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Maternal Serum Placental Growth Factor and Doppler Ultrasound of Uterine Arteries Predict Pre-eclampsia in First Trimester

Ibrahim ZM[1], Madny EH[1], Hegazi HM[1], Gharib WF[1], Gadalla AM[1], Shora HA[2*] and Khodair AS[1]

[1]Obstetrics and Gynecology Department Faculty of Medicine, Suez Canal University, Ismailia., Egypt.

*[*2]Medicine and Diabetes Center, Ismailia General Hospital, Ismailia and Port-Said University, Egypt.*

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ABSTRACT

Background: Placental growth factor (PGF) is a member of the vascular endothelial growth factor (VEGF) family of growth factors. Some studies suggested its role in diagnosis of pre-eclampsia. Doppler study of the uterine artery was also suggested as a predictor of pre-eclampsia.

Aim of study: The present study aims to investigate the predictive value of maternal serum placental factor (PGF) and Doppler ultrasound on uterine arteries for first-trimester prediction of pre-eclampsia.

Subjects and methods: Pregnant women at high risk for developing pre-eclampsia were included in the study. At their first trimester, maternal serum was withdrawn for PGF assay and uterine artery Doppler was performed. Those who developed pre-eclampsia in the subsequent weeks were included in the statistical analysis as the study group that included 40 patients. In addition to the study group, another 40 pregnant women who were matched with the control group for age and gestational age were included in the study as control group. They were also subjected to blood sample withdrawal for PGF assay and uterine artery Doppler evaluation.

Results: Among the initially included 200 women at high risk for development of pre-eclampsia, 40 women actually developed pre-eclampsia (20.0%). Pre-eclamptic patients had significantly higher BMI when compared with controls. They also had significantly higher frequency of nulliparous women. The study group patients had significantly lower levels of placental growth factors when compared with women in the control group. Also, patients had significantly higher uterine artery pulsatility index (PI) when compared with controls. At a cut-off of 86.75, PGF had a sensitivity of 50.0%, specificity of 75.0%, PPN of 67.0% and NPV of 60.0%. At cut-off of 1.36, UAPI had a sensitivity of 85.0%, specificity of 65.0%, PPN of 71.0% and NPV of 81.0%.

Conclusion: Uterine artery pulsatility index is more sensitive than PGF in prediction of pre-eclampsia in the first trimester.

Keywords: Pre-eclampsia, Uterine artery Doppler, Placental growth factor

INTRODUCTION

Pre-eclampsia is a syndrome of new-onset hypertension and proteinuria after 20 weeks of gestation in a previously normotensive non-proteinuric female [1,2]. Pre-eclampsia develops in 3-14% of pregnancies worldwide and in 5-8% in the USA [3].

Early detection of pre-eclampsia is a major focus of maternity care as it remains a significant cause of maternal and perinatal morbidity and mortality [2]. The only treatment for pre-eclampsia currently available is delivery and therefore accurate diagnosis with the aid of a biomarker could allow adjustment to clinical care [4].

Prior to the onset of pre-eclampsia, abnormal uterine artery Doppler ultrasound results suggest increased uteroplacental resistance to blood flow. Thus, placental ischemia may be an early or precipitating event in the development of pre-eclampsia [5].

Corresponding author: Hassan A Shora, Senior Research Scientist, Head of Medicine and Diabetes Center, Ismailia General Hospital, Ismailia and Port-Said University, Egypt, Tel: +201224020233; E-mail: hassanshora56@gmail.com

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Doppler measurements can be obtained from the uterine, middle cerebral and umbilical arteries. The pulsatility index (PI) and resistance index (RI) are used for the arteries and the peak velocity index (PVI) is used for the veins [6,7]. Doppler studies of uterine artery blood flow in the second trimester may be useful in predicting pre-eclampsia and/or intra-uterine growth retardation (IUGR) [8,9].

Uterine artery Doppler evaluation has been studied extensively for the prediction of preeclampsia and IUGR that reflects the involvement of a defective trophoblastic invasion. However, it has scarcely been evaluated as a prognostic tool at the onset of preeclampsia [10].

Placental Growth Factor (PlGF) is one of the several biomarkers which have been shown to have a predictive capacity for the screening and detection of pre-eclampsia [11,12]. PlGF is produced by the syncytiotrophoblast and is identifiable in maternal blood from as early as 12 weeks [13] with concentrations increasing with gestation until around 30 weeks before declining until birth [14]. A decline in PlGF appears to represent a negative variety of insults ranging from hypoxia, [15] inflammation, oxidative stress [16] and is as such also seen as a part of syncytiotrophoblast aging. PlGF concentrations are lower in pre-eclampsia [11] and extremely low in severe early-onset pre-eclampsia [17]. Recently, it has also been suggested that low PlGF concentrations are associated with fetal growth restriction (FGR) [18,19] and placental dysfunction [20].

Placental growth factor (PGF) levels are reduced in the serum of women during clinical pre-eclampsia. Reduced PGF have been found at least 5 weeks prior to the onset of pre-eclampsia. *In vitro* studies have shown that the anti-angiogenic state in pre-eclampsia could be rescued by giving PGF [20,21]. One study evaluated the utility of angiogenic proteins levels to differentiate severe pre-eclampsia from normal pregnancy, non-pregnant controls and pregnant women with hypertension and proteinuria who did not meet the diagnosis for severe pre-eclampsia. They found that severe pre-eclampsia was associated with reduced PGF [22]. However, Davison et al. [23] conducted a study to investigate the maternal serum concentration of PGF in pregnancies that subsequently developed pre-eclampsia. They concluded that in the pre-eclampsia group, serum PGF level during the first trimester is normal which suggests that it is unlikely that this factor plays a role in the pathogenesis of pre-eclampsia. Due to this controversy, prospective studies are needed to definitively answer whether angiogenic markers can be used to aid in the diagnosis of pre-eclampsia.

AIM OF THE WORK

The aim of this work is to investigate the predictive value of maternal serum placental factor (PGF) and Doppler ultrasound on uterine arteries for first-trimester prediction of pre-eclampsia.

SUBJECTS AND METHODS

The present study is a prospective case control study. It was conducted in Obstetrics and Gynecology Department, Suez Canal University Hospital in the period extending from January, 2012 to January, 2013. The study protocol was approved by the local research ethics committee. The participant women gave informed consent before the start of the study.

Women included in the present study were divided into two groups: The first group (study group) included 200 pregnant women with risk or previous history of pre-eclampsia or hypertensive disorders of pregnancy according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) classification (National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, 2000). Exclusion criteria for the study group were women with congenital malformations and women who refused to participate.

A second group of 40 healthy pregnant women matching age of the study group were included as a control group and were used for comparison. The women who attend the outpatient for regular follow-ups of normal pregnancy were recruited from outpatient clinic of Gynecology and Obstetrics Department, Suez Canal University Hospitals.

All women were subjected to history taking, clinical examination, recording blood pressure using an average of two consecutive sitting blood pressure readings using mercury sphygmomanometer, 6 h apart then the mean value was calculated.

Laboratory investigations include complete blood picture (CBC), fasting blood sugar, complete urine analysis and maternal serum concentration of PGF. Maternal serum concentration of PGF (R&D Systems, USA).

This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for PGF has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any PGF present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for PGF is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of PGF bound in the initial step. The color development is stopped and the intensity of the color is measured.

Assay procedure

Bring all reagents and samples to room temperature before use. It is recommended that all standards, samples, and controls be assayed in duplicate.

1. Prepare all reagents, samples and working standards as directed in the previous sections.

2. Remove excess micro plate strips from the plate frame, return them to the foil pouch containing the desiccant pack and reseal.
3. Add 100 µL of Assay Diluent RD1-22 to each well. Assay Diluent RD1-22 may contain crystals. Warm to room temperature and mix well to resuspend before using.
4. Add 100 µL of Standard, control, or sample per well. Cover with the adhesive strip provided. Incubate for 2 h at room temperature. A plate layout is provided as a record of standards and samples assayed.
5. Aspirate each well and wash, repeating the process three times for a total of four washes. Wash by filling each well with wash buffer (400 µL) using a squirt bottle, manifold dispenser or auto washer. Complete removal of liquid at each step is essential to good performance. After the last wash, remove any remaining wash buffer by aspirating or decanting. Invert the plate and blot it against clean paper towels.
6. Add 200 µL of PlGF conjugate to each well. Cover with a new adhesive strip. For cell culture supernate samples: Incubate for 1 h at room temperature. For serum/plasma/urine samples: Incubate for 2 h at room temperature.
7. Repeat the aspiration/wash as in step 5.
8. Add 200 µL of substrate solution to each well. Incubate for 30 min at room temperature. Protect from light.
9. Add 50 µL of stop solution to each well. The color in the wells should change from blue to yellow. If the color in the wells is green or the color change does not appear uniform, gently tap the plate to ensure thorough mixing.
10. Determine the optical density of each well within 30 min, using a micro plate reader set to 450 nm. If wavelength correction is available, set to 540 nm or 570 nm. If wavelength correction is not available, subtract readings at 540 nm or 570 nm from the readings at 450 nm. This subtraction will correct for optical imperfections in the plate. Readings made directly at 450 nm without correction may be higher and less accurate.

A 3.5 MHz real-time linear array ultrasound scanner combined with a 2 MHz pulsed ultrasound Doppler, was used to record blood flow velocity waveforms (FVW) in the uterine arteries. A 100 Hz high-pass filter will be used to remove signals from slow-moving tissue in the path of the Doppler ultrasound beam. Uterine artery Doppler waveform was obtained. Doppler examination was performed on admission. All scans were performed by one experienced observer. Uterine artery Doppler examination identified the vessel in an oblique plane, with the sample volume placed distal to the anatomic crossing with the external iliac artery. Pulsatility index (PI) of the left and right arteries was measured, and the mean was calculated. Gestational age was calculated according to the crown rump length at the first-trimester ultrasound examination. When the best quality was obtained for flow velocity waveforms, at least three waveforms were measured and averaged.

A sample size of 80 women was required to obtain a power of 90% with an assumption of α as 0.05. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data, the following tests were used to test differences for significance; Chi square t-test, student t-test. The assessment of Odd's ratio and multiple logistic regression analysis were used to test relationship between different dependent and independent variables. P value was set at <0.05 for significant results.

RESULTS

The present study showed a prevalence of 21.5% of pre-eclampsia in high risk patients while in control women, the prevalence of pre-eclampsia was 4.0%.

Comparison between the demographic, obstetric and blood pressure measurement in patients and controls is shown in **Table 1**. It was shown that patients had significantly higher BMI when compared with controls. There were no significant differences between the studied groups regarding GA, mode of conception and mean of number of deliveries. However, pre-ecalmptic patients had significantly higher frequency of nulliparous women. Patients also had significantly higher SBP and DBP when compared with controls.

Table 1. Comparison between the demographic, obstetric and blood pressure measurement in patients and controls.

		Patients (n=40)	Controls (n=40)	p
Age (years)		23.3 ± 2.4	23.1 ± 2.4	**0.68**
BMI (kg/m^2)		28.5 ± 1.8	27.6 ± 1.3	**0.018***
GA		12.2 ± 0.8	11.9 ± 0.8	**0.13**
Parity		1.03 ± 1.1	1.45 ± 1.01	**0.076**
Null parity		18 (45.0%)	8 (20.0%)	**0.017***
Conception	Normal	2 (5.0%)	1 (2.5%)	**0.56**
	ART	38 (95.0 %)	39 (97.5)	
SBP		149.3 ± 6.0	116.6 ± 4.3	**0.0001***
DBP		95.4 ± 3.2	76.5 ± 3.5	**0.0001***

**Significant results*

Comparison between the studied groups regarding serum PGF and different UAPI values is shown in **Table 2**. Patients had significantly lower PGF when compared with controls. Also, it was shown that patients had significantly higher UAPI^{1st}, UAPI^{2nd} and UAPI^{difference} when compared with controls. However, patients had significantly lower UAPI^{Ratio} when compared with controls.

Table 2. Comparison between the studied groups regarding serum PGF and different UAPI values.

	Patients (n=40)	Controls (n=40)	p
PGF	82.7 ± 13.4	135.0 ± 33.1	**0.0001***
UAPI^{1st}	1.74 ± 0.3	1.31 ± 0.16	**0.0001***
UAPI^{2nd}	1.13 ± 0.23	0.83 ± 0.13	**0.0001***
UAPI^{Ratio}	1.55 ± 0.084	1.58 ± 0.080	**0.043***
UAPI^{difference}	0.61 ± 0.08	0.48 ± 0.048	**0.0001***

** Significant results*

Correlations between serum PGF and the demographic characteristics, obstetric parameters and blood pressure measurements in the study group were revealed in **Table 3**. There were no significant correlations between PGF and the demographic characteristics, obstetrical parameters and SBP and DBP. Correlations between serum UAPI and the demographic characteristics, obstetric parameters and blood pressure measurements in the study group were revealed in **Table 4**. There were no significant correlations between UAPI and the demographic characteristics, obstetrical parameters and SBP and DBP.

Table 3. Correlations between serum PGF and the demographic characteristics, obstetric parameters and blood pressure measurements in the study group.

	PGF	
	r	p
Age	0.24	**0.13**
BMI	-0.01	**0.95**
GA	-0.18	**0.24**
Parity	-0.06	**0.71**
SBP	0.06	**0.7**
DBP	0.13	**0.4**

Table 4. Correlations between serum UAPI and the demographic characteristics, obstetric parameters in the study group.

	UAPI	
	r	**p**
Age	-0.03	**0.88**
BMI	-0.1	**0.56**
GA	-0.14	**0.37**
Parity	0.01	**0.95**

Regression analysis of PGF and UAPI as predictors of pre-eclampsia is shown in **Table 5**. It was noted that PGF and UAPI are significant predictors of pre-eclampsia in logistic regression model.

Table 5. Logistic regression analysis for PGF and UAPI and predictors of pre-eclampsia.

	OR	**P**	**95.0% CI**
PGF	1.1	0.0001*	**1.03-1.12**
UAPI	1.2	0.001*	**0.0-0.042**

**Significant results*

Sensitivity and specificity of PGF and UAPI as predictors of pre-eclampsia was illustrated in **Table 6**. At a cut-off of 86.75, PGF had a sensitivity of 50.0%, specificity of 75.0%, PPN of 67.0% and NPV of 60.0%. At a cut-off of 1.36, UAPI had a sensitivity of 85.0%, specificity of 65.0%, PPN of 71.0% and NPV of 81.0%.

Table 6. Cut-off value, sensitivity, specificity, PPV and NPV of PGF and UAPI as predictors of pre-eclampsia.

	PGF	**UAPI**
Cut-off	86.75	1.36
Sensitivity	50.0	85.0%
Specificity	25.0	65.0%
PPV	67.0	71.0%
NPV	60.0	81.0%

DISCUSSION

Pre-eclampsia (PE) is a serious complication of pregnancy that affects approximately 1% to 2% of pregnant women worldwide. It is a leading cause of maternal and perinatal morbidity and mortality, particularly when it occurs at a gestational age of less than 34 weeks [24]. PE is considered to result from a complex interaction between placental factors, maternal constitutional factors, and pregnancy-specific vascular and immunologic adaptation. These interactions predominantly involve the cardiovascular and inflammatory systems, resulting in marked maternal endothelial dysfunction and organ damage due to vascular compromise [25].

Despite a current lack of effective preventive strategies, risk assessment for PE early in pregnancy may be of benefit for both pregnancy outcome and optimization of resource utilization in antenatal care. Stratification of women by risk category, as early as the first-trimester of pregnancy, could enable intensified antenatal surveillance, timely intervention and better outcomes in those who are at high risk, and less intensified antenatal care and additional testing in those at low risk [26].

However, so far we have no reliable single screening test to identify women who are at high risk before the clinical manifestation of PE. Among the investigated predictors for pre-eclampsia is placental growth factor (PIGF) which is a member of the platelet derived growth factor family, is an important local mediator of angiogenesis in the human placenta [27]. Several studies have shown that the concentration of PIGF is dramatically decreased in the plasma of pre-eclamptic women [28]. Also, it was found that Doppler ultrasound studies of the uterine arteries have demonstrated that the clinical manifestations of pre-

eclampsia are preceded by evidence of impaired placental perfusion [29].

So, the aim of the present study is to investigate the predictive value of maternal serum placental factor (PGF) and Doppler ultrasound on uterine arteries for first-trimester prediction of pre-eclampsia.

To accomplish this target, pregnant women at high risk for developing pre-eclampsia were included in the study. At the first trimester, maternal serum was withdrawn for PGF assay and uterine artery Doppler was performed. Those who developed preeclampsia in the subsequent weeks were included in the statistical analysis as the study group that included 40 patients (2 patients were excluded to satisfy the sample size requirements).

In addition to the study group, another 40 pregnant women who were matched with the control group for age and gestational age were included in the study as control group. They were also subjected to blood sample withdrawal for PGF assay and uterine artery Doppler evaluation.

Among the initially included 200 women at high risk for development of pre-eclampsia, 40 women actually developed pre-eclampsia (20.0%). This figure is close to what is found by Caritis et al. [30], who found a prevalence of 19.0% of women who developed pre-eclampsia among 2503 high risk women. However, Shaker and Shehata [31] reported that 46.4% of high risk women developed pre-eclampsia. This discrepancy may be explained by the fact that they included in their study, women with at least one of the following risk factors for pre-eclampsia: pregestational diabetes mellitus, maternal age of 18 years, systemic lupus erythematous (SLE), or prior history of pre-eclampsia; conditions that may be associated with higher frequency of progression to pre-eclampsia that our study and other did.

In the present study, comparison between the studied groups regarding the demographic characteristics had revealed that patients had significantly higher BMI when compared with controls. This is in agreement with the recent study of Anderson et al. [32], who studied the role of BMI as a risk factor for pre-eclampsia. In multivariate logistic regression analysis, they found that increased BMI is a risk factor for the development of pre-eclampsia.

Comparison between the studied groups regarding the obstetric parameters had revealed no significant differences between the studied groups regarding gestational age at the time of performing study investigations as our study was initially designed.

In the present study, there was no significant difference between the studied groups regarding mode of conception and mean of number of deliveries. However, pre-eclamptic patients had significantly higher frequency of nulliparous women. This is in accordance with the findings of Kashanian et al. [33], who studied the risk factors for pre-eclampsia and found that parity more than one is a significantly protective factor against pre-eclampsia.

Comparison between the studied groups regarding maternal level of placental growth factor had shown that the study group patients had significantly lower levels when compared with women in the control group. This is in agreement with Wortelboer et al. [34], who investigated the predictive value of maternal serum placental growth factor (PlGF) for first-trimester identification of early-onset pre-eclampsia. The authors concluded that PlGF in the first-trimester might be promising markers in risk assessment for early pre-eclampsia/HELLP syndrome but for an adequate screening test, additional characteristics are necessary.

In another study, Law et al. [35] investigated the association between first trimester maternal placental growth factor (PlGF) with subsequent development of pre-eclampsia (PE). They found that median PlGF level in the 27 study cases with PE was lower than that of the matched controls.

Recently, a systematic review found that concentrations of PlGF (27 studies) were lower in women who developed pre-eclampsia and concluded that PlGF showed modest but significantly different concentrations before 30 weeks of gestation in women who developed pre-eclampsia [36].

Most recently, Madazli et al. [37], Agarwal et al. [38] and Boutin et al. [39] investigated whether the serum levels of PIGF early in pregnancy differ in women who develop pre-eclampsia from those who remain normotensive. They found that PIGF levels are altered in the first trimester serum of women destined to become pre-eclamptic, reflecting placental dysfunction. PIGF may have a potential to be used as a first-trimester biomarker of pre-eclampsia.

Regarding the uterine artery pulsatility index (PI), the present study found that patients had significantly higher when compared with controls. This is in accordance with the findings of Herraiz et al. [40], who assessed the value of a prediction model for pre-eclampsia (PE) in the first trimester for the prediction of late (>34 weeks) and early (≤ 34 weeks) PE in a high-risk population. Mean uterine artery pulsatility index at 11 to 13+6 weeks and a series of maternal variables were combined in order to obtain the estimated 'a posteriori risk for PE' in each woman. Late PE developed in 13 (8.6%) pregnancies and early PE in seven (4.6%). The median 'a posteriori risk for PE' in the unaffected, late PE, and early PE groups was 0.62%, 1.22%, and 2.49% ($P<0.01$), respectively. For a false-positive rate of 10%, the detection rates of late and early PE were 23.1 and 42.9%, respectively. The authors concluded this referenced model shows a modest performance when applied to high-risk women.

Also, the present study findings are in agreement with Meler et al. [41], who evaluated the predictive capacity of umbilical, cerebral and uterine artery Doppler in women admitted for pre-eclampsia (PE). In this study, a total of 82 (43%) women had an abnormal uterine artery Doppler on

admission, being more prevalent in early-onset (<32 weeks) than in the late-onset PE (62 vs. 27%, p<0.05). In both early- and late-onset forms, uterine artery Doppler showed a greater capacity than umbilical and middle cerebral artery Doppler for predicting adverse perinatal outcome.

In a recent systematic review performed to evaluate tests combining uterine artery Doppler with other markers for screening for pre-eclampsia, the authors reported the performance of screening tests according to the target population (low- or high-risk), the trimester of screening (first and/or second) and the subset of PE screened for (early and late). They concluded encouraging results for the prediction of early PE, even in the first trimester of pregnancy [36].

Napolitano et al. [42], assess the relationship of changes in uterine artery (UtA) Doppler pulsatility indices (PI) between first and second trimesters and the subsequent development of pre-eclampsia. Three thousand five hundred sixty women had UtA Doppler screening in the first and second trimesters. Out of the 3549 women recruited, 126 developed pre-eclampsia (PE: 22 early PE delivered <34 weeks and 41 preterm PE delivered <37 weeks). The best index for predicting pre-eclampsia was the difference between the mean second trimester and mean first trimester UtA PI (areas under the ROC for early PE and preterm PE of 0.851 and 0.786, respectively).

Yıldırım et al. [43] and Chyad et al. [44] studied one hundred and ninety-three singleton pregnant women admitted to outpatient clinic at 11-13+6 weeks for first trimester combined with screening test were included in the study. Uterine artery Doppler examination and serum biomarker screening (PAPP-A, PIGF, sEndoglin) were conducted.

The results revealed that maternal serum PAPP-A, PIGF, sEng levels were not significantly different between preeclampsia group and control group, whereas uterine artery Doppler pulsatility index (PI) values were significantly higher in preeclampsia group (p=0.023). The sEng levels were significantly higher in group with severe than those with mild pre-eclampsia (p=0.001). If uterine artery PI cut-off level was taken as >2.23 in ROC curve analysis, sensitivity was 42.31% and specificity was 82.10% for detecting pre-eclampsia they concluded that maternal serum PAPP-A, PIGF and sEng were not effective in predicting pre-eclampsia. However, these markers can be used to distinguish between mild and severe pre-eclampsia. First trimester uterine artery Doppler examination is an effective screening method for predicting pre-eclampsia.

CONCLUSION

PGF and UAPI are significant first trimester predictors for pre-eclampsia. UAPI had better sensitivity and specificity than PGF.

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