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ORIGINAL ARTICLE

First-Trimester Uterine Artery Pulsatility Index and Maternal Serum PAPP-A and PlGF in Prediction of Preeclampsia in Primigravida

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Abstract

Background Preeclampsia is a heterogeneous disorder affecting different body systems and frequently associated with morbidity and mortality. Early preeclampsia prediction will reduce this associated morbidity and mortality as it will give the chance for frequent maternal and fetal surveillance and application of prophylactic procedures.

Objective The aim of this work is to evaluate the role of mean pulsatility index (PI) of the uterine arteries and maternal serum concentrations of pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PlGF) in early preeclampsia prediction in primigravida.

Patients and Methods Three hundred primigravida attending the antenatal care clinic in Zagazig University Hospitals were included in the study. The mean PI of the uterine arteries was calculated. Maternal serum levels of PAPP-A and PIGF were analyzed by specific immunoassay.

Results Three hundred women were included in the final analysis, of them 30 patients (10%) suffered from preeclampsia. There was a significant difference between preeclamptic and normal women as regards the mean PI of the uterine arteries and levels of PAPP-A and PIGF at 11–13 weeks. When combining the cutoff levels of the three methods, mean PI of the uterine arteries ≥1.69,

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PAPP-A assay <0.96 multiple of median (MoM) and PlGF assay <0.91 MoM, the sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy were 56.7, 99.3, 89.5, 95.4 and 67%, respectively. *Conclusion* The combined measurement of maternal serum PAPP-A and PlGF concentrations and mean PI of the uterine arteries at 11–13 weeks of pregnancy may help to predict preeclampsia in primigravida when other parameters of preeclampsia prediction are normal. However, we need more studies on larger and variable populations to evaluate the use of those combined methods in preeclampsia prediction.

Keywords Preeclampsia · PAPP-A · PIGF · Pulsatility index

Introduction

Preeclampsia is a major cause of maternal and neonatal mortality and morbidity. It is the second largest cause of maternal mortality worldwide and affects 5–7% of pregnant women. The main etiology of preeclampsia is impaired invasion of the spiral arterioles by the trophoblastic villi leading to reduced placental perfusion and release of pro-inflammatory mediators causing platelets activation, maternal renal dysfunction, generalized endothelial damage and abnormal oxidative stress and contributing in preeclampsia pathogenesis [1]. The final result is defective uteroplacental circulation due to failure of formation of low-resistant circulation from the highly resistant blood vessels. This phenomenon could be easily detected by uterine artery Doppler studies [2, 3].

Many maternal biochemical markers have been studied extensively to detect its role in prediction of PE. Most of those markers denote impaired, abnormal and defective placentation. Maternal serum concentrations of pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PIGF) are two of them [4].

A relationship was established between maternal serum concentrations of PAPP-A and the pathogenesis of preeclampsia [5]. Abnormal placentation that is the main etiology of preeclampsia is associated with decreased production of PIGF [6]. Pregnant women who will develop preeclampsia usually experience decreased first-trimester levels of serum PAPP-A [5] and PIGF [6].

Many trials were performed to predict preeclampsia accurately using a combination of Doppler analysis of the uterine arteries and various biochemical serum markers. However, up till now there is no any method that has a good predictive value [7]. The aim of this work was to evaluate the role of the mean PI of the uterine arteries and maternal serum concentrations of PAPP-A and PlGF in the early prediction of preeclampsia in primigravida.

Patients and Methods

This study was carried out in the Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, between July 2015 and March 2016 (9 months). The study included 300 primigravida women attending antenatal care clinic in Zagazig University Hospitals and fulfilled the following inclusion criteria: (1) spontaneous pregnancy; (2) single pregnancy; (3) gestational age between 11 and 13 weeks; (4) no history of infertility; (5) no history of medical disorders. Exclusion criteria were: (1) multigravida women; (2) women with multiple pregnancies; (3) smokers; (4) women with a body mass index (BMI) $\geq$25 kg/m^2.

This study was a prospective observational study. The study protocol was approved by the Institutional Research Ethical Committee. All patients and their husbands gave an informed written consent before participating in the study and had the right to leave the study at any time. Full detailed history was taken from all patients followed by general and abdominal examination to exclude any associated medical disorders.

Transabdominal ultrasound (TAS) was performed for all cases by the same sonographer. Transabdominal 2D color Doppler probe of Voluson 730 pro V machine (GE healthcare, Austria, with a 3.5-MHz sector transducer for TAS and 7.5-MHz sector transducer for TVS) was used to confirm a live fetus and to determine the gestational age. Uterine artery PI was then measured. Each uterine artery was identified lateral to the uterus using color Doppler, at the level of the internal os. Pulsed-wave Doppler was used with the angle of insonation <30 and the sampling gate set at 2 mm and with the appearance of three typical and identical consecutive waves, the PI of both uterine arteries was detected, and the mean PI of them was calculated.

Basic investigations were performed for all patients in the first antenatal care visit including CBC, Rh, blood group, random blood sugar and urine analysis. Maternal serum levels of PAPP-A and PIGF were analyzed by specific immunoassay (ELISA) in the Laboratory of Zagazig University Hospitals, and all results were expressed as multiple of the median (MoM) of the expected normal median for a pregnancy of the same gestational age. Gestational age (in days) at sampling was recorded.

All pregnant women included in the study were advised to come to the antenatal care clinic monthly till 28 weeks, every 2 weeks till 36 weeks and weekly till delivery. At every visit a morning urine sample was collected from

patients and urine analysis was performed to detect proteinuria and arterial blood pressure was measured to detect hypertension. All women were screened for gestational diabetes at 24–28 weeks.

Preeclampsia was diagnosed by the new appearance of hypertension and proteinuria after 20 weeks gestation. Hypertension was diagnosed when systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg measured twice 6 h apart. Proteinuria was diagnosed when 24-h urine collection contained ≥300 mg protein, or two readings >+1 proteinuria on dipstick analysis.

Statistical Methodology

Data were checked, entered and analyzed using SPSS version 20 for data processing. Quantitative data were presented as mean and SD. Independent Student's *t* test was used for comparing normally distributed quantitative variables. The best cutoff values for uterine artery PI, PAPP-A and PIGF were determined using the receiver operating characteristic (ROC) curve.

Results

At the beginning of the study, 400 pregnant women were included; however, 60 experienced spontaneous abortion, 36 were lost and four patients experienced unexplained intrauterine fetal death during the period of follow-up. So, only 300 pregnant women were followed up by us till the time of delivery. Demographic data and clinical features of pregnant women are presented in Table 1. Thirty pregnant women (10%) developed preeclampsia from a total of 300 participants with no significant difference between normal and preeclamptic groups as regards maternal age, weight, height, BMI and gestational age at sampling; however, there was a highly significant difference as regards gestational age at delivery and significant difference as regards birth weight as given in Table 1.

The mean PI of the uterine artery at 11–13 weeks' gestation showed highly significant difference between preeclamptic (2.4 ± 0.2) and healthy women (1.4 ± 0.4), as given in Table 2. The optimal cutoff PI value using the ROC curve was ≥1.69, gave sensitivity of 100%, specificity of 70%, positive predictive value (PPV) of 27%, negative predictive value (NPV) of 100% and an accuracy of 73%, as given in Table 3.

Serum PAPP-A concentration showed significant decrease in preeclamptic women (0.97 ± 0.2) when compared to healthy women (1.1 ± 0.3) as given in Table 2. The optimal cutoff PAPP-A value using the ROC curve was ≤0.96 MoM, resulting in a sensitivity of 63.3% and a specificity of 90.4%, a positive predictive value of 42.2%, a negative predictive value of 95.7% and an accuracy of 88% as given in Table 3.

Serum PlGF concentration showed significantly decrease in preeclamptic women (0.85 ± 0.2) when compared to healthy women (1.02 ± 0.3) as given in Table 2. The optimal cutoff PlGF value using the ROC curve was ≤0.91 MoM, resulting in a sensitivity of 90%, a specificity of 82.6%, a positive predictive value of 36.5%, a negative predictive value of 98.7% and an accuracy of 83% as given in Table 3.

Combining the three cutoff levels (mean uterine artery PI ≥ 1.69, PAPP-A assay ≤0.96 MoM and PlGF assay ≤0.91 MoM), the sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy were 56.7, 99.3, 89.5, 95.4 and 67%, respectively, as given in Table 3.

Discussion

Preeclampsia is a main cause of maternal and fetal mortality and morbidity. Many screening tests have been investigated to predict preeclampsia, including the biochemical screening markers used for Down's syndrome as

Table 1 Demographic data and clinical features of patients with preeclampsia and normal pregnant women

Variable	Normal (270) mean ± SD	Preeclamptic (30) mean ± SD	*P* value
Maternal age (years)	27.01 ± 4.11	26.22 ± 3.99	0.2
Maternal weight (kg)	75.11 ± 6.89	74.87 ± 7.55	0.8
Maternal height (m)	1.75 ± 0.12	1.71 ± 0.11	0.06
Maternal BMI	24.1 ± 4.1	23.7 ± 4.3	0.6
Gestational age at sampling (days)	83.2 ± 3.9	84.3 ± 4	0.1
Gestational age at delivery (weeks)	38.7 ± 2.8	33.8 ± 2.55	0.001**
Birth weight (g)	2500 ± 600	2150 ± 550	0.002*

BMI body mass index

* Statistically significant difference ($P \leq 0.05$); ** statistically highly significant difference ($P \leq 0.001$)

Table 2 Mean PI of the uterine arteries and serum PAPP-A and PIGF levels in women with preeclampsia and normal women

Variable (No.)		Range		Mean ± SD	*P* value
		Min	Max		
Uterine artery PI	Preeclampsia (30)	1.91	2.73	2.4 ± 0.2	0.001**
	Normal (270)	0.8	2.5	1.4 ± 0.4	
PAPP-A (MOM)	Preeclampsia (30)	0.52	1.22	0.97 ± 0.2	0.02*
	Normal (270)	0.71	1.61	1.1 ± 0.3	
PIGF (MOM)	Preeclampsia (30)	0.59	1.09	0.85 ± 0.2	0.002*
	Normal (270)	0.79	1.41	1.02 ± 0.3	

MoM multiple of median, *PI* pulsatility index, *PAPP-A* pregnancy-associated plasma protein A, *PIGF* placental growth factor

Table 3 Diagnostic accuracy of mean PI of the uterine arteries and maternal serum PAPP-A and PIGF levels in prediction of preeclampsia

Variable	AUC	Sensitivity	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy	95%CI
Mean PI of the uterine arteries ≥1.69	0.95	100%	70	27	100	73%	(0.91–0.97)
PAPP-A ≤0.96	0.89	63.3%	90.4	42.2	95.7	88%	(0.85–0.95)
PIGF ≤0.91	0.97	90%	82.6	36.5	98.7	83%	(0.94–0.99)
Mean PI of the uterine arteries ≥1.69, PAPP-A ≤0.96 and PIGF ≤0.91	56.7%		99.3	89.5	95.4	67%	

AUC area under the curve

they have been proposed for their relation to abnormal uteroplacental circulation, and only a few of them reached satisfactory sensitivities and specificities. Due to its heterogeneous nature, preeclampsia prediction could not be achieved by a single test [8].

The use of uterine artery Doppler study in predicting preeclampsia has been previously extensively investigated in the second and first trimesters of pregnancy. Abnormal placental behavior that characterizes preeclampsia is associated with increased vascular resistance in the placenta. Ultrasonographic evidence of that problem includes an increase in the pulsatility index (PI) of the uterine artery or persistent diastolic 'notch' in its Doppler waveform [9].

A meta-analysis that was published in 2008 regarding the role of uterine artery Doppler study in prediction of preeclampsia confirmed that using this procedure in the second trimester of pregnancy is better than in the first trimester, and it had a major role in predicting severe or early-onset preeclampsia in low-risk population. Raised PI of the uterine artery has a sensitivity of 78% and specificity of 95% in predicting severe preeclampsia if used in the second trimester [10]. There is a recent meta-analysis including 11 studies found that using the first-trimester uterine artery Doppler in preeclampsia prediction had an overall sensitivity of 26% and specificity of 91% [11]. Doppler studies of the uterine artery may be more predictive of preeclampsia if measured in a repeated manner in the first half of pregnancy. However, this will abolish the chance to start prophylaxis early [12].

In a study by Gomaa et al., they found that at 11–13 weeks of pregnancy the mean PI of uterine arteries was significantly higher in preeclamptic (2.46 ± 0.28) than in normal women (1.435 ± 0.45), and this is similar to our results. A value of PI ≥ 1.7 using the ROC curve gave sensitivity of 100%, specificity of 84.4%, PPV of 41.7%, NPV 100% and an accuracy of 94.3% [13]. In our study, using a lower cutoff value for uterine artery Doppler study (PI > 1.69), we found higher sensitivity rates (100%). Our results confirmed the data previously mentioned in the review article of Carbillon [14] in that although the high sensitivity of uterine artery PI in preeclampsia prediction, it will have a limited role in clinical practice due to a low PPV. All data do not support the routine introduction of uterine artery PI alone as a sole predictive test, but it should be combined with serum biochemical markers to increase its predictive value.

No single maternal serum biomarker has a satisfactory predictive value of clinical importance in preeclampsia prediction; however, they are more beneficial when combined with other parameters (mainly Doppler study). Markers of placental function include PAPP-A, which is routinely used in first-trimester screening of Down syndrome. PAPP-A is released from syncytiotrophoblast as a protease and may affect placenta formation through its influence on insulin-like growth factors (IGFs). Angiogenic agents include placental growth factor (PlGF), which has been proposed to have a role in women who will develop preeclampsia [15].

In a study by Ozdamar o et al., serum levels of PAPP-A showed significant decrease in the preeclamptic women (0920) when compared to normal women (1.252), and this is similar to our results. In ROC analysis, a value of 0.956 gave a sensitivity of 70%, a specificity of 65.6%, a PPV of 67% and a NPV of 68.6% [16]. In a study by Myatt et al., PlGF (0.83 vs. 1.04, $P < 0.001$) was significantly decreased in women who developed preeclampsia when compared to controls, and this is similar to our results. PlGF had the highest area under the curve (0.61) with a sensitivity of 32% and specificity of 80% [17].

The low sensitivity (56.7%) from the combination of uterine artery PI and maternal serum biochemical markers (PAPP-A–PIGF) in our study may be due to the heterogeneity and complexity of preeclampsia syndrome, difficult identification of at-risk patients from among low-risk population and of defining an enriched population for preeclampsia study.

As regards preeclampsia, early prediction could potentially improve the outcome by close surveillance of the patient and would be the basis of the prophylactic medications such as aspirin, starting from the first trimester to improve placental invasion, uteroplacental circulation and so decreasing the prevalence of the disease [18].

In the present study, we discovered that adding the first-trimester PAPP-A serum level using a cutoff value $\leq$0.96 MoM and PIGF serum level using a cutoff value $\leq$0.91MoM to mean PI of uterine arteries at 11–13 weeks of pregnancy using a cutoff value $\geq$ 1.69 showed increased specificity (99.3%) and PPV (89.5%).

Conclusion

The combined measurement of maternal serum PAPP-A and PlGF concentrations and mean PI of the uterine arteries at 11–13 weeks of pregnancy may help to predict preeclampsia in primigravida when other parameters of preeclampsia prediction are normal. However, we need more studies on larger and variable populations to evaluate the use of those combined methods in preeclampsia prediction.

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Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest.

Informed Consent All patients and their husbands gave an informed written consent before starting the study and had the right to leave the study at any time.

Ethical Standards The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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