Assessment of placental protein 13 as a new marker for early diagnosis of preeclampsia

Marwa M. H. Mohamed, Lubna M. T. El-Din, Dalia A. A. E. Nigm, Tarek A. Farghaly

Department of Clinical Pathology, Assiut University, Assiut, Egypt

Correspondence to Marwa M. H. Mohamed, MSc in clinical pathology, Department of Clinical Pathology, Faculty of medicine, Assuit University, Assuit, Egypt. Tel:+201005745012; Postal Code: 71717; Fax: 0020882500366; e-mail: meromagdy381991@gmail.com

Received 18 November 2020
Revised 19 November 2020
Accepted 26 November 2020
Published 30 December 2021

Journal of Current Medical Research and Practice
2021, 6:399–404

Background
Preeclampsia is an important cause of maternal and perinatal morbidity and mortality, affecting 2–8% of pregnancies worldwide.

Aim
The study aimed to examine the potential value of maternal serum concentration of placental protein 13 (PP13) in early diagnosis of preeclampsia (11–13 weeks of gestation).

Patients and methods
This study was carried out on 120 pregnant women at risk for preeclampsia (60 women with advanced maternal age >35 years, and 60 women with a history of chronic hypertension, diabetes, kidney disease, and systemic lupus erythematosus) and 40 women apparently healthy as controls. Serum PP13 was measured by the enzyme-linked immunosorbent assay kits from SinoGeneClon Biotech Co. Ltd, catalog number: SG-10912. Patients signed an informed consent form. Assiut Faculty of Medicine approved The study was approved by the Ethical Committee of Faculty of Medicine Assiut University, with registration number IRB: 17101046.

Results
PP13 was significantly decreased in pregnant women with risk factors for preeclampsia (women with advanced maternal age > 35 years, as well as women with a history of chronic hypertension, diabetes, kidney disease, and systemic lupus erythematosus) compared with the control group.

Conclusion
This study has revealed that serum levels of PP13 can be used as a predictive test in preeclampsia.

Keywords:
placental protein 13, Preeclampsia, enzyme-linked immunosorbent assay technique

J Curr Med Res Pract 6:399–404

2357-0121

Introduction

Preeclampsia is a significant cause of maternal and perinatal morbidity and mortality, affecting 2–8% of pregnancies worldwide [1].

It is defined by the International Society for the Study of Hypertension in pregnancy as the development of new-onset hypertension of 140/90 mmHg (systolic/diastolic) or greater after 20 weeks of gestation in earlier normotensive women together with elevated protein levels in urine (>0.3 g/day). It may additionally progress to eclampsia, an obstetric emergency related with brain convulsion, cerebral edema, and stroke, a life-threatening condition to the mother and her baby [2].

The progress of biomarkers to predict preeclampsia was started with markers that can expect the disorder 2–4 weeks before the onset of clinical symptoms using the increase in serum soluble fms-like tyrosine kinase-1 combined with the decrease in serum placental growth factor. The increased soluble fms-like tyrosine kinase-1: placental growth factor ratio was developed as the main tool to recognize the risk to develop preeclampsia near the time of beginning of clinical symptoms [3].

Placental protein 13 (PP13) was originally isolated by Bohn *et al*. [4].

PP13 binds to β-galactoside residues of several proteins on the cell surface, cytoskeleton, and extracellular matrix, thus generating different responses such as immune responses and influencing other functions like apoptosis and molecular recognition [5].

PP13 is produced in the placenta and is thought to be involved in normal placentation and maternal artery remodeling [6].

Patients and methods

This study was carried out on 120 pregnant women at risk for preeclampsia [60 women with advanced maternal age >35 years and 60 women with a history of chronic hypertension, diabetes, kidney disease, and systemic lupus erythematosus (SLE)] and 40 women apparently healthy as controls. All studied pregnant women were between 11 and 15 weeks of gestation. Follow-up after 20 weeks of gestation was done for those women by measuring blood pressure and 24-h protein in urine to detect the development of preeclampsia. They were selected from Women's Health Hospital of Assiut University Hospitals in the period between May 2018 and May 2019.

Patients signed an informed consent form.

Assiut Faculty of Medicine approved the study, with registration number IRB 17101046.

Inclusion criteria

Patients with risk factors to preeclampsia (advanced maternal age >35 years, chronic hypertension, diabetes, kidney disease, and SLE) were included.

Sample collection, storage, and handling

Blood sample collection was performed at weeks 11–15 of gestation.

(1) Overall, 6 ml of venous blood was collected under complete aseptic conditions and divided into the following:
   (a) 2 ml of venous blood was collected into EDTA-containing tube for complete blood count.
   (b) 4 ml was collected into a plain tube.
   (c) Blood was allowed to clot for 15 min at 37°C, and serum was separated by centrifugation at 3000 rpm for 20 min. Collected serum was inspected to ensure it was clear and nonhemolyzed or lipemic, and serum was divided into two aliquots: one of them for kidney functions, random serum glucose, and liver functions, and the second one is for PP13 stored at −20°C.
(2) Urine for 24 h was collected to measure protein at 11–15 week of gestation and after 20 weeks of gestation by sulfosalicylic acid turbidimetric method [7].

Routine investigations

Random serum glucose, serum urea, serum creatinine, and liver functions were done on Dimension RxL Max (SIEMENS In Brookfield , USA).

Assessment of 24-hour protein in urine was done by sulfosalicylic acid turbidimetric method. A complete blood count was done by CD-Ruby.

Special investigations

PP13 was measured by enzyme-linked immunosorbent assay technique and read on Stat-Fax 303 plus (Cat. no.: SG-10912). The kit provided by Sinogeneclon Biotech in Hangzhou, China.

Detection range was 3–200 pg/ml and sensitivity was 0.8 pg/ml.

Statistical analysis

Data were collected and analyzed using Statistical Package for the Social Science (version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD, whereas nominal data were expressed in the form of frequency (percentage).

χ^2 test was used to compare the nominal data of different groups in the study and analysis of variance test for more than two groups. Receiver operating characteristic curve was used to assess the diagnostic accuracy of PP13 in the prediction of preeclampsia in different studied groups. The level of confidence was kept at 95%, and *P* value was considered significant if less than 0.05.

Normality test for quantitative data was performed by Shapiro test, where it was insignificant (>0.05). Hence, it was considered as normally distributed data.

Ethical consideration

Formal consent was obtained from patients and controls. The study was approved by the Ethical Committee of Faculty of Medicine Assiut University.

Results

Age of women in studied groups

Table 1.

Frequency of preeclampsia in studied women

Table 2.

Diseases in pregnant women with chronic diseases

Table 3.

Frequency of preeclampsia in women with chronic disease

Table 4.

Table 1 Age of women in the studied groups

	GI	GII	GIII
Age (years)	37.71±1.13	25.33±2.84	24.72±2.60
Significance	*P*1	*P*2	*P*3
	<0.001	<0.001	0.06

Data were expressed in the form of mean±SD. GI: included women with advanced maternal age. GII: included women with chronic diseases. GIII: included normal pregnant women. *P*<0.05. *P*1, compared between GI and GII. *P*2, compared between GI and GIII. *P*3, compared between GII and GIII.

Table 2 Frequency of preeclampsia in the studied women

	GI	GII	GIII
Preeclampsia	33 (55)	42 (70)	3 (7.5)
Significance	*P*1	*P*2	*P*3
	0.04	0.01	0.01

Data were expressed in the form of *n* (%). GI: included pregnant women with advanced maternal age. GII: included pregnant women with chronic diseases. GIII: included normal pregnant women. *P*<0.05. *P*1, compared between GI and GII. *P*2, compared between GI and GIII. *P*3, compared between GII and GIII.

Table 3 Diseases in pregnant women with chronic diseases

	n=60/120
Diabetes mellitus	17/60 (28.3)
Hypertension	16/60 (26.7)
Chronic renal disease	16/60 (26.7)
Systemic lupus erythematosus	10/60 (16.7)
Diabetes mellitus and hypertension	1/60 (1.7)

Data was expressed in form of *n* (%).

Table 4 Frequency of preeclampsia in women with chronic disease

	n=42/60
Diabetes mellitus	12/17 (70.5)
Hypertension	12/16 (75)
Chronic renal disease	13/16 (81.25)
Systemic lupus erythematosus	4/10 (40)
Diabetes mellitus and hypertension	1/1 (100)

Data was expressed in form of *n* (%).

Baseline laboratory data of studied groups

(1) Blood glucose level was significantly higher in women with chronic diseases (7.17 ± 4.23 mmol/l) in comparison with normal pregnant women (4.31 ± 0.97 mmol/l) (P = 0.01).
(2) Blood urea nitrogen was significantly higher in women with chronic diseases (9.74 ± 1.47 mmol/l) in comparison with normal pregnant women (3.13 ± 0.97 mmol/l) (P = 0.02).
(3) Serum creatinine level was significantly higher in women with chronic diseases (139.98 ± 34.87 μmol/l) in comparison with normal pregnant women (64.75 ± 19.98 μmol/l) (P = 0.02).

Table 5.

Level of placental protein 13 in the studied women

Levels of PP13 of pregnant women with chronic diseases (mean ± SD = 158.24 ± 42.14 pg/ml) and pregnant women with advanced maternal age (186.59 ± 40.95 pg/ml) were significantly lower in comparison with level of PP13 in normal pregnant women (343.49 ± 38.87 pg/ml), as shown in Table 6 and Fig. 1.

Changes in 24-h protein in urine and blood pressure in women who developed preeclampsia

In all studied groups, women who developed preeclampsia, 24 h protein in urine, systolic blood pressure, and diastolic pressure showed a significant increase after diagnosis of preeclampsia in comparison with baseline data at first trimester, as shown in Table 7.

Diagnostic accuracy of placental protein 13 in prediction of preeclampsia in studied groups

It was noticed that at cutoff point less than 186.5 pg/ml, PP13 had 82% sensitivity and 93% specificity for prediction of preeclampsia in women with advanced maternal age with an area under the curve of 0.91.

In case of women with chronic disease, at cutoff point less than 155 pg/ml, PP13 had 83.33% sensitivity and 83.33% specificity for prediction of preeclampsia, with area under curve was 0.90, but in case of normal pregnant women, at cutoff point less than 134.5 pg/ml, it had 33.30% sensitivity and 97.30% specificity for prediction of preeclampsia with area under curve of 0.70.

In all studied women, at cutoff point less than 184.5 pg/ml, PP13 had 83.30% sensitivity and 78% specificity for prediction of preeclampsia, with an area under the curve of 0.88, as shown in Table 8 and Fig. 2.

Discussion

Preeclampsia is a disorder of pregnancy, associated with new-onset hypertension, although often accompanied by new-onset proteinuria which occurs most often after 20 weeks of gestation and frequently near term, systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mmHg or more, on two occasions at least 4 h apart after 20 weeks of gestation by American College of Obstetricians and Gynecologists [8]. Proteinuria during pregnancy is defined as 300 mg/dl of protein or more in a 24-h urine collection by Dong *et al.* [9], which is consistent with the current study that shows systolic blood pressure in the first trimester significantly increased after 20 weeks of gestation when preeclampsia developed in women with advanced maternal age, women with chronic diseases, and normal pregnant women (P < 0.001, P < 0.001, and P = 0.01, respectively). Moreover, diastolic blood pressure in the

Table 5 Baseline laboratory data of studied groups

	GI	GII	GIII	*P*1	*P*2	*P*3
TLC (×10^9/l)	7.66±2.51	7.26±2.90	7.14±1.88	0.54	0.53	0.43
Hemoglobin (g/dl)	10.31±1.21	11.03±1.43	12.32±1.05	0.03	0.01	0.45
Platelets (×10^3/l)	236.91±79.49	250.83±58.90	257.55±75.39	0.32	0.38	0.28
Glucose (mmol/l)	4.46±1.19	7.17±4.23	4.31±0.97	0.03	0.87	0.01
Urea (mmol/l)	3.91±1.23	9.74±1.47	3.13±0.97	0.04	0.11	0.02
Creatinine (μmol/l)	53.65±13.01	139.98±34.87	64.75±19.98	0.01	0.33	0.02
Total bilirubin (mg/dl)	0.24±0.14	0.26±0.14	0.29±0.19	0.45	0.34	0.22
Direct bilirubin (mg/dl)	0.11±0.07	0.09±0.03	0.11±0.05	0.08	0.08	0.23
Proteins (g/dl)	6.86±0.90	7.31±0.68	7.54±0.74	0.11	0.10	0.51
Albumin (g/dl)	3.63±0.63	4.43±0.96	3.85±0.46	0.21	0.40	0.55
AST (U/l)	21.33±9.51	21.05±7.68	23.01±8.42	0.45	0.31	0.53
ALT (U/l)	20.45±6.51	17.06±8.06	21.62±7.99	0.48	0.31	0.52
ALP (U/l)	82.28±15.82	70.53±14.44	76.12±16.41	0.09	0.07	0.43
GGT (U/l)	28.51±5.98	28.38±4.13	24.87±5.82	0.11	0.13	0.09

Data were expressed in the form of mean±SD. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transferase; TLC, total leukocytic count. GI: included women with advanced maternal age. GII: included women with chronic diseases. GIII: included normal pregnant women. *P*<0.05. *P*1, compared between GI and GII. *P*2, compared between GI and GIII. *P*3, compared between GII and GIII.

Table 6 Level of placental protein 13 in studied women

	GI	GII	GIII
PP13 (pg/ml)	186.59±40.95	158.24±42.14	343.49±38.87
Significance	*P*1	*P*2	*P*3
	0.04	0.03	0.01

Data were expressed in the form of mean±SD. PP13, placental protein 13. GI: included women with advanced maternal age. GII: included women with chronic diseases. GIII: included normal pregnant women. *P*<0.05. *P*1, compared between GI and GII. *P*2, compared between GI and GIII. *P*3, compared between GII and GIII.

Table 7 Changes in 24-h protein and blood pressure in studied women

	GI (33 women)	GII (42 women)	GIII (3 women)
Proteinuria (mg/day)			
At 1st trimester	108.15±23.69	117.23±24.52	124.011±22.53
After 20th week	344.81±44.26	351.59±45.19	322.10±10.58
P	<0.001	<0.001	<0.001
SBP (mmHg)			
At 1st trimester	113.63±8.22	116.67±8.45	116.67±5.77
After 20th week	146.36±6.03	156.67±7.21	153.33±5.77
P	<0.001	<0.001	0.01
DBP (mmHg)			
At 1st trimester	69.69±8.83	71.90±8.33	70±10.12
After 20th week	98.15±6.18	99.76±7.40	99.11±2.22
P	<0.001	<0.001	0.01

Data were expressed in the form of mean±SD. DBP, diastolic blood pressure; SBP, systolic blood pressure. GI: included women with advanced maternal age. GII: included women with chronic diseases. GIII: included normal pregnant women. *P*<0.05.

first trimester significantly increased after 20 weeks of gestation when preeclampsia developed in women with advanced maternal age, women with chronic diseases, and normal pregnant women *P* value less than 0.001, less than 0.001, and 0.01, respectively). Moreover, 24-h proteins in urine in the first trimester significantly increased after 20 weeks of gestation when preeclampsia developed in women with advanced maternal age, women with chronic diseases, and normal pregnant women ($P < 0.001$, <0.001, and < 0.001, respectively).

The current study shows that preeclampsia has a higher incidence in pregnant women with chronic diseases such as hypertension, diabetes, SLE, and chronic kidney disease (70%) ($P = 0.01$) and pregnant women with advanced maternal age over 35 years old (55%) ($P = 0.01$) in comparison with normal pregnant women (7.5%). This is consistent with the study done by Rodriguez-Lopez *et al.* [10], which showed women who have had chronic diseases such as chronic hypertension (high blood pressure before becoming pregnant), kidney disease, systemic lupus, and diabetes and women who are over the age of 35 years are at risk for preeclampsia.

Preexisting diabetes mellitus (DM) causes nephropathy by the effect on small blood vessels associated with higher rates of preeclampsia. [11]. In comparison to the relatively low incidence of preeclampsia in nondiabetic women (2–7%) [12], in the current study, preeclampsia developed in 12 (28.5%) patients with DM out of 42 patients with preeclampsia. This result is consistent with the study done by Knight *et al.*[13] in which preeclampsia was diagnosed in 15–20% of pregnancies in women with diabetes.

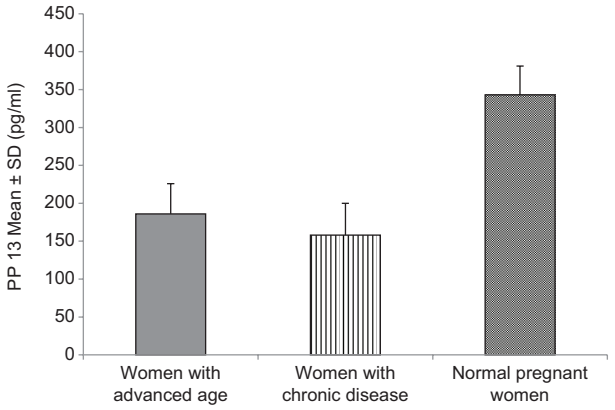
Women with chronic hypertension who become pregnant have an increased risk of preeclampsia and adverse neonatal outcomes[14] owing to reduce placental perfusion, inducing systemic vascular endothelial dysfunction [15]. This arises owing to a less effective cytotrophoblastic invasion of the uterine spiral arteries. The resultant placental hypoxia induces a cascade of inflammatory events, disrupting the balance of angiogenic factors, and inducing

Table 8 Diagnostic accuracy of placental protein 13 in the prediction of preeclampsia

	Women with advanced age (%)	Women with chronic disease (%)	Normal pregnant women (%)	All women (%)
Sensitivity	82	83.33	33.30	83.30
Specificity	93	83.33	97.30	78
PPV	93	92	50	78
NPV	81	68	95	83
AUC	0.91	0.90	0.70	0.88
Cutoff point	<186.5	<155	<134.5	<184.5
P	<0.001	<0.001	0.03	0.01

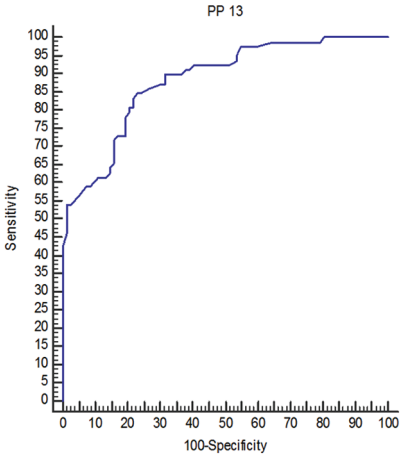
AUC, area under curve; NPV, negative predictive value; PPV, positive predictive value. $P<0.05$.

Figure 1



Mean ± SD level of PP13 of studied women. PP13, placental protein 13.

Figure 2



ROC curve of diagnostic performance of PP13 in the prediction of preeclampsia in all studied women. PP13, placental protein 13; ROC, receiver operating characteristic.

platelet aggregation, all of which result in endothelial dysfunction manifested clinically as the preeclampsia syndrome by Ngene and Moodley [16]. Moreover, it is consistent with the current study, which showed preeclampsia developed in 12 (28.5%) women with hypertension of 42 patients with preeclampsia.

In early pregnancy, increased renal blood flow leads to an increase in glomerular filtration rate, so women with chronic renal disease are at greatest risk of an accelerated decline in renal function during pregnancy owing to preexisting proteinuria and hypertension, both increasing this risk [17]. Women with chronic kidney disease and an increased creatinine threshold have a high risk of developing preeclampsia and delivering preterm, as stated by the study done by Maruotti *et al.*[18] on the group with serum creatinine more than 125 μmol/l. There is an increased incidence of preeclampsia (78.6%; $P < 0.0001$). The current study shows that preeclampsia developed in 13 (30.9%) patients with chronic renal disease out of 42 patients with preeclampsia, and their mean ± SD serum creatinine was 139.98 ± 34.87 μmol/l.

The current study showed that preeclampsia developed in four (9.5%) patients with SLE out of 42 patients with preeclampsia, which is consistent with Chakravarty *et al.* [19], who showed that women with SLE had significantly increased rates of hypertensive disorders compared with the general obstetric population (23.2%) owing to active maternal disease, nephritis, proteinuria, hypertension, thrombocytopenia, and presence of anti-phospholipid antibodies, especially lupus anticoagulant [20]. Moreover, Qazi *et al.*[21] showed that 17% of pregnancies with SLE developed preeclampsia.

The studied pregnant women were between 11 and 15 weeks of gestation. Serum PP13 levels between 11 and 13 weeks of gestation are promising for the prediction of early preeclampsia [22]. The current study shows that level of PP13 was significantly low in women with chronic disease and advanced maternal age (P = 0.01 and 0.03, respectively), in comparison with the control group, which shows high level of PP13. This is consistent with the study done by El Sherbiny *et al.* [23], who showed maternal serum PP13 is reduced during the first trimester in women who subsequently developed preeclampsia and they have risk factors for preeclampsia such as chronic hypertension, kidney disease, systemic lupus, women who are over the age of 35 years, women who are experiencing a first pregnancy, DM, and family history of preeclampsia compared with controls. The maternal serum PP13 level in the preeclamptic group was 157.9 ± 45.5 pg/ml, which is significantly lower than that of the control

group (225 ± 67.3 pg/ml), with a highly statistically significant difference ($P < 0.0001$) [24].

In the current study, PP13 had 83.30% sensitivity and 78% specificity in prediction of preeclampsia in all women ($P = 0.01$), with positive predictive value (PPV) of 78%, negative predictive value (NPV) of 83%, and area under curve (AUC) of 0.88. These results are close to the study done by Romero *et al.*[25] who found serum PP13 concentration in the first trimester was significantly lower in women who developed preeclampsia than in those with normal pregnancies and had 80% specificity and 85% sensitivity for prediction of preeclampsia. Moreover, in the current study, we found that PP13 had 82% sensitivity and 93% specificity in the prediction of preeclampsia in women with advanced maternal age (over 35 years old) ($P < 0.001$), with PPV 93%, NPV 81%, and AUC 0.91, and had 83.3% sensitivity and 83.3% specificity in women with chronic diseases ($P < 0.001$), with PPV 92%, NPV 68%, and AUC 0.90.

Conclusion

This study has revealed that serum levels of PP13 can be used as a predictive test in preeclampsia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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