

Evaluation of First Trimester Uterine Artery Doppler, Placental Growth Factor and Maternal Characteristics in Prediction of Preeclampsia

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ABSTRACT

Background: Preeclampsia is a major contributor of maternal and perinatal morbidity and mortality. The purpose of this study was to look at the predictive usefulness of placental growth factor (PLGF), maternal characteristics (MC), and uterine artery Doppler for preeclampsia in the first trimester.

Patients and methods: A cross-sectional survey was conducted on 805 pregnant women between 11 + 0 and 13 + 6 weeks' gestation. A complete history and clinical examination were taken at the booking visit, a bilateral uterine artery Doppler study was estimated, and the mean pulse index (PI) was computed and recorded. A venous blood sample was drawn and centrifuged for 10 minutes at 3000 rpm to extract the serum, which was then frozen at 80 C for further examination for placental growth factor (PLGF).

Results: PE developed in 54 (6.7%) cases; 11 (20.4%) early-onset and 43 (79.6%) late-onset. The following parameters were calculated: sensitivity, specificity, positive and negative value (PPV and NPV), and accuracy. The sensitivities for MC, PLGF and UADPI for prediction of early-onset preeclampsia were 27.3%, 54.5%, and 72.7%, respectively. The sensitivities for MC, PLGF and UADPI for prediction of late-onset preeclampsia were 14%, 55.8%, and 51.2%, respectively. The sensitivity for combination between the three factors used to predict PE were 85.7% for early-onset and 79.4% for late-onset preeclampsia, respectively.

Conclusions: Effective screening for PE may be accomplished in the first trimester of pregnancy, at 11-14 weeks' gestation, by combining maternal features with the findings of uterine artery Doppler and placental growth factor to determine the risk of PE development.

Keywords: Preeclampsia, Placental growth factor, Maternal characteristics, Uterine artery Doppler pulsatility index.

INTRODUCTION

Preeclampsia (PE) is a pregnancy complication marked by hypertension and proteinuria, and which may occasionally result in a multi-organ cluster with quite varied clinical characteristics ^[1]. Preeclampsia affects roughly 2 to 8% of pregnancies and is a major cause of maternal and perinatal death and morbidity ^[2].

Identifying the risk of developing preeclampsia is an essential part of prenatal care, and research to perfect it is continuing. There are many prediction models for early prediction of preeclampsia have been developed ^[3]. These prediction models may play a role in improving risk selection by identifying risks early and allowing for preventative actions such as low-dose aspirin therapy ^[4]. Women can be categorized according to prediction models into "low" and "high" risk groups. Pregnant ladies can receive care based on their risk (tailored care pathways) ^[5].

The degree of trophoblastic invasion of the spiral arteries is inversely linked to the uterine artery pulsatility index (PI). Impaired placentation is characterized by an aberrant functional and biochemical environment that includes an increase in uterine artery PI, an increase in antiangiogenic factors, such as Soluble Endoglin (sEng), Soluble fms, such as Tyrosine Kinase-1 (sFLT1) and Inhibin-A; a side from a decrease in angiogenic and mitogenic hormones, such Pregnancy Associated Plasma Protein-A (PAPP-A), Placental Growth Factor (PLGF), and Placental Protein 13, (PP13). These indicators are crucial for subclinical syncytiotrophoblastic damage

and preeclampsia in the first trimester. In the first trimester, a combined evaluation of "maternal history and features" together with the aforementioned biomarkers and uterine artery Doppler demonstrated great specificity in identifying women at risk of developing preeclampsia ^[6].

The purpose of this study was to look at the predictive usefulness of placental growth factor (PLGF), maternal characteristics (MC), and uterine artery Doppler for preeclampsia in the first trimester.

PATIENTS AND METHODS

The research was carried out at the Zagazig Faculty of Medicine's Department of Obstetrics and Gynecology and the Laboratory Unit. This research was divided into two phases: phase I was a cross-sectional study, and phase II was a case control study.

The study started with 909 cases from these, 35 cases aborted and 69 cases missed during follow up and the remaining ones were 805 cases. In phase II, the sample was categorized according to results of phase I during follow up. Inclusion criteria were pregnant women between 11 + 0 and 13 + 6 weeks' gestation. Multiple pregnancy, chronic renal illness, chronic hypertension, antiphospholipid syndrome, pregestational diabetes mellitus, or systemic lupus erythematosus were all exclusion factors. Withdrawal criteria included cases that couldn't be followed up or those missed during the study were excluded (69 cases) and cases of abortion or when termination of pregnancy

occurred early in pregnancy were also excluded (35 cases).

The patients were chosen from the outpatient prenatal clinic at Zagazig University Hospital. The following were done to all of the women:

- A. History taking** includes demographic data, socioeconomic situation, obstetric history, co-morbid conditions, drug history, assessment of other systems, and previous and family history.
- B. Clinical examination** includes a general, heart, chest, and abdomen examination as well as the measurement of blood pressure. Each blood pressure was determined by taking an average of two consecutive seated blood pressure measurements using a mercury sphygmomanometer, five minutes apart, and calculating the mean value. To formulate a relationship between different maternal characteristics to deal with as single parameter and one number, we choose to use the NICE formula. The NICE has produced recommendations proposing that women with any one high risk factor or any two moderate risk factors be regarded to be at high risk of having PE. Chronic renal illness, diabetes mellitus, autoimmune disease, or chronic hypertension are high risk factors, whereas first pregnancy, inter-pregnancy interval >10 years, age >40 years, and body mass index (BMI) at first visit of >35 kg/m² are moderate risk factors [7].
- C. Doppler Ultrasound Assessment:** Patients who agreed to participate in the research also had bilateral uterine artery Doppler testing. A transabdominal technique with color flow mapping was used for this examination. The cervical canal was detected after obtaining a midsagittal image of the uterus. The transducer was therefore adjusted to identify the paracervical vessels. The PI was then determined and averaged for each uterine artery.
- D.** A venous blood sample was collected from each patient and centrifuged for 10 minutes at 3000 rpm, after which the serum was extracted and stored at 80°C for further analysis with ELIZA. The laboratory employees who conducted the tests were not aware of the pregnancy result.

The study group was followed up as routine antenatal care for prediction of occurrence of preeclampsia by blood pressure measurement and urine analysis for detection of proteinuria, also for detection of maternal and fetal complications occurring in preeclamptic patients. The International Society for the Study of Hypertension in Pregnancy standards were used to make the diagnosis of preeclampsia. After 20 weeks' gestation, an earlier normotensive woman must have two recordings of diastolic blood pressure 90 mmHg at least 4 h apart, and proteinuria 300 mg in 24 h, or two readings at least ++ on dipstick analysis of a

midstream or catheter specimen of urine (if no 24-h urine collection is available).

Thereafter, the patients were classified into case group (who developed preeclampsia) and control group (who remained normotensive throughout pregnancy). Blood samples were then tested to placental growth factor for case group (54 cases) and specific proportion to the control group (32 cases) based on systematic random sampling with fixed interval.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 18 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) and Fisher's exact test to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean and standard deviation (SD). Independent samples t-test was used to compare between two independent groups of normally distributed variables. The optimal cut-off value for the analyzed diagnostic indicators was determined using receiver operator characteristic (ROC) analysis. The diagnostic performance of a test or the accuracy of a test to discriminate diseased cases from non-diseased cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis. Sensitivity and Specificity were detected from the curve and positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated through cross tabulation. Binary stepwise logistic regression analysis was used for prediction of independent variables of binary outcome. Significant predictors in the Univariate analysis were entered into regression model using Enter method. Adjusted odds ratios and their 95% confidence interval were calculated. P value ≤ 0.05 was considered significant.

RESULTS

The study recruited 805 cases, fulfilling the inclusion and exclusion criteria. PE developed in 54 (6.7 %) cases; 11 (20.4%) early-onset and 43 (79.6%) late-onset. The mean age was 28.8 (SD 4.9) years for the PE group and 26.8 (SD 5.6) years for the No PE group. Body mass index (BMI) was 28.4 (SD 2.1) and 25.2 (SD 2.2) KG/M² for PE and No PE group, respectively. Primigravidas were 18 (33.3%) cases and 190 (25.3%) cases in the PE and No PE group,

respectively. Multigravidas were 36 (66.7%) cases and 561 (74.7%) cases in the PE and No PE group, respectively. This research found no link between the kind of parity and the incidence of PE. Blood pressure in the studied group is shown in Table (1) that revealed significant higher peak systolic and diastolic blood pressure in the PE group.

Table (1): Blood pressure in the studied groups.

Variable	PE (n=54)		No PE (n=751)		t-test	P-value
	Mean	SD	Mean	SD		
Highest SBP	150.55	13.65	109.92	9.54	29.22	0.00*
Highest DBP	102.40	9.09	70.73	8.96	25.04	0.00**

Preeclampsia was significantly associated with high rate of cesarean section (CS). In the PE group, 11 (20.4%) cases delivered vaginal and 43 (79.6%) cases delivered by CS, but in the No PE group, 346 (46.1%) cases delivered vaginal and 405 (53.9%) cases delivered by CS. Baby birth weight was significantly lower in case with PE. The mean birth weight in the PE group was 2907 (SD 523) gm but it was 3312 (SD 380) gm in the No PE group.

The studied groups are classified according to maternal characteristics (MC) in NICE 2010 to be or not to be risky to develop PE. The incidence of PE in those who proved to be risky were 27%, 14% and 0.4% in the early PE, late PE and No PE groups, respectively, but the incidence of PE in those who proved to be not risky were 72%, 86% and 99.6% in the early PE, late PE and No PE groups, respectively

PLGF distribution among studied groups showed that PLGF was significantly lower in cases with preeclampsia. The mean of PLGF in the PE group was 93.05 (SD 16.88) pg/ml but in the control group it was 126.57 (SD 38.45) pg/ml. ROC curve was used to get the PLGF cutoff for prediction of PE, PLGF cutoff was 103.5 pg/ml and area under the curve was 0.748 as shown in **Figure 1**.

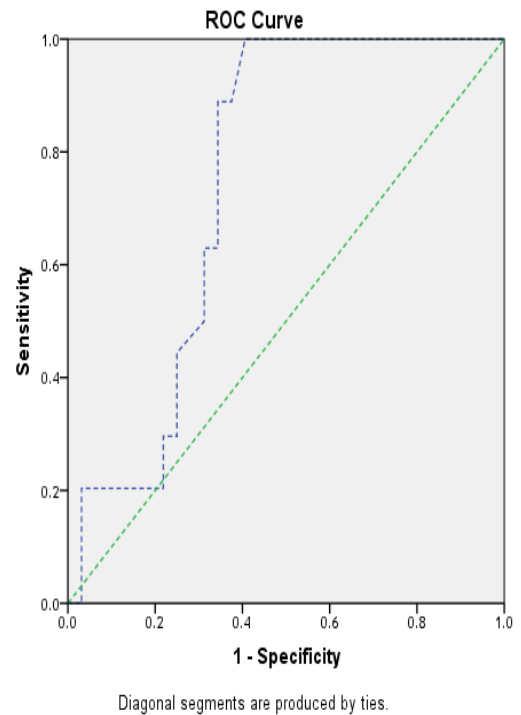


Figure (1): ROC curve for PLGF cutoff for prediction of PE.

Validity of PLGF in prediction of PE showed that the sensitivity of overall PE, early-onset and late-onset PE was 46.3%, 54.5% and 55.8%, respectively. Specificity of overall PE, early-onset and late-onset PE was 31.2%, 32.3% and 31.2%, respectively. Positive predictive value of overall PE, early-onset and late-onset PE was 53.1%, 21.4% and 52.1%, respectively.

Negative predictive value of overall PE, early-onset and late-onset PE was 25.6%, 66.7% and 34.4%, respectively.

UADPI distribution among studied groups showed that UADPI was significantly higher in cases with preeclampsia. The mean of UADPI in the PE group was 1.89 (SD 0.12) but in the no PE group it was 1.71 (SD 0.10). ROC curve was used to get the UADPI cutoff for prediction of PE, UADPI cutoff was 1.84 and area under the curve was 0.866 as shown in **Figure 2**.

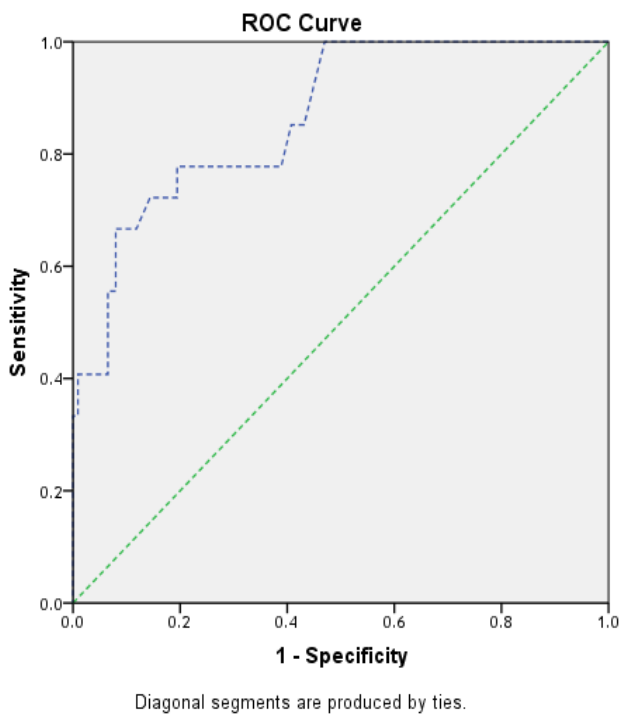


Figure (2): ROC curve for UADPI cutoff for prediction of PE.

Validity of UADPI in prediction of PE showed that the sensitivity of overall PE, early-onset and late-onset PE was 55.6%, 72.7% and 51.2%, respectively. Specificity of overall PE, early-onset and late-onset PE was 93.5%, 93.5% and 93.5%, respectively. Positive predictive value of overall PE, early-onset and late-onset PE was 37.9%, 14% and 30.9%, respectively. Negative predictive value of overall PE, early-onset and late-onset PE was 96.6%, 99.5% and 97%, respectively.

Validity of combination between MC, PLGF and UADPI mean in prediction of early and late preeclampsia are shown in tables 2 and 3, respectively.

Table (2): Validity of combination between MC, PLGF and UADPI mean in prediction of early preeclampsia.

Variable	Sensitivity	Specificity	+ve Predictive	-ve Predictive
MC	27.3%	99.6%	66.7%	98.9%
PLGF	54.5%	31.2%	21.4%	66.7%
UADPI	72.7%	93.5%	14%	99.5%
MC and/or PLGF	65.5%	98.8%	33.3%	93.5%
PLGF and/or UADPI	82.3%	93.8%	45.6%	92.2%
MC and/or PLGF and/or UADPI	85.7%	94.8%	35.6%	97.4%

Table (3): Validity of combination between MC, PLGF and UADPI mean in prediction of late preeclampsia.

Variable	Sensitivity	Specificity	+ve Predictive	-ve Predictive
MC	14%	99.6%	65.5%	95.2%
PLGF	55.8%	31.2%	52.1%	34.4%
UADPI	51.2%	93.5%	30.9%	97%
MC and/or PLGF	58.6%	89.7%	22.3%	84.6%
PLGF and/or UADPI	70.7%	89.6.8%	36.5%	90.6%
MC and/or PLGF and/or UADPI	79.4%	90.1%	17.6%	92.2%

DISCUSSION

To develop risk identification, PE is an important component of prenatal care, and research to enhance it is underway. A wide variety of first-trimester estimation techniques for PE have been created in particular [8]. The use of these prediction models may enhance risk selection by allowing for early detection and also allows for preventative interventions such as the administration of low-dose aspirin [9].

Therefore, the study's goal is to look at the predictive usefulness of maternal characteristics, maternal serum placental growth factor, and Doppler ultrasonography on uterine arteries for preeclampsia in the first trimester. Among, the initially included 805 pregnant women, 54 (6.7%) women actually developed preeclampsia, 11 (20.4%) women as early PE and 43 (79.6%) women as late PE. These figures are close to what found by **Elkholi et al.** [10]. They found a prevalence of pregnant women who developed preeclampsia 14 (5.26%) among 266 women of which 2 (14.3%) cases early PE and 12 (85.7%) case late PE, which also comes in accordance of our study.

In the current research, a comparison of the analyzed groups based on demographic parameters indicated that preeclamptic patients had considerably greater BMI than controls. This is consistent with the findings of **Anderson et al.** [11], who investigated the impact of BMI as a risk factor for preeclampsia.

There were no significant variations in parity or mean number of delivery between the analyzed groups in this research. This contradicts the results of **Kashanian et al.** [12], who analyzed preeclampsia risk variables and discovered that having more than one child is a major protective factor against preeclampsia.

To formulate a relationship between different maternal characteristics to deal with as single parameter and one number, we choose to use the NICE formula. The NICE has produced recommendations proposing that women with any one high-risk factor or any two modest-risk factors be regarded at high risk of having PE. Chronic renal illness, diabetes mellitus, autoimmune disease, and chronic hypertension are all

high-risk factors. First pregnancy, age >40 years, pregnancy interval >10 years, and BMI at first visit >35 kg/m² are moderate risk factors [7].

In our study, all the items in the high risk group are of the exclusion criteria, so we considered the patient to be at risk to develop PE according to maternal characteristics if she developed 2 of 3:- first pregnancy, age >40 years, body mass index (BMI) at first visit of >35 kg/m². A maternal characteristic alone when used for prediction of PE in our study, its detection rate was 27.3% and 14% in early and late PE, respectively. These result are in accordance with **Parra-Cordero et al.** [13], who stated that the sensitivity of maternal characteristics in detection of PE was 29.4% and 20.85% in early and late PE respectively (based on BMI and smoking for the early PE group and BMI for the late PE group).

When the maternal levels of PLGF in the study groups were evaluated, the PE patients had considerably lower levels than the women in the control group. This is consistent with **Mosimann et al.** [14], who explored the significance of timing first trimester PLGF and the utility of repeated first trimester PLGF in preeclampsia screening. In another study, **Zhong et al.** [15] explored the influence of PLGF as a screening parameter between 11 and 14 weeks for the early prediction of PE, and summarized their findings in a recently published meta-analysis (16 included studies) that confirmed that PLGF is a good predictive indicator for PE, particularly PE occurring before 34 weeks of gestation. Its result was in accordance of our study as the sensitivity of PLGF was 43% and 37% with specificity 91% and 89% in prediction of early and late PE, respectively.

However, **Andrietti et al.** [16] discovered that measuring PLGF in the first and/or second trimester had little to no influence on PE prediction when compared to screening in the early third trimester. This might be because they screening at 30-34 weeks in comparison to biomarker readings obtained at 11-13 and/or 19-24 weeks did not result in an increase in the identification rate of early PE.

The current research discovered that preeclamptic patients had considerably greater uterine artery pulsatility index (UADPI) as compared to controls. This is consistent with the results of **Parra-Cordero et al.** [13], who attempted to develop a prediction model for preeclampsia during the first trimester of pregnancy using biochemical, clinical, and ultrasound indicators. Additionally, our findings agree with **Audibert et al.** [17], who decided to make screening for PE in nulliparous women and found about 35% overall detection rate and 50% detection rate in early PE when uterine artery PI was added to maternal characteristics.

"Notching" seems to be a prevalent characteristic of the uterine artery Doppler wave shape in pregnancy, seen in 46-64 percent of normal first-trimester gestations [18]. Early diastolic notching is assumed to represent aberrant maternal vascular tone, while poor

placentation leads in chronically elevated uterine artery impedance. Overall, notching had a poor positive predictive value for preeclampsia and FGR in a high risk research group, but a 97 percent negative predictive value for both diseases [19].

Combined PLGF and UADPI in our study proved to be 65.5% sensitivity, 98.8% specificity, 33.3% PPV and 93.5% NPV value, which come in accordance with **Elkholi et al.** [10], whose outcome of coupled UADPI and PLGF for PE prediction: There were 13 confirmed positives and one false negative. As a result, the combined UADPI and PLGF had a sensitivity of 92.85% for PE prediction, a specificity of 99.60%, a PPV of 92.85%, and an NPV of 99.60%. Lastly, regarding combination between the three elements (maternal characteristics with PLGF and UADPI), results are variable between different studies with wide range of sensitivity. While the present study shows the detection rate (DR) to be 85.7% in early PE and 79.4% in late PE, **Parra-Cordero et al.** [13] concluded the DR was 46.7% in early PE and 29.4 in late PE.

Strengths and limitations:

The study's key strengths include, first and foremost, a prospective analysis of a large number of pregnancies in which particular questions were addressed to detect recognized risk factors for PE. Second, multivariate survival analysis was used to identify the components and characterize their role in the prediction of PE. Third, the creation of a survival-time framework that enables for the assessment of individual patient-specific risks of PE necessitating delivery before any certain gestation. Also uterine artery Doppler was done by the same sonographer using the same machine, which decreases the incidence of bias and intersonographers differences. The same was done for the kits, as all of them were investigated in high quality lab and professional unit in Zagazig University.

A limitation of the study is the limited factors discussed in patient characteristics (age, parity and BMI) but so many studies discussed other factors (ethnicity, smoking, alcohol intake, interpregnancy interval, medications during pregnancy, mode of conception, etc.) this limitation has decreased the detection rate as compared to other studies. Another limitation of the study is that, we couldn't make analysis of PLGF to all the control group (751 case) and we only investigated 32 cases of them due to the limited number of kits, high cost and to provide chance to investigate all the case groups. Also we didn't use more than one biomarker in the study which could improve the results, but it would markedly increase the cost so we chose the biomarker with the best detection rate in this study (PLGF). Another limitation of the study was that, not only one cut off value for either UADPI or PLGF and most of the papers had its own cut off value but all of them reached to the same result, increased UADPI and reduced PLGF in patients with PE

compared to the control group at various levels and sensitivities.

In conclusion, this research indicated that efficient screening for PE may be accomplished in the first trimester of pregnancy at 11-14 weeks gestation by combining maternal features with the findings of uterine artery Doppler and placental growth factor to estimate the risk for PE development. The major goal is to identify instances that might benefit from preventative pharmacological treatments to improve placentation; the need of early screening; and the treatment of the high-risk group with low-dose aspirin. Hopefully, new approaches will give sets of several indicators, leading to a screening program with clinically meaningful performance.

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