that sFlt-1, sFlt-1/PlGF ratio and BMI were not correlated ($r \leq 0.2$) or associated (χ^2; $P > 0.05$) with each other and therefore included in the final model (Table 4). For external validation of the model, remaining 30% of the normotensive data (validation data) with these selected variables were used to calculate the prediction probabilities. Accuracy of the model was determined by testing the expected frequency of the outcome with the observed frequency at 50% probability cutoff. ROC curve and AUC with 95% CI were used to evaluate the performance of the model (Fig. 1). We found that sFlt-1 was associated with decreased PE (OR = 0.988, CI = 0.982–0.993), whereas sFlt-1/PlGF ratio (OR = 1.577, CI = 1.344–1.920) and BMI (OR = 1.334, CI = 1.87–1.520) were associated with increased PE (Table 4). Using validation data set, this model resulted in approximately 88% accuracy in predicting cases at 0.5 probability cutoff. ROC resulted in 89% sensitivity and 87% specificity with AUC of 0.9542, CI: (0.9124–0.996) at 0.50 predicted probability

Table 4 Analysis of parameters for multi-colinearity and associations

Model Parameters	Coefficient	Standard Error	Exp(B)	95% CI for Exp(B)
sFlt-1	−0.011	0.002	0.988	0.982–0.993
sFlt-1/PlGF	0.455	0.090	1.577	1.344–1.920
BMI	0.288	0.062	1.334	1.187–1.520
Constant	−7.046	1.694		

Summary of the proposed prediction model. Exp(B) represents the adjusted odds ratio

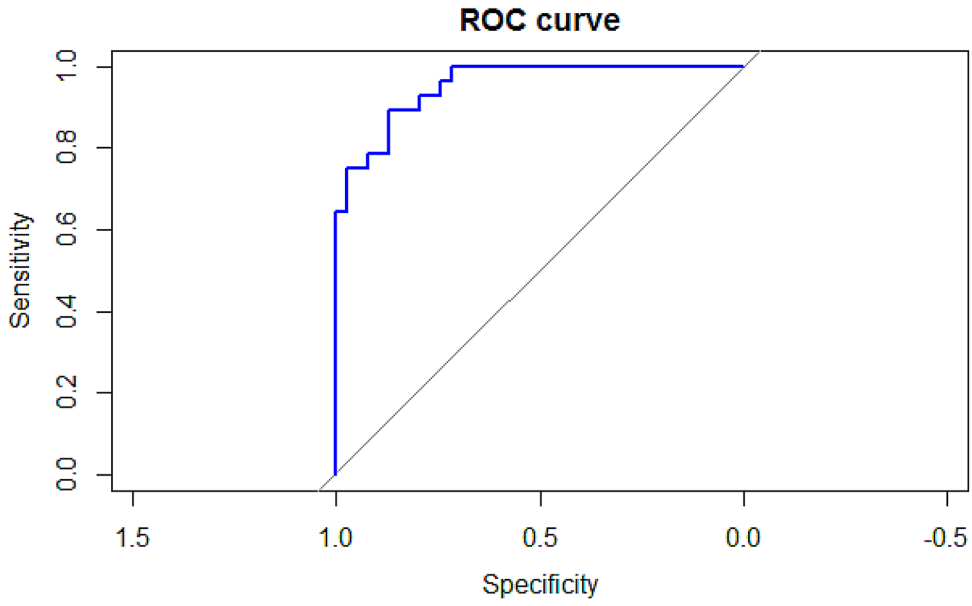

Fig. 1 Receiver operating characteristics (ROC) curve for PE prediction model. ROC curve and AUC with 95% C.I. were used to evaluate the performance of the model

cutoff suggesting to be better in screening for PE when compared to sFlt/PlGF ratio alone in 12–20 weeks of gestation (Table 5). Using sFlt-1, sFlt-1/PlGF and BMI values, the given formula may be used for predicting PE.

$$\mathbf{Pr(PE)} = \frac{e^{-7.046+0.455*\text{Ratio}+0.288*\text{BMI}-0.011*\text{sFlt}-1}}{1+e^{-7.046+0.455*\text{Ratio}+0.288*\text{BMI}-0.011*\text{sFlt}-1}}$$

Discussion

Despite the limited numbers of reports, an imbalance of circulating anti-angiogenic (sFlt1) and angiogenic factors (PlGF, VEGF) levels has been proposed to contribute in the genesis of preeclampsia and therefore, could predict PE [3, 11–13]. Individual levels of one or more of these factors in combination of maternal characteristics and obstetric history were shown to predict PE as early as 11th week of gestation [14–16]. However, in the meta-analysis by Kleinrouweler et al., the test accuracy of angiogenic/anti-angiogenic factors was found too weak for accurate prediction of onset of preeclampsia in the clinical setting [16, 17]. The meta-analysis had several studies from various countries, but did not contain even a single study from India. Nevertheless, the meta-analysis also emphasized that a generalized 'abnormal' value of angiogenic/anti-angiogenic factors is too risky to be used for preeclampsia prediction. Since 'normal' values for these factors may vary between individuals and with ethnic and socioeconomic variations, a relative change in these factors could be tried as an approach for diagnosis. Here, we report temporal changes in maternal VEGF, PlGF and sFlt-1 levels during pregnancy in a cohort of Indian women. We found lower levels of PlGF and VEGF throughout pregnancy in women who developed PE. These women also showed an excessive increase in sFlt-1 levels compared to pregnant women who remained normaotensive. Besides, an early prediction model for PE, as early as GW 20, has been developed using the following parameters: sFlt-1, sFlt-1/PlGF ratio and BMI data, with ~ 88% accuracy.

Previous studies have suggested that higher sFlt-1 levels and lower PlGF levels could predict PE in < 34 weeks of pregnancy [11, 17]. Although these changes are more pronounced in preeclamptic women, this inverse relation between sFlt-1 and PlGF was also reported in normotensive controls, especially at the last two months of pregnancy [3]. In recent years, sFlt-1/PlGF ratio has been used for predicting PE; however, the optimal values for cutoff ratio vary and depend on gestational weeks and several other maternal parameters [17–23]. In this study, we observed lower levels of PlGF in PE cases compared to age-matched controls. Unlike, studies that reported higher circulating total VEGF in women with preeclampsia compared to controls; in our study, VEGF levels also remained low throughout pregnancy. In most of these studies, VEGF levels were estimated in the third trimester after the PE diagnosis [11, 24–28]. Further, radioimmunoassay was used for VEGF measurements, which may not differentiate between total and free VEGF as compared to ELISA-based method that specifically measure free VEGF [11, 27, 28]. There are conflicting reports about the association between sFlt-1 levels and adverse pregnancy outcomes [11]. In pregnant rats, Jiang et al. showed that high levels of circulating sFlt-1 precede the development of preeclampsia like phenotype [27]. However, in human studies, high concentration of sFlt-1 (before clinical onset of disease) was associated with increased risk of preeclampsia late in second trimester [12, 15, 28]. Other studies failed to show any association of preeclampsia with sFlt-1.

Our study suggested that although sFlt-1 levels were significantly low in cases compared to controls at early weeks (12–20 week), it progressively increased in cases at much higher levels from 20th week onwards and peaked at 29 weeks-term. Since hypoxia during pregnancy is considered as a major stimulus for rise in sFlt-1 levels, it antagonizes the functions of angiogenic factors leading to endothelial dysfunctions [29, 30]. Although we did not measure the hypoxia in this study, the inadequate rise in PlGF and VEGF levels was observed in PE cases.

As mentioned earlier, a balance between these factors is required for healthy pregnancy, and several prospective multi-centric studies have utilized sFlt-1/PlGF ratio to predict PE [6, 19, 21]. One of the recent prognostic

Table 5 Sensitivity, specificity and ROC analysis of sFlt-1, PlGF and ratio

Variables	Cutoff	Sensitivity (%)	Specificity (%)	*P* value	AUC	95%CI
Model	0.5055	89	87	Ref.	0.9542	0.9124–0.996
PlGF	53.71	96	56	0.014	0.8846	0.8081–0.9612
sFlt-1	261.31	85	66	< 0.001	0.7418	0.6129–0.8706
Ratio	5.40	92	56	0.012	0.8544	0.7639–0.9448

Sensitivity–specificity tradeoff and AUC trend of previously studied PE parameters and the proposed model

studies suggested a cutoff vale of < 38 for sFlt-1/PlGF ratio to rule out PE during 24–36 weeks of gestation in clinically suspected cases. In our study, we utilized sFlt-1, sFlt-1/PlGF ratio and BMI variables from normotensive subjects (women with no/low risk for PE) and developed a model to predict PE as early as 12–20 weeks with 89% sensitivity and 87% specificity. Several other prediction models, using combinations of physiological and clinical parameters, were previously reported; however, our model could predict at relatively earlier GW with better diagnostic power compared to most of these models [14, 15, 17, 31, 32]. For example, Baschat et al. reported a first-trimester prediction model with 55% sensitivity with a 10% false positive rate using clinical variables such as maternal blood pressure, history of prior PET, diabetes, null parity, and low PAPP-A [31]. Similarly, another prediction model resulted in 67% sensitivity and 96% specificity for predicting PE at 24 weeks based on sFlt-1 levels [32]. In STEPS study, an early onset PE prediction model was developed using sFlt-1/PlGF ratio, mean arterial pressure, parous and previous PE as parameters to PE from 20 weeks onwards with ~ 60% sensitivity [17].

Conclusion

In summary, our data suggest that inadequate rise in the concentration of PlGF and VEGF; during early course of pregnancy could be used in the clinic as biomarkers to predict the onset of preeclampsia. In addition, the formulae developed by us using sFlt-1, sFlt-1/PlGF ratio and BMI variables could predict preeclampsia as early as 12–20 week of gestation, with optimal sensitivity and specificity.

Acknowledgements We are grateful to Science and Engineering Research Board (SERB), Department of Science & Technology for financially support to S.Y. under National Post-Doctoral Fellowship (PDF/2016/003785).

Authors contribution YS—project development, data collection and manuscript writing. KS—data analysis. YYS—data collection. GMM, SU, and SS: project development. KV—data analysis. SLK—manuscript editing. TS—manuscript writing and data analysis.

Funding This study was supported by Science and Engineering Research Board (SERB), Department of Science & Technology for financially support to S.Y. under National Post-Doctoral Fellowship (PDF/2016/003785). S.K. was supported by Indian Council of Medical Research (Coord/7 (1)/CARE-KD/2018/NCD-II, No.5/4/7-12/13/NCD-II) grant to ST.

Declarations

Conflict of interest Authors declare that there are no conflicts of interest with regard to this manuscript.

Ethical Statement This study has been ethically approved from King George's Medical University, Uttar Pradesh ethics committee (Approval No. XLIIIECM/B-P15).

References

1. AbouZahr C, Boerma T, Hogan D. Global estimates of country health indicators: useful, unnecessary, inevitable? Glob Health Action. 2017;10(sup1):1290370.
2. Osungbade KO, Ige OK. Public health perspectives of preeclampsia in developing countries: implication for health system strengthening. J Pregnancy. 2011;2011:481095.
3. Ngene NC, Moodley J. Role of angiogenic factors in the pathogenesis and management of pre-eclampsia. Int J Gynaecol Obstet. 2018;141(1):5–13.
4. Herraiz I, Llurba E, Verlohren S, et al. Update on the diagnosis and prognosis of preeclampsia with the aid of the sFlt-1/ PlGF ratio in singleton pregnancies. Fetal Diagn Ther. 2018;43(2):81–9.
5. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350(7):672–83.
6. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016;374(1):13–22.
7. Bilano VL, Ota E, Ganchimeg T, et al. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. PLoS ONE. 2014;9(3):e91198.
8. Endeshaw M, Abebe F, Bedimo M, et al. Diet and pre-eclampsia: a prospective multicentre case-control study in Ethiopia. Midwifery. 2015;31(6):617–24.
9. Jovicic S, Siodmiak J, Watson ID, et al. Quality evaluation of smartphone applications for laboratory medicine. Clin Chem Lab Med. 2019;57(3):388–97.
10. FIGO Working Group on Good Clinical Practice in Maternal–Fetal Medicine. Good clinical practice advice: first trimester screening and prevention of pre-eclampsia in singleton pregnancy. Int J Gynaecol Obstet. 2019;144(3):325–9.
11. March MI, Geahchan C, Wenger J, et al. Circulating angiogenic factors and the risk of adverse outcomes among haitian women with preeclampsia. PLoS ONE. 2015;10(5):e0126815.
12. Nikuei P, Malekzadeh K, Rajaei M, et al. The imbalance in expression of angiogenic and anti-angiogenic factors as candidate predictive biomarker in preeclampsia. Iran J Reprod Med. 2015;13(5):251–62.
13. Saleh L, van den Meiracker AH, Geensen R, et al. Soluble fms-like tyrosine kinase-1 and placental growth factor kinetics during and after pregnancy in women with suspected or confirmed pre-eclampsia. Ultrasound Obstet Gynecol. 2018;51(6):751–7.
14. Pihl K, Sorensen S, Stener JF. Prediction of preeclampsia in nulliparous women according to first trimester maternal factors and serum markers. Fetal Diagn Ther. 2020;47(4):277–83.
15. Tan MY, Syngelaki A, Poon LC, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. Ultrasound Obstet Gynecol. 2018;52(2):186–95.
16. Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, et al. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. BJOG. 2012;119(7):778–87.
17. Perales A, Delgado JL, de la Calle M, et al. sFlt-1/PlGF for prediction of early-onset pre-eclampsia: STEPS (Study of

Early Pre-eclampsia in Spain). Ultrasound Obstet Gynecol. 2017;50(3):373–82.
18. Caillon H, Tardif C, Dumontet E, et al. Evaluation of sFlt-1/PlGF ratio for predicting and improving clinical management of pre-eclampsia: experience in a specialized perinatal care center. Ann Lab Med. 2018;38(2):95–101.
19. Nikuei P, Rajaei M, Roozbeh N, et al. Diagnostic accuracy of sFlt1/PlGF ratio as a marker for preeclampsia. BMC Pregnancy Childbirth. 2020;20(1):80.
20. Soncini E, Paganelli S, Vezzani C, et al. Intrapartum fetal heart rate monitoring: evaluation of a standardized system of interpretation for prediction of metabolic acidosis at delivery and neonatal neurological morbidity. J Matern Fetal Neonatal Med. 2014;27(14):1465–9.
21. Stepan H, Herraiz I, Schlembach D, et al. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. Ultrasound Obstet Gynecol. 2015;45(3):241–6.
22. Chaiworapongsa T, Romero R, Korzeniewski SJ, et al. Maternal plasma concentrations of angiogenic/antiangiogenic factors in the third trimester of pregnancy to identify the patient at risk for stillbirth at or near term and severe late preeclampsia. Am J Obstet Gynecol. 2013;208(4):287.
23. Varughese B, Bhatla N, Kumar R, et al. Circulating angiogenic factors in pregnancies complicated by pre-eclampsia. Natl Med J India. 2010;23(2):77–81.
24. Atakul T. Serum levels of angiogenic factors distinguish between women with preeclampsia and normotensive pregnant women but not severity of preeclampsia in an obstetric center in Turkey. Med Sci Monit. 2019;25:6935–42.
25. Cindrova-Davies T, Sanders DA, Burton GJ, et al. Soluble FLT1 sensitizes endothelial cells to inflammatory cytokines by antagonizing VEGF receptor-mediated signalling. Cardiovasc Res. 2011;89(3):671–9.
26. Tandon V, Hiwale S, Amle D, et al. Assessment of serum vascular endothelial growth factor levels in pregnancy-induced hypertension patients. J Pregnancy. 2017;2017:3179670.
27. Jiang Z, Zou Y, Ge Z, et al. A role of sFlt-1 in oxidative stress and apoptosis in human and mouse pre-eclamptic trophoblasts. Biol Reprod. 2015;93(3):73.
28. Khalil A, Maiz N, Garcia-Mandujano R, et al. Longitudinal changes in maternal serum placental growth factor and soluble fms-like tyrosine kinase-1 in women at increased risk of pre-eclampsia. Ultrasound Obstet Gynecol. 2016;47(3):324–31.
29. Jardim LL, Rios DR, Perucci LO, et al. Is the imbalance between pro-angiogenic and anti-angiogenic factors associated with preeclampsia? Clin Chim Acta. 2015;447:34–8.
30. Murphy SR, Cockrell K. Regulation of soluble fms-like tyrosine kinase-1 production in response to placental ischemia/hypoxia: role of angiotensin II. Physiol Rep. 2015;3(2):e12310.
31. Baschat AA, Magder LS, Doyle LE, et al. Prediction of preeclampsia utilizing the first trimester screening examination. Am J Obstet Gynecol. 2014;211(5):514.
32. Moore Simas TA, Crawford SL, Bathgate S, et al. Angiogenic biomarkers for prediction of early preeclampsia onset in high-risk women. J Matern Fetal Neonatal Med. 2014;27(10):1038–48.

About the Author

Dr. Sonali Yadav is Ph.D. from King George's Medical University, Lucknow, U.P. (2014). She is National Post Doctoral Fellowship (N-PDF) from SERB, DST, India (2019). She has worked as Senior Demonstrator in the Department of Molecular Medicine & Biotechnology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow. Her area of interest includes Obstetrics (preeclampsia).

Authors and Affiliations

Sonali Yadav[1,5] · Sukhanshi Khandpur[5] · Yogendra Singh Yadav[2] · Madhu Mati Goel[1] · Urmila Singh[3] · Shankar Madhav Natu[1] · Mahendra Pal S. Negi[4] · Lokendra Kumar Sharma[5] · Swasti Tiwari[5]

Sonali Yadav
sonalikgmu@gmail.com

Sukhanshi Khandpur
sukhanshi.khandpur@gmail.com

Yogendra Singh Yadav
dryogendra83@gmail.com

Madhu Mati Goel
madhukgmc@gmail.com

Urmila Singh
drsinghkgmu@gmail.com

Shankar Madhav Natu
smnatu.natu@gmail.com

Mahendra Pal S. Negi
mps_negi@rediffmail.com

Lokendra Kumar Sharma
rajlokendra@yahoo.co.in

[1] Department of Pathology, King George's Medical University, Lucknow, U.P., India

[2] Department of Pediatrics, Uttar Pradesh University of Medical Science, Saifai, U.P., India

[3] Department of Obstetrics and Gynecology, King George's Medical University, Lucknow, U.P., India

[4] Institute for Data Computing & Training, Lucknow, U.P., India

[5] Department of Molecular Medicine & Biotechnology, Sanjay Gandhi Post Graduate Institute of Medical Science (SGPGIMS), 4th Floor PMSSY Building, Raebareli Rd, Lucknow, U.P. 226014, India