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First Trimester Maternal Serum PP13 in the Risk Assessment for Preeclampsia

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Abstract

Objective—To determine whether first trimester maternal serum Placental Protein 13 (PP13) concentrations can be used in the risk assessment for preeclampsia.

Study Design—This case-control study included 50 patients with preeclampsia and 250 patients with normal pregnancies. Samples were collected between 8-13 weeks of gestation. Serum PP13 concentrations were measured by ELISA and expressed as medians and multiples of the median (MoM) for gestational age. Sensitivity and specificity were derived from receiver operating characteristic curve analysis.

Results—1) Serum PP13 concentration in the first trimester was significantly lower in patients who developed preterm and early-onset preeclampsia than in those with normal pregnancies; and 2) At 80% specificity, a cutoff of 0.39 MoM had a sensitivity of 100% for early-onset preeclampsia and 85% for preterm preeclampsia.

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Conclusion—Maternal serum first trimester PP13 appears to be a reasonable marker for risk assessment, but a weak marker for severe preeclampsia at term, and ineffective for identifying mild preeclampsia at term.

Keywords

Risk assessment; screening; maternal serum biochemistry; high-risk pregnancy; prenatal care

INTRODUCTION

Preeclampsia complicates approximately 5% of all pregnancies and remains a leading cause of maternal and perinatal morbidity and mortality.[1–6] It is increasingly recognized that patients presenting with preeclampsia at early gestational ages have a worse form of the disease with a higher frequency of multi-systemic involvement and small for gestational age (SGA) fetuses than those presenting at term.[4;7–16] Early-onset preeclampsia (<34 weeks of gestation) is characterized by uteroplacental vascular insufficiency and damage to the placental villous tissues.[2;13;17–22] Indeed, patients with early-onset disease are more likely to have abnormal uterine and umbilical artery Doppler velocimetry studies[23–31] and lesions recognized by placental histological examination.[20;32–44] Moreover, the perinatal morbidity and mortality is higher in early-onset disease,[4;8;15] as are the frequencies of HELLP syndrome[10;45–48] and placental abruption.[49–52]

Risk assessment for preeclampsia remains a major challenge in prenatal care. A wide range of markers have been the subject of investigation, ranging from uterine artery Doppler velocimetry[23-31] to analytes such as soluble vascular endothelial growth factor receptor-1,[16;53-76] placental growth factor,[16;53;61;70;72-83] soluble endoglin[70;74;84-87] and others.[88]

Placental Protein 13 (PP13)[89-92] is a member of the galectin family,[93;94] predominantly expressed by the placenta, specifically by the syncytiotrophoblast, where it is localized on the brush-border membrane at the maternal-fetal interface.[94;95] Recently, maternal serum PP13 concentrations were found to be significantly reduced during the first trimester among women who subsequently developed preeclampsia.[96;97]

The purpose of this study was to determine whether PP13 serum concentrations in the first trimester of pregnancy can be used in the risk assessment for preeclampsia. We have conducted a nested case-control study in a Hispanic population, which has been reported to have an increased relative risk for preeclampsia than that of non-Hispanic Caucasian women.[98]

MATERIALS AND METHODS

A nested case-control study was designed using data from a prospective, longitudinal study conducted by the Perinatology Research Branch of the National Institute of Child Health and Human Development (NICHD). This cohort included pregnant patients seeking care at the prenatal clinics of the Sotero del Rio Hospital in Santiago, Chile. First trimester blood samples were obtained upon enrollment, beginning at 7 weeks of gestation.[54] All women provided written informed consent prior to the collection of samples. The collection and utilization of the samples was approved by the Institutional Review Boards of both the Sotero del Rio Hospital, Santiago, Chile, and the National Institute of Child Health and Human Development (NICHD/NIH/DHHS) Bethesda, Maryland.

Women aged 18-45 years with a singleton gestation who delivered after 26 weeks were eligible for inclusion. Patients were classified into the following study groups: 1) preeclampsia (n=50), and 2) normal pregnancy (n=250). Women in the preeclampsia group were further classified

as: 1) preterm preeclampsia (n=13); 2) severe preeclampsia at term (n=21); and 3) mild preeclampsia at term (n=16). From the group of patients with preterm preeclampsia, six women with early-onset preeclampsia (preeclampsia requiring delivery before 34 weeks of gestation) were examined as a separate group. Each patient with preeclampsia was matched to five women with normal pregnancies. The cases were matched by gestational age at venipuncture (±1 week) and duration of storage of the specimen (±2 weeks).

Baseline demographics, blood pressure measurements, and urinalyses from the first prenatal visit through the postpartum period as well as subsequent outcome of pregnancy were collected prospectively by practitioners throughout prenatal care. Serum samples were collected at the time of the first prenatal visit and at regular intervals thereafter.

Definitions

Gestational age (GA) was determined by the last menstrual period (LMP) and verified by fetal biometry in the first or second trimester of pregnancy in all patients. Preeclampsia was defined as hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least two occasions, 4 hours to 1 week apart) associated with proteinuria (>300 mg in a 24-hour urine collection or one dipstick measurement of ≥2+).[99] Severe preeclampsia was defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg and/or proteinuria greater than 5 grams in a 24-hour collection or ≥3+ on dipstick.[5] Patients with preeclampsia were sub-classified as either early-onset (<34 weeks) or preterm (<37 weeks) preeclampsia according to the gestational age at which delivery was required. Small for gestational age (SGA) was defined as a birthweight below the 10th percentile for the gestational age at birth, according to the national birthweight distribution of a Hispanic population.[100] Normal pregnancy was defined as one that resulted in the delivery of an appropriate-for-gestational age neonate at term without complications.

PP13 immunoassay

Samples of peripheral blood from pregnant women were obtained by venipuncture, centrifuged and stored at -80°C. Maternal serum concentration of PP13 was measured using a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) with a pair of PP13-specific monoclonal antibodies, marked with amplified biotin-extravidin-horseradish-peroxidase complex, and developed with tetramethylbenzidene substrate, as previously described.[92] Optical density was measured at 450 nm against a 650 nm background. Concentrations were determined by extrapolation from a standard curve constructed using recombinant PP13 standards (0-500 pg/mL). The sensitivity of the assay was 5 pg/ml. The intra-and inter-assay coefficients of variation (CV) for this study were 7.3% and 19.5%, respectively. The laboratory staff performing the assays was blinded to pregnancy outcome.

Statistical analysis

Baseline demographics, clinical and delivery characteristics were compared using Fisher's exact test for categorical variables and Wilcoxon Rank-sum test for continuous variables. The first trimester concentration of PP13 for each subject was converted into a multiple of the gestational age-specific median (MoM) following the method described by Cuckle and Wald.[101] In brief, this was done by computing the median PP13 concentration of pregnancies with normal outcomes. Medians were calculated for each completed week of gestation at venipuncture and adjustment was then made using weighted (by number of patients) regression to model the relationship between PP13 concentration and gestational age. Because of the wide window range of gestational age the cubic weighted regression model showed superior fit over the linear weighted regression model for this population.

MoM was then computed for all subjects (cases and controls) with the following formula:

$$\text{MoM} = \frac{\text{PP13}_{ij}}{\text{Median}_j}$$

Where, i = subject, j = GA, Median is the regressed value.

The gestational age adjusted PP13 MoM was then further adjusted to body mass index (BMI) because of the significant correlation between PP13 MoM and BMI (p=0.048). In the normal pregnancy group, there was no association between PP13 MoM and maternal age (p=0.34) or parity (p=0.15), thus, PP13 MoM was initially adjusted only to GA and BMI. However, due to the correlation of PP13 MoM to parity and maternal age in the preeclampsia group, PP13 MoM was subsequently adjusted to four parameters: GA, BMI, maternal age and parity. No adjustment was made to ethnicity considering the common Hispanic origin.

PP13 MoM was first compared between women with normal pregnancy and those with preeclampsia. Subsequently, a subgroup analysis was performed based on the clinical subtypes of preeclampsia. The comparison of PP13 MoM between groups was performed with the Wilcoxon Rank-sum test.

The sensitivity and specificity for different thresholds of PP13 MoM were derived from receiver operating characteristic (ROC) curves, which included all cases with preeclampsia and then a set of curves generated for the different clinical subtypes of the syndrome (mild preeclampsia at term, severe preeclampsia at term, preterm and early-onset preeclampsia). The area under the curve (AUC), along with the 95% CI and p-values were derived. Diagnostic indices (sensitivity and specificity) for first trimester maternal serum PP13 MoMs were calculated. Data were analyzed using SAS®.

RESULTS

Demographic and clinical characteristics

Table I displays the demographic characteristics of the study population. Women with severe preeclampsia at term were younger than those with normal pregnancies. Patients with other clinical subtypes of preeclampsia did not differ in maternal age from the group of normal pregnancy. The mean BMIs at enrollment for patients with mild and severe preeclampsia at term, and for patients with preterm preeclampsia were significantly higher than those of patients with normal pregnancies. The proportion of nulliparous women was significantly higher in the group of severe preeclampsia at term than in all other study groups. The median gestational age at venipuncture did not differ among the study groups.

Table II displays the clinical characteristics of the study population. Cesarean delivery was more frequent in the groups with preeclampsia than among women with normal pregnancies. The mean birthweight of neonates born to women with severe preeclampsia at term and to those with preterm preeclampsia was significantly lower than for those born to women with normal pregnancies. In the group of patients with preterm preeclampsia, 9 of the 13 patients delivered an SGA neonate. In the group of patients with term preeclampsia there were 7 SGA neonates (5 with severe preeclampsia).

PP13 concentrations and MoMs across the first trimester

The week-specific PP13 concentration medians between eight to thirteen weeks of gestation (for each completed week of gestation) in women with a normal pregnancy were 60.25 pg/mL (n=23), 67.59 pg/mL (n=46), 167.41 pg/mL (n=33), 114.33 pg/mL (n=40), 88.62 pg/mL

(n=49), and 135.00 pg/mL (n=59), respectively. This pattern fitted a cubic weighted regression model compared to linear or other weighted regression models.

First trimester PP13 MoMs in patients with preeclampsia

Patients with preeclampsia were first studied as one group in both models; they had a significantly lower median PP13 MoM than women who had a normal pregnancy (Figure 1). The comparison of the sub-groups of preeclampsia to the normal pregnancy group demonstrated the following: 1) In the first model (Table IIIA), the median PP13 MoM was significantly lower in patients who subsequently developed preterm preeclampsia, early-onset preeclampsia, and severe preeclampsia at term than in women with a normal pregnancy.2) In the second model (Table IIIB), only patients who subsequently developed preterm preeclampsia and early-onset preeclampsia had a significantly lower PP13 MoM than in women with a normal pregnancy.

Preeclampsia risk assessment by median PP13 MoMs

ROC curves for PP13 MoMs were generated for all cases of preeclampsia (Figure 2) and for the clinical subtypes of preeclampsia (Figures 3A and 3B) according to both adjustment models. The diagnostic indices of each model that were generated according to the ROC curves are presented in Tables IVA and IVB.

Using the first model, the following results were found: 1) When the specificity was fixed at 80% (20% false positive rate), the sensitivity was 83% for early-onset preeclampsia, 77% for preterm preeclampsia, 24% for severe preeclampsia at term and 44% for preterm and term severe preeclampsia combined. 2) When the sensitivity was fixed at 80%, the specificity was 82% for early-onset preeclampsia, 80% for preterm preeclampsia, 52% for severe preeclampsia at term, and 55% for the latter two combined (Table IVA).

Using the second model, the following results were found: 1) PP13 MoMs had a better sensitivity for early-onset preeclampsia (100%) and preterm preeclampsia (85%) when the specificity was fixed at 80%; however, the changes in other subgroups of preeclampsia were less prominent. 2) The specificity (at 80% sensitivity) of PP13 MoMs were lower in the subgroups of severe preeclampsia at term, preterm and term severe preeclampsia combined, and mild preeclampsia at term (Table IVB), indicating that the adjustment to a larger repertoire of confounders improve the accuracy only for preeclampsia that develops preterm.

DISCUSSION

Principal findings of the study

1) The maternal serum concentration of PP13 in the first trimester was significantly lower in patients who subsequently developed early-onset and preterm preeclampsia than in those who had a normal pregnancy outcome; 2) Maternal serum concentrations of PP13 may be of use in the risk assessment for preterm preeclampsia; and 3) The first trimester serum concentration of PP13 did not identify women who will develop mild preeclampsia at term.

Placental Protein 13 (galectin-13) – structure, function, and localization

PP13 was first isolated and cloned from human term placenta.[89;90] The protein was mainly found as a homodimer of 16 kDa subunits linked by disulfide bonds.[89-91;94] PP13 has been designated as galectin-13 because of its conserved structural homology and carbohydrate-recognition domain, as well as its ability to bind sugars resembling to members of the galectin family.[93;94] The protein demonstrated endogenous lysophospholipase activity[91;94] and elicited, through influx of calcium ions, depolarization of trophoblasts, as well as liberation of linoleic and arachidonic acids from the trophoblast membrane.[92] PP13 is a soluble protein

which can be externalized to the cell surface by non-classical pathways, though it lacks a transmembrane domain and a transport signal.[94] It is predominantly expressed by the placenta, specifically, the syncytiotrophoblast, where it is localized on the brush-border membrane at the maternal-fetal interface.[94;95] In addition to its detection in maternal serum, PP13 has been isolated from fetal serum and amniotic fluid.[92]

Maternal serum PP13 and adverse pregnancy outcome

Two previous studies have examined the potential value of maternal serum PP13 in the risk assessment for preeclampsia in the first trimester.[96;97] Nicolaides et al. reported a case-control study indicating that patients who developed preeclampsia requiring delivery before 34 weeks of gestation had a lower median PP13 serum concentration expressed in MoMs than those who had a normal delivery at term (MoM: 0.07; $p<0.001$).[96] Moreover, the information derived from maternal serum PP13 concentrations could be combined with the results of uterine artery Doppler velocimetry in the first trimester to estimate the risk for the subsequent development of preeclampsia requiring delivery before 34 weeks. The combination could accomplish a detection rate of 90% with a false-positive rate of 6%.[96] Spencer et al. reported the results of a nested case-control study which examined the value of PP13 combined with second-trimester Doppler velocimetry of the uterine arteries in the prediction of early-onset preeclampsia (delivery prior to 35 weeks).[97] The median PP13 concentrations as well as MoMs were significantly lower in patients who subsequently developed early-onset preeclampsia than in those in the control group. However, second-trimester Doppler velocimetry did not add significant information to that provided by PP13.[97] Therefore, there are now three studies indicating that patients who subsequently develop early-onset preeclampsia have lower maternal serum concentrations of PP13 in early pregnancy. The sensitivity and specificity reported by Spencer et al.[97] were lower than those reported by Nicolaides et al.[96] Our results are in keeping with those reported by Nicolaides et al.

The prevalence of preterm preeclampsia in the general population is very low;[16;102] resulting in a low positive predictive value for first trimester PP13 concentrations. Therefore, the combination of PP13 with other biomarkers or first and/or second trimester ultrasound measurements would increase its positive predictive value. In fact, this approach has not only been used for PP13,[96;97] but also for the combination of maternal plasma PlGF with abnormal uterine artery Doppler velocimetry in the second trimester.[16]

Previous investigations have studied patients from other ethnic groups. For example, 30% of patients with preeclampsia in one study were Caucasian,[96] whereas in another study, this proportion was 86%.[97] Our findings suggest that PP13 performs well in a Hispanic population.

Potential mechanisms for a reduction in maternal serum PP13 concentration in patients destined to develop preeclampsia

The expression of PP13 is down-regulated in the placentas of patients with preterm preeclampsia.[95] However, the mechanisms responsible for this have not been determined. Because the syncytiotrophoblast is in direct contact with the maternal blood, it is tempting to speculate that a deficient production of PP13 may account for the lower maternal serum concentration of this protein in patients destined to develop preeclampsia. Since the lower concentration of PP13 is observed in the first trimester of pregnancy,[96;97] months before the development of clinical disease, this suggests that the decreased concentration in maternal blood is not the consequence of the disease.

Strengths and limitations

The strength of this study is that it provides evidence that a low concentration of PP13 in the first trimester is a risk factor for preterm preeclampsia and severe preeclampsia at term. These

data have been generated in a different ethnic group from those studied in the past.[96;97] The limitations of this study are those inherent to any case-control study, namely the potential for biases and the inability to calculate predictive values.

The relatively high inter-assay CV for PP13 (19.5%) could be attributed to the very low maternal serum concentrations of PP13 (at the pg range). This is challenging for the detection accuracy of the ELISA method. To improve the test accuracy, a new amplification method for the PP13 ELISA is currently being developed, to replace the use of the biotin-avidin-HRP amplification system by other amplification methods, such as with the use of lanthanides.

A considerable source of variability for serum markers, such as PP13, whose concentrations change with gestation is the inaccuracy in dating the pregnancy. When gestational age is estimated by ultrasound biometry, this source of variability is reduced, and as a consequence, there is less overlap in the distribution of marker concentrations in MoMs between affected and unaffected pregnancies. In the present study, gestational age was largely based on menstrual dates. Thus, the observed discriminatory power of PP13 in the detection of preeclampsia is likely to have underestimated the true performance. However, in both this study and previous studies where gestation was based on an ultrasound scan,[96;97] the overlap in serum PP13 concentrations between preeclampsia and unaffected pregnancies was small. Therefore, any improvement brought about by more precise dating is probably marginal.

Future investigation

A large cohort study is required to determine whether the observations reported from nested case-control studies can be replicated in a large population and whether the likelihood ratios are such that PP13 determinations in early pregnancy can contribute to the risk assessment for preeclampsia. The identification of an analyte which changes in the first trimester of pregnancy in patients destined to develop preeclampsia is attractive because it offers the maximal opportunity for intervention. Future studies are required to determine the factors responsible for deficient production of PP13 in the placentas of patients who subsequently develop preeclampsia and the consequences of reduced PP13 bioavailability. Moreover, Nicolaides et al.[96] and Spencer et al.[97] reported the value of maternal serum PP13 measurements combined with Doppler sonography for the risk assessment for preeclampsia. Furthermore, a recent study[103] has indicated benefit for sequential testing with PP13, suggesting that a prospective study that will combine first trimester PP13 with other analytes and sonographic findings may yield an effective assessment tool for the risk of subsequently developed preeclampsia in later stages of pregnancy.

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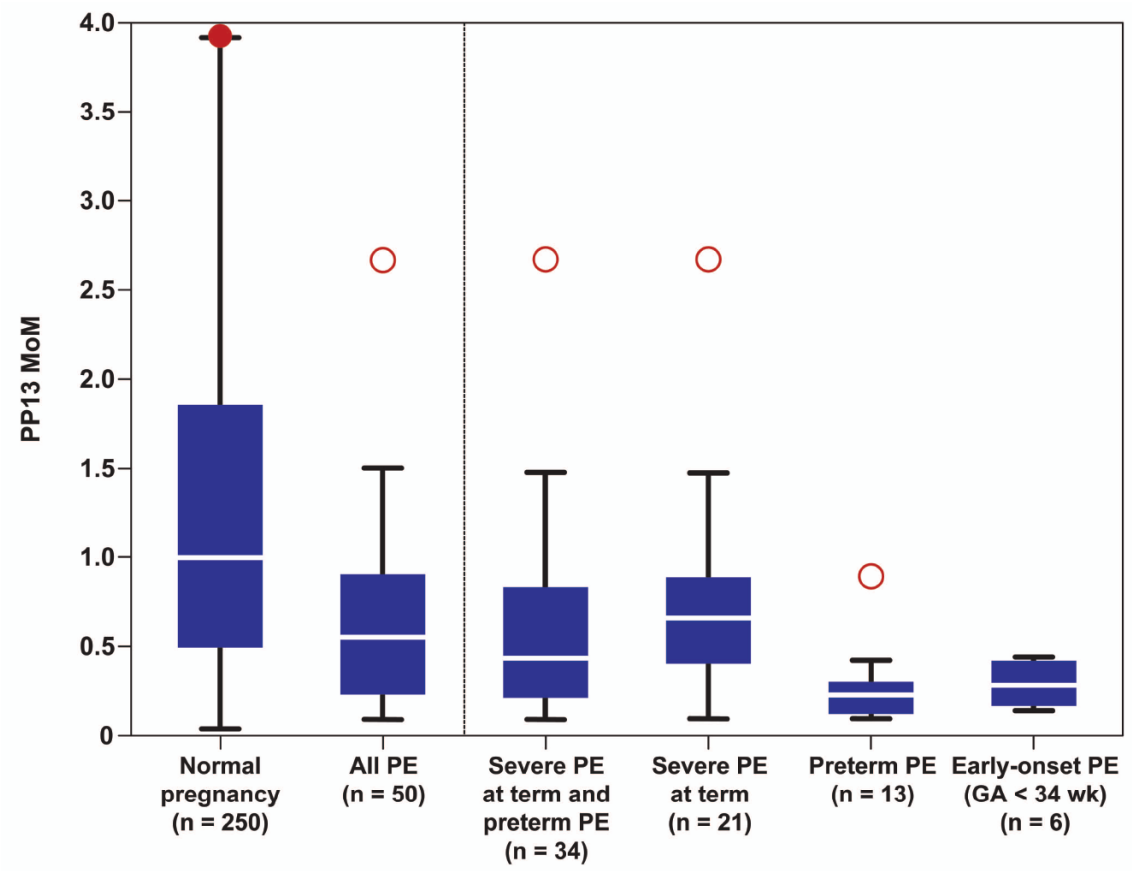


Figure 1. PP13 multiples of the median (MoMs) according to the study groups

The results are based on the first model where PP13 MoM was adjusted to GA and BMI. The boxplot represents the medians (as a horizontal line within the box), the 25th and 75th quartiles and the maximum and minimum for each group. Red dots refer to outliers in the right position, the filled red dot refers to a clipped outlier outside the range of the figure. PE: preeclampsia.

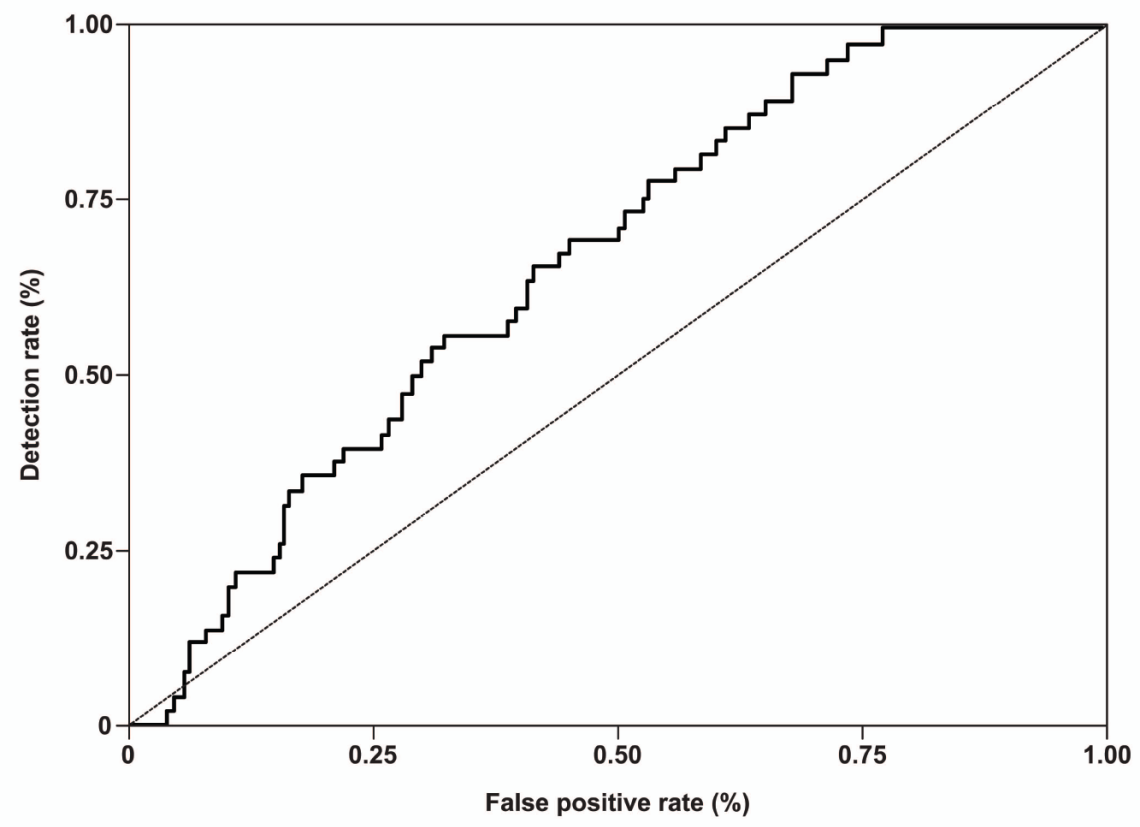
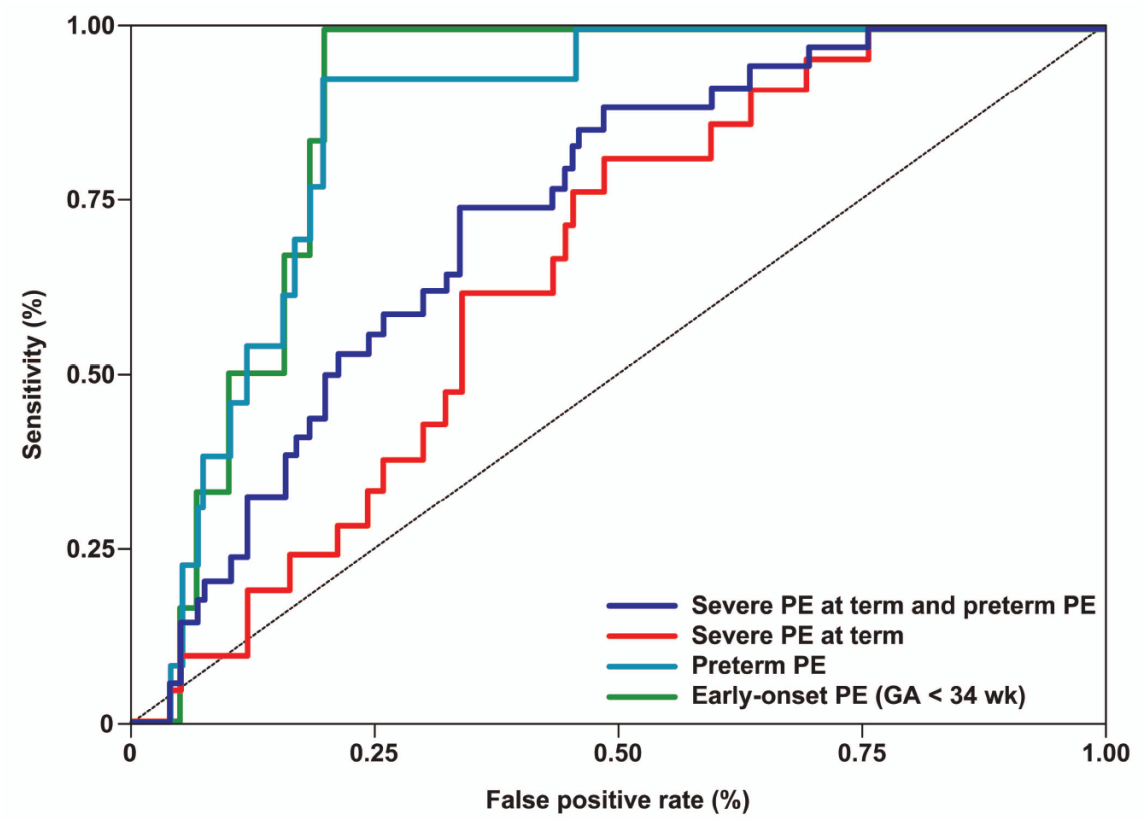


Figure 2. Receiver operating characteristic (ROC) curve depicting the sensitivity and specificity of PP13 MoM in maternal serum for the identification of all cases of preeclampsia

The results are based on the second model where PP13 MoM was adjusted to GA, BMI, maternal age and parity.



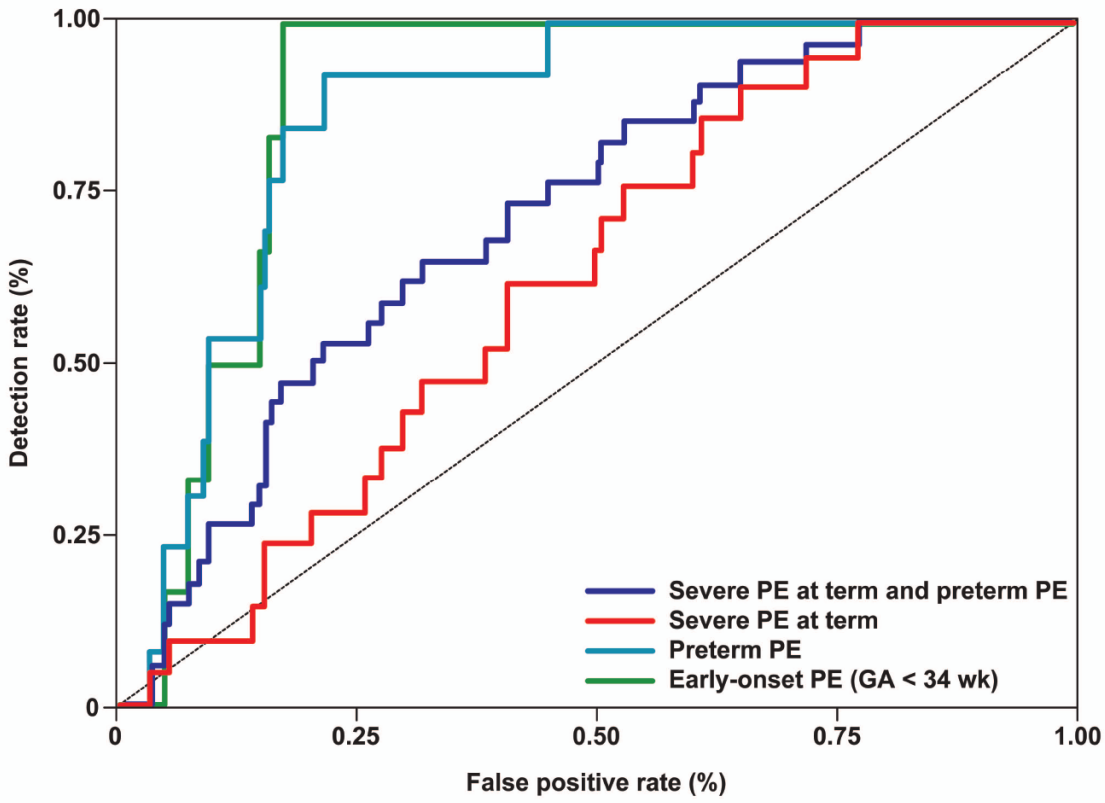


Figure 3. Receiver operating characteristic (ROC) curves depicting the sensitivity and specificity of first trimester maternal serum PP13 MoM for the identification of the different clinical subtypes of preeclampsia

A: ROC curves were generated based on the first model where PP13 MoM was adjusted to GA and BMI. PE = preeclampsia. The diagnostic indices that were generated from these curves are presented in Table IVA.

B: ROC curves were generated based on the second model where PP13 MoM was adjusted to GA,BMI, maternal age, and parity. PE = preeclampsia. The diagnostic indices that were generated from these curves are presented in Table IVB.

Table I

Demographic characteristics of the study groups.

	Study groups				
	Normal pregnancy (n=250)	**Mild preeclampsia at term (n=16)**	**Severe Preeclampsia at term (n=21)**	**Preterm preeclampsia (n=13)**	**Early-onset preeclampsia (n=6)**
Maternal age (years)	24.5 ± 5.6	27.2 ± 7.6	21.5 ± 4.7†	27.2 ± 7.1	28.3 ± 7.7
Maternal body mass index (kg/m^2)	22.1 ± 2.0	24.3 ± 2.6‡	25.7 ± 5.1‡	25.9 ± 5.3†	26.5 ± 5.7
Nulliparity (%)	49.2	56.3	81.0†	46.2	33.3
Gestational age at blood draw (weeks)	11.1 (8.0-13.9)	11.5 (8.6-13.4)	11.9 (9.3-13.9)	11.6 (8.4-13.7)	10.6 (9.0-13.3)

Values are expressed as mean ± standard deviation or median (range)

† p<0.01, compared to the normal pregnancy group

‡ p<0.001 compared to the normal pregnancy group

Early-onset preeclampsia cases were included in the preterm preeclampsia group

Table II

Clinical characteristics of the study groups.

	Study groups				
	Normal pregnancy (n=250)	**Mild preeclampsia at term (n=16)**	**Severe preeclampsia at term (n=21)**	**Preterm preeclampsia (n=13)**	**Early-onset Preeclampsia (n=6)**
GA at delivery (weeks)	39.7 ± 1.1	39.1 ± 1.2	39.0 ± 1.0†	34.0 ± 3.0‡	31.5 ± 2.5‡
Cesarean delivery (%)	8.4	18.8 ‡	33.3 ‡	61.5 ‡	83.3 ‡
Birthweight (grams)	3448.0±278.2	3386.3±545.0	3143.8±472.9†	1872.3±722.7‡	1226.7±383.3‡
Female neonates (%)	44.4	50.0	33.3	46.2	33.3
Highest systolic BP (mmHg)	122.5 ± 6.9	144.1 ± 5.8‡	158.9 ± 17.0‡	163.1 ± 22.5‡	165.0 ± 18.7‡
Highest diastolic BP (mmHg)	77.2 ± 5.0	95.1 ± 5.8‡	101.8 ± 12.5‡	106.2 ± 13.2‡	108.3 ± 14.7‡
Highest Proteinuria (by dipstick)	0 (0-1)	2 (1-2)	3 (2-4)	3 (2-4)	3 (2-4)

Values are expressed as percent, mean ± standard deviation, or median (range)

† p<0.01, compared to the normal pregnancy group

‡ p<0.001 compared to the normal pregnancy group

Early-onset preeclampsia cases were included in the preterm preeclampsia group

P < 0 .01 compared with the normal pregnancy group

BP, blood pressure

Table IIIA

Median first trimester maternal serum PP13 MoMs according to the study groups adjusted to gestational age and body mass index

Study groups	Median MoMs	95% CI for the median MoMs	p-values†
Normal pregnancy (n=250)	1.00	0.83 - 1.10	Reference value
All preeclampsia (n=50)	0.59	0.41 - 0.83	<0.001
Early-onset preeclampsia (n=6)	0.26	0.10 - 0.40	0.002
Preterm preeclampsia (n=13)	0.24	0.11 - 0.40	<0.001
Severe preeclampsia at term (n=21)	0.65	0.43 - 0.85	0.022
Mild preeclampsia at term (n=16)	0.89	0.66 - 1.24	0.491

† p-values for the comparison of each study group with the normal pregnancy group. Median PP13 MoMs were significantly lower ($p<0.05$) than in the normal pregnancy group for each of the following groups: all preeclampsia, severe preeclampsia at term, preterm preeclampsia, and early-onset preeclampsia. Early-onset preeclampsia cases were included in the preterm preeclampsia group.

Table IIIB

Median first trimester maternal serum PP13 MoMs according to the study groups adjusted to gestational age, body mass index, parity, and maternal age.

Study groups	Median MoMs	95% CI for the median MoMs	p-values†
Normal pregnancy (n=250)	1.00	0.87 - 1.11	Reference value
All preeclampsia (n=50)	0.59	0.41 - 0.80	<0.001
Early-onset preeclampsia (n=6)	0.25	0.10 - 0.38	0.001
Preterm preeclampsia (n=13)	0.22	0.13 - 0.38	<0.001
Severe preeclampsia at term (n=21)	0.73	0.41 - 1.03	0.073
Mild preeclampsia at term (n=16)	0.84	0.57 - 1.26	0.390

† p-values for the comparison of each study group with the normal pregnancy group. Median PP13 MoMs were significantly lower ($p<0.05$) than in the normal pregnancy group for each of the following groups: all preeclampsia, preterm preeclampsia, and early-onset preeclampsia. Early-onset preeclampsia cases were included in the preterm preeclampsia group.

Table IVA

Diagnostic indices and area under the curve (AUC) of first trimester maternal serum PP13 MoMs for the subsequent development of preeclampsia after adjustment for gestational age and body mass index.

Study groups	AUC (95% CI)	p-value[†]	Sensitivity at 80% specificity (MoM cutoff)	Specificity at 80% sensitivity (MoM cutoff)
All preeclampsia (n=50)	0.67 (0.60-0.74)	<0.001	34% (0.40)	43% (1.12)
Early-onset preeclampsia (n=6)	0.87 (0.81-0.93)	0.002	83% (0.40)	82% (0.33)
Preterm preeclampsia (n=13)	0.86 (0.79-0.92)	<0.001	77% (0.40)	80% (0.40)
Severe preeclampsia at term (n=21)	0.65 (0.55-0.75)	0.022	24% (0.40)	52% (0.98)
Preterm and term severe preeclampsia combined (n=34)	0.73 (0.65-0.81)	<0.001	44% (0.40)	55% (0.85)
Mild preeclampsia at term (n=16)	0.55 (0.45-0.66)	0.490	13% (0.40)	39% (1.24)

[†] p-values of the AUC was calculated compared to AUC = 0.5, which is a random prediction.

Early-onset preeclampsia cases were included in the preterm preeclampsia group.

CI, Confidence Interval

Table IVB

Diagnostic indices and area under the curve (AUC) of first trimester maternal serum PP13 MoMs for the subsequent development of preeclampsia after adjustment for gestational age, body mass index, parity and maternal age.

Study groups	AUC (95% CI)	p-value†	Sensitivity at 80% specificity (MoM cutoff)	Specificity at 80% sensitivity (MoM cutoff)
All preeclampsia (n=50)	0.66 (0.5-0.74)	<0.001	36% (0.39)	44% (1.10)
Early-onset preeclampsia (n=6)	0.88 (0.83-0.93)	0.001	100% (0.39)	84% (0.31)
Preterm preeclampsia (n=13)	0.86 (0.79-0.93)	<0.001	85% (0.39)	82% (0.38)
Severe preeclampsia at term (n=21)	0.62 (0.52-0.72)	0.073	24% (0.39)	40% (1.19)
Preterm and term severe preeclampsia combined (n=34)	0.71 (0.63-0.79)	<0.001	47% (0.39)	49% (1.01)
Mild preeclampsia at term (n=16)	0.56 (0.45-0.68)	0.389	13% (0.39)	36% (1.26)

† p-values of the AUC was calculated compared to AUC = 0.5, which is a random prediction.

Early-onset preeclampsia cases were included in the preterm preeclampsia group.

CI, Confidence Interval