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Pigment epithelium–derived factor/vascular endothelial growth factor ratio for early prediction of preeclampsia: A prospective multicenter study in China

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ABSTRACT

Background: Imbalance of circulating factors related to angiogenesis plays a central role in the pathogenesis of preeclampsia (PE).
Objective: The aim of this study was to discover and validate a cutoff value of pigment epithelium–derived factor (PEDF)/vascular endothelial growth factor (VEGF) ratio for early prediction of PE before 20 weeks of gestation.
Study design: This prospective multicenter study was performed in mainland China, and was divided into 3 phases to discover, develop, and validate a cutoff value of PEDF/VEGF ratio that could predict PE prior to diagnosis in pregnant women at high risk of PE (12 weeks 0 days to 19 weeks 6 days of gestation). We estimated PEDF/VEGF ratio at 5 visits: from visit 0 (baseline) to the postpartum visit.
Results: In the discovery phase (200 women), we found that antiangiogenic PEDF was higher and angiogenic VEGF was lower in the PE group than in the control group before 20 weeks of gestation. In the development phase (650 women), we found that a cutoff value of 800 for PEDF/VEGF ratio demonstrated a preferably predictive value. Subsequently, in the validation phase (additional 900 women), we found that the negative predictive value of PEDF/VEGF ratio ≤800 at the visit 1 was 98.6% (95% CI, 97.3–99.4), at the visit 2 was 96.9% (95% CI, 95.1–98.1) and at the visit 3 was 95.1% (95% CI, 93.0–96.7). ORs were 4.40, 6.27, and 5.73, respectively.
Conclusions: PEDF/VEGF ratio ≤800 may have some predictive value for early diagnosis of PE. Further multicenter studies with larger sample sizes are necessary to confirm our findings.

1. Introduction

Preeclampsia (PE) is typically characterized by new-onset hypertension and proteinuria occurring after 20 weeks of gestation, and affects 5%–7% of all pregnancies worldwide, especially in developing countries. PE is a major cause of maternal and perinatal morbidity and mortality [1], which are usually accompanied by a series of adverse obstetric outcomes, such as maternal liver dysfunction, acute renal failure, visual impairment, myocardial ischemia, heart failure, seizure, cerebral accident, fetal growth restriction, and fetal distress [2–4]. PE can also threaten the cardiovascular and/or cognitive status of the mother and/or child over the long term [5,6]. Despite numerous studies, the etiology and pathogenesis of PE are not completely understood [7]. However, there is accumulating evidence that imbalance of circulating factors related to angiogenesis may play a central role in development of PE via uterine spiral artery remodeling and trophoblast invasion [8]. Screening before disease onset is important for management of PE in order to prevent adverse obstetric outcomes [2]. Recently, extensive research has shown that altered plasma levels of circulating angiogenic/anti-angiogenic factors, such as vascular endothelial growth factor (VEGF), vascular endothelial growth receptor-1 (FLT-1), and endoglin (ENG), might be useful to predict subsequent PE [9–11]. In addition, other studies have reported that antiangiogenic pigment epithelium–derived factor (PEDF) and angiogenic VEGF are altered in PE [12,13]. We hypothesized that imbalance of PEDF and VEGF may play a certain role in development of PE.

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Table 1
Baseline characteristics of the study participants, maternal and fetal adverse outcomes and high risk for PE.

Characteristic	discovery Phase		development Phase		validation Phase	
	No Preeclampsia (n = 179)	Preeclampsia (n = 21)	No Preeclampsia (n = 581)	Preeclampsia (n = 69)	No Preeclampsia (n = 798)	Preeclampsia (n = 102)
Gestational age at samples collecting (week)	16.36 ± 3.88	16.81 ± 2.84	16.65 ± 3.81	16.39 ± 3.74	16.55 ± 3.59	16.78 ± 3.61
Maternal Age (year)	31.38 ± 5.63	32.78 ± 2.82	31.21 ± 6.58	32.84 ± 2.37	31.65 ± 5.29	32.76 ± 2.35
Pre-pregnancy BMI (kg/m2)	21.53 ± 3.65	23.06 ± 3.36*	21.66 ± 3.45	23.13 ± 3.92*	21.29 ± 3.57	23.85 ± 3.61*
Gestational age at delivery (week)	39.78 ± 2.55	36.47 ± 2.30†	39.44 ± 2.74	36.28 ± 2.31†	39.58 ± 2.10	36.18 ± 2.43†
Systolic (mmHg)	120.43 ± 11.28	151.02 ± 11.36‡	121.35 ± 12.19	150.29 ± 12.66‡	120.66 ± 12.37	150.65 ± 12.29‡
Diastolic (mmHg)	80.25 ± 8.26	103.03 ± 5.91‡	81.48 ± 7.87	102.38 ± 8.24‡	81.39 ± 6.32	102.10 ± 6.30‡
Proteinuria (g/24 h)	0	3.10 ± 2.69‡	0.20 ± 0.14	3.20 ± 3.13‡	0.23 ± 0.37	3.10 ± 2.65‡
VEGF Median (ng/ml)	15.38	12.73	16.15	12.62	17.23	11.49
PEDF median (ng/ml)	9499.71	10165.18	10660.15	11791.10	11166.25	12791.68
High risk for preeclampsia						
Family history of hypertension (n, %)	41 (22.91%)	5 (23.81%)	66 (11.36%)	8 (11.59%)	99 (12.41%)	13 (12.75%)
family history of diabetes	33 (18.44%)	4 (19.05%)	75 (12.91%)	9 (13.04%)	97 (12.15%)	13 (12.75%)
premature infant history (n, %)	15 (8.38%)	2 (9.52%)	55 (9.47%)	7 (10.14%)	68 (8.52%)	9 (8.82%)
history of spontaneous abortion > 3 (n, %)	17 (9.50%)	2 (9.52%)	56 (9.64%)	7 (10.14%)	75 (9.40%)	10 (9.80%)
gravidity > 5 (n, %)	16 (8.94%)	2 (9.52%)	58 (9.98%)	7 (10.14%)	88 (11.03%)	12 (11.76%)
MAP > 85 mmHg (n, %)	17 (9.50%)	2 (9.52%)	63 (10.84%)	8 (11.59%)	85 (10.65%)	11 (10.78%)
poor family economy (n, %)	15 (8.38%)	2 (9.52%)	49 (8.43%)	6 (8.70%)	77 (9.65%)	10 (9.80%)
Less than 15 years of Education (n, %)	8 (4.47%)	1 (4.76%)	41 (7.06%)	5 (7.25%)	64 (8.02%)	9 (8.82%)
Pre-pregnancy BMI > 25 (n, %)	13 (7.26%)	2 (9.52%)*	56 (9.64%)	7 (10.14%)	71 (8.90%)	10 (9.80%)
maternal year > 35 (n, %)	17 (9.50%)	3 (14.29%)*	64 (11.02%)	10 (14.49%)*	66 (8.27%)	13 (12.75%)*
Maternal and Fetal Adverse Outcomes						
Maternal Thrombocytopenia (platelet < 100×10^9/L) (n, %)	2 (1.12%)	1 (4.76%)*	5 (0.86%)	2 (2.90%)*	8 (1.00%)	5 (4.90%)*
newborn-weight (g, n)	3331.5 ± 512.27	3012.2 ± 588.45†	3319.8 ± 529.77	2972.3 ± 573.86†	3360.1 ± 524.61	2964.7 ± 601.35†
SGA newborns (n, %)	2 (1.12%)	4 (19.05%)‡	5 (0.86%)	17 (24.64%)‡	7 (0.88%)	26 (25.49%)‡
FGR (n, %)	1 (0.56%)	2 (9.52%)‡	3 (0.52%)	11 (15.94%)‡	3 (0.38%)	16 (15.69%)‡
Cesarean or section Forceps delivery or induced labor (n, %)	2 (1.12%)	5 (23.81%)‡	10 (1.72%)	21 (30.43%)‡	15 (1.88%)	30 (29.41%)‡
Stillbirth (n, %)	0 (0)	0 (0)	0 (0)	3 (4.35%)*	0 (0)	5 (4.90%)*
Preterm delivery (n, %)	2 (1.12%)	4 (19.05%)‡	5 (0.86%)	19 (27.54%)‡	7 (0.88%)	27 (26.47%)‡

P values were calculated using the Mann–Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. *P < 0.05. †P < 0.01. ‡P < 0.001. There may have been more than one reason for suspected PE. Abbreviations: BMI, body mass index; FGR, fetal growth restriction; MAP, mean arterial pressure; PE, preeclampsia; SGA, small for gestational age.

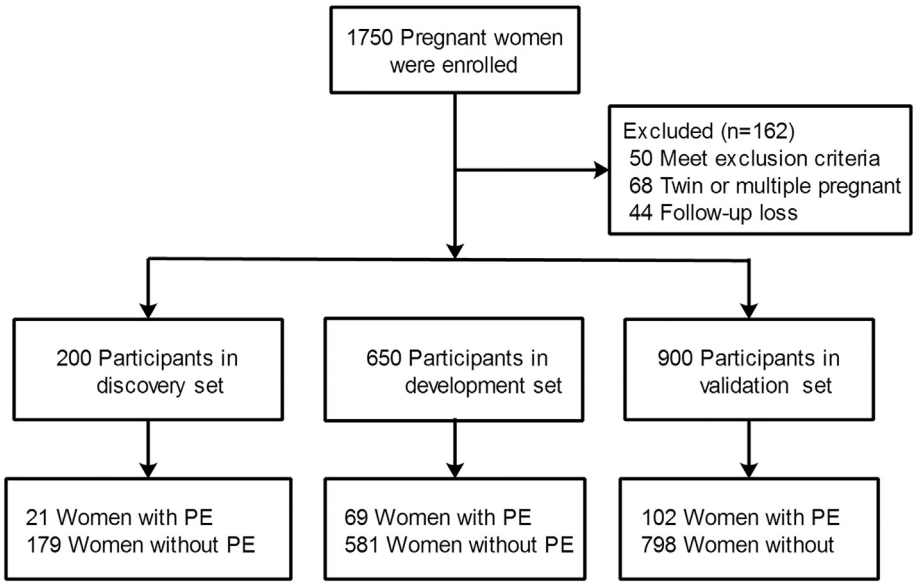

Fig. 1. Study design. The study was designed to discover and validate a cutoff value of PEDF/VEGF ratio for early prediction of PE before 20 weeks of gestation according to a 3-phase method: discovery, development, and validation. Abbreviations: PE, preeclampsia.