Med Glas (Zenica)

ORIGINAL ARTICLE

First trimester placental growth factor and uterine artery pulsatility index in the prediction of preeclampsia in high-risk pregnancy

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ABSTRACT

Aim To identify the most effective screening method for preeclampsia by evaluating the predictive significance of measuring serum placental growth factor (PlGF) concentration and using Doppler ultrasound assessments of uterine artery blood flow during the first trimester in high-risk pregnancies as predictors of preeclampsia.

Methods A prospective screening study involving 173 high-risk pregnant women for preeclampsia, between 11 + 0 and 13 + 6 weeks of gestation was conducted. Women were divided into two groups based on pregnancy outcome: a control group of 158 pregnant women who remained normotensive, and a group of 15 high-risk pregnant women who developed symptoms of preeclampsia during pregnancy. Serum PlGF concentration using a quantitative enzyme-linked immunosorbent assay was determined.

Results PlGF level was significantly reduced in women who later developed preeclampsia (14.06 pg/mL) compared to controls (37.46 pg/mL). The uterine artery pulsatility index (UtA-PI) was significantly increased in the preeclamptic group (1.73) compared to the control group (1.44). For screening preeclampsia using the combination of PlGF and UtA-PI, the estimated detection rates were 66.67% at the fixed false-positive rate (FPR) of 5% and 73.33% at the FPR of 10%. The best screening results were obtained using regression models including maternal characteristics PlGF, and UtA-PI, yielding estimated detection rates of 73.33% at the FPR of 5% and 86.67% at the FPR of 10%, respectively.

Conclusion Placental growth factor level, in conjunction with uterine artery pulsatility index during the first trimester was a valuable and accurate biomarker for predicting preeclampsia in high-risk pregnancies. When integrated with comprehensive medical history, these markers enhance the assessment of preeclampsia risk.

Keywords: biomarkers, placenta growth factor, pre-eclampsia, uterine artery

INTRODUCTION

Preeclampsia, a significant obstetric complication, has a variable rate globally, as reported by the World Health Organization (WHO) among 2%-10% of pregnancies. Prevalence of preeclampsia is markedly higher in developing countries, estimated at 16.7%, compared to its occurrence in developed countries (1). This condition contributes substantially to maternal and foetal morbidity and mortality, with an annual estimate of over 70,000 maternal deaths and 500,000 foetal deaths worldwide (2). Despite significant research efforts, the diagnosis and treatment of preeclampsia have remained largely unchanged for decades. In recent years, numerous studies have explored the role of angiogenic factors in the prediction, differential diagnosis, and classification of hypertensive disorders in pregnancy. However, data on many of these factors lack reliability, and some are not specific or predictive enough for routine clinical application (3). Yet at present there is no screening test for preeclampsia that is both highly reliable and economically feasible (4).

New biomarkers for preeclampsia have emerged due to significant progress in understanding its pathophysiology (5). It is now understood that angiogenic imbalance (6), characterized by elevated levels of soluble fms-like tyrosine kinase 1(sFlt-1), soluble endoglin (sEng), and endothelin-1 (ET-1) alongside reduced concentrations of placental growth factor (PlGF) in the mother's circulation, serves as a key link between this syndrome and reduced placental perfusion, particularly in early-onset preeclampsia. This imbalance is also related to maternal genetic predisposition in cases of late-onset preeclampsia (7). Consequently, sFlt-1, sEng, and PlGF are considered biomarkers for the diagnosis of preeclampsia (5,6).

Preeclampsia is recognized as a systemic disease characterized by generalized endothelial damage impacting almost all organs (8). PlGF is an angiogenic protein that is highly ex-

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 Submitted: 30. Jul. 2024. Revised: 15 Dec. 2024. Accepted: 17 Dec. 2024.

pressed during pregnancy and is closely associated with placental function. Research has shown that serum and urinary PlGF concentrations are decreased in women at the time of preeclampsia diagnosis and even before the onset of the syndrome (9). This deficiency is likely due to a combination of reduced PlGF expression and a decrease in free PlGF level due to binding with elevated sFLT-1 in women with preeclampsia (9).

The underlying mechanism of preeclampsia is thought to be impaired placentation due to inadequate trophoblastic invasion of the maternal spiral arteries. This has been documented both through histological studies and Doppler ultrasound examinations of the uterine arteries (10–12).

The use of Doppler studies of uterine arteries for predicting preeclampsia has gained considerable attention in recent years (13). Increased resistance to blood flow within the uterine arteries leads to an abnormal waveform, indicated by an elevated resistance index or pulsatility index, or the presence of unilateral or bilateral diastolic notch (14). The Fetal Medicine Foundation (FMF) has developed an algorithm incorporating maternal risk factors, mean arterial pressure, Doppler measurements of uterine arteries, and serum PlGF concentration. The primary advantage of this model, compared to others (15–17), is that it allows clinicians and researchers to select their own gestational age threshold to define a high-risk group that could potentially benefit from therapeutic intervention starting in the first trimester of pregnancy (18,19). Current evidence suggests that combining these biomarkers with Doppler examination of uterine arteries can provide the highest accuracy in predicting early onset preeclampsia (20).

Bosnia and Herzegovina (B&H), as a developing country, currently lacks comprehensive epidemiological data on preeclampsia. The country has reiterated its position against the implementation of population screening for this condition. Additionally, serum angiogenic biomarkers are not routinely collected in our healthcare facilities, resulting in a paucity of evidence regarding their efficacy as screening tools for preeclampsia. Moreover, there has been a noticeable absence of research conducted in our region to determine the most effective screening model for predicting preeclampsia. This lack of data underscores the need for further investigation to establish evidence-based screening protocols.

To assess whether measuring serum PlGF concentration and Doppler flow measurements in uterine arteries during the first trimester of high-risk pregnancies has clinical significance in predicting potential development of preeclampsia, we conducted a prospective screening study involving 173 high-risk pregnancies, between 11+ 0 and 13 + 6 weeks of gestation.

The aim of this study was to identify the most effective screening method for preeclampsia that would be generally accepted across healthcare institutions in B&H in order to enhance clinical outcome for pregnancies complicated by preeclampsia.

PATIENTS AND METHODS

Patients and study design

In this prospective screening study, 173 pregnant women in the first trimester of a high-risk pregnancy were included, with ages ranging from 18 to 43 years. All women were carrying singleton pregnancies and had at least one anamnestic risk factor for the development of preeclampsia, including nulliparity, previous preeclampsia, chronic hypertension, chronic kidney disease, thrombophilia, in vitro fertilization (IVF), family history of preeclampsia, preexisting diabetes, obesity, systemic lupus erythematosus (SLE), threatened miscarriage, intrauterine growth restriction (IUGR) in previous pregnancy, maternal age over 40 years (21). The women were admitted to the Department of Gynaecology and Obstetrics of Cantonal Hospital Zenica for routine ultrasound measurement of nuchal translucency as a marker for chromosomal abnormalities between 11 + 0 and 13 + 6 weeks of gestation, from December 2018 to November 2019.

The women were divided into two groups based on pregnancy outcome. The control group included 158 high-risk pregnant women who remained normotensive throughout their pregnancies. This control group matched the group of pregnant women with preeclampsia in terms of parity and gestational age. The group of pregnant women with preeclampsia included 15 high-risk individuals who developed preeclampsia during their pregnancies.

All women provided a written informed consent prior to their inclusion in the study. The cohort consisted exclusively of women of white European ancestry residing in B&H.

The research received ethical approval from the Ethics Committee of School of Medicine, University of Sarajevo, B&H (No. 02-3-4-2376/18, 2018).

Methods

We measured body mass index (BMI), blood pressure, haematological and biochemical parameters in all patients using standard diagnostic methods. Gestational age was calculated from the first day of the mother's last menstrual period and by measuring the Crown rump length as the most accurate method to establish or confirm gestational age (22).

Pregnancy outcome data were extracted from medical records maintained by the Department of Gynaecology and Obstetrics at the Cantonal Hospital Zenica, the fourth-largest maternity hospital in Bosnia and Herzegovina, which handles over 2,000 deliveries annually.

The diagnosis of preeclampsia was made based on the revised strict criteria and definition established by the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2018. This includes hypertension (systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation) alongside one or more of the following new-onset conditions occurring at or after 20 weeks of gestation: proteinuria, other maternal organ dysfunctions (including acute kidney injury, liver involvement, neurological complications, and haematological complications) and uteroplacental dysfunction (23).

A transabdominal ultrasound examination was performed on all women by the same physician. Each uterine artery was located laterally in relation to the uterus using colour Doppler, at the level of the internal os. Three consecutive waveforms were recorded, and the average of pulsatility index (PI) of both uterine arteries was recorded.

Blood samples were collected from all women between 11 + 0 and 13 + 6 weeks of gestation at the Transfusion Centre of

the Cantonal Hospital Zenica to determine serum PlGF concentration. Venipuncture of the cubital vein was used to collect 10 mL of venous blood into vacuette serum tubes containing coagulation activator. After allowing the blood to coagulate, samples were centrifuged at 1500g for 10 minutes and then frozen at -75 °C until the time of measurement.

PlGF concentration in serum was determined using a quantitative enzyme-linked immunosorbent assay (ELISA) (DAS APE ELITE A2 apparatus, Rome, Italy). Commercial ELISA kits for human PlGF (DRG Instruments GmbH, Marburg, Germany) were used, following the manufacturer's instructions.

The samples were thawed at room temperature immediately before analysis. None of the samples had been previously thawed and refrozen. The minimum detection level of the immunoassay for PlGF was <1.06 pg/mL. The inter-assay coefficient of variation for PlGF was 2.8% at PlGF of 50.5 pg/mL and 1.7% at PlGF of 478.6 pg/mL, while the intra-assay coefficient of variation for PlGF was 4.10% at PlGF of 45.8 pg/mL and 7.0% at PlGF of 421.4 pg/mL. All measurements were conducted at the University Clinical Centre Sarajevo, Department of Clinical Chemistry and Biochemistry.

Statistical analysis

The normality of data distribution was assessed using the Kolmogorov-Smirnov test. For data that did not follow a normal distribution, non-parametric tests were used. Pearson's linear correlation coefficient (r) was used for determining correlations, and Spearman's coefficient was employed for categorical variables (rho). To compare the values of uterine artery PI and PlGF between the study and control groups, the non-parametric Mann-Whitney U test was utilized. Multivariate linear regression was conducted to identify factors significantly affecting serum PlGF concentration and uterine artery PI values in the control group. The results were expressed as multiples of the median (MoM) values. A repeated analysis of variables was performed to assess the influence of gestational age on the measured variables. Receiver operating characteristic (ROC) curve analysis was used to determine the detection rate (DR) of each marker and their combinations for predicting subsequent onset of preeclampsia at a fixed false-positive rate (FPR). The results were presented in both tables and graphics with a statistical significance level set at $p<0.05$.

RESULTS

The pre-eclamptic group was characterized by higher maternal age and BMI. In the pre-eclamptic group compared with controls, more women had PE in their previous pregnancies and family history of PE. There were no significant differences in gestational age at enrolment and cigarette consumption between each group (Table 1).

In pregnant women with preeclampsia, the serum concentration of PlGF was significantly lower (14.06 pg/ml; 0.45 MoM) compared to the control group of healthy pregnant women (37.46 pg/ml; 1.19 MoM) (Figure 1). Additionally, the uterine artery pulsatility index (UtA-PI) was significantly higher in the preeclampsia group (1.73; 1.20 MoM) compared to the control group (1.44; 1.00 MoM) (Figure 2).

Correlation analysis revealed several significant relationships within the control group of healthy pregnant women. There was a positive correlation between serum PlGF concentration and gestational age ($r=0.725$; $p<0.05$), crown-rump length (CRL) ($r=0.887$; $p<0.05$), and cigarette consumption ($r=0.671$; $p<0.05$). Conversely, there was a negative correlation between PlGF and body mass index (BMI) ($r=-0.883$; $p<0.05$), as well as UtA-PI ($r=-0.6908$; $p<0.05$). A positive correlation was observed between UtA-PI and BMI ($r=0.746$; $p<0.05$), while negative correlations were found between UtA-PI and gestational age ($r=-0.635$, $p<0.05$), CRL ($r=-0.762$; $p<0.05$), and cigarette consumption ($r=-0.566$; $p<0.05$). A significant negative correlation was also noted between PlGF concentra-

Table 1. Clinical characteristics of two groups of women.

Characteristics	Controls (N=158)	Preeclampsia (N=15)
	Median (range)	
Age of the mother (years)	26.0 (18–39)	34.0 (17–43)*
CRL (mm)	60.10 (49.80–70.20)	50.80 (47.95–64.58)
	Median (IQR)	
BMI at 12 weeks (kg/m²)	24.30 (23.00-25.70)	26.70 (25.48-31.43)*
Gestational age (weeks)	12.60 (11.50-13.60)	12.00 (11.33-13.15)
	No (%) of women	
Nulliparity	119 (75.3)	8 (53.3)
Multiparity	39 (24.7)	7 (46.7)
Parity without previous pre-eclampsia	37 (94.9)	4 (57.1)
Parity with previous pre-eclampsia	2 (5.1)	3 (42.9)*
Cigarette consumption		
Non-smokers	127 (80.4)	10 (66,7)
Smokers	31 (19,6)	5 (33,3)
Family history of PE	0	1 (6.7)*

*Mann–Whitney U Test. Significance level *p<0.05; CRL, crown rump length; BMI, body mass index; PE, preeclampsia

tion and UtA-PI values (r=-0.6908; p<0.05) in the control group of healthy pregnant women (Table 2).

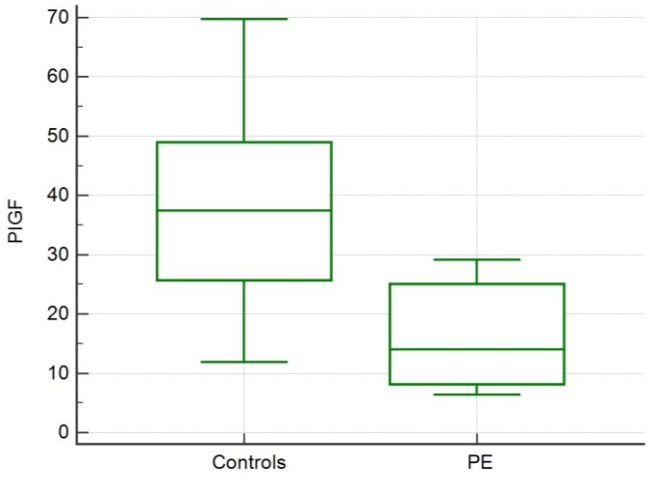

Figure 1. Median, interquartile range and range of placental growth factor (PlGF) at 11+0 to 13+6 weeks of gestation in 15 women who subsequently developed pre-eclampsia (PE) and in 158 controls

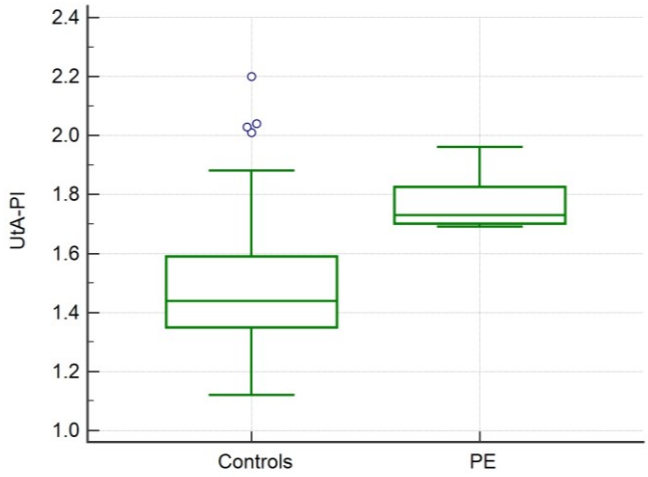

Figure 2. Median, interquartile range and range of uterine artery pulsatility index (UtA-PI) at 11+0 to 13+6 weeks of gestation in 15 women who subsequently developed pre-eclampsia and in 158 controls

The analysis of the univariate receiver operating characteristic (ROC) curve for each parameter yielded the following classification rates: maternal factors in the first trimester of high-risk pregnancies correctly classified 48.67% with a fixed rate of 5% FPR and 59.56% with a fixed rate of 10% FPR. The value of PlGF (MoM) in the first trimester of high-risk pregnancies correctly classified 64.24% of pregnant women with a fixed rate of 5% FPR and 70.25% with a fixed rate of 10% FPR. The value of UtA-PI (MoM) in the first trimester of high-risk pregnancies correctly classified 29.67% with a fixed rate of 5% FPR and 70.67% with a fixed rate of 10% FPR (Table 3).

Multivariate ROC curves (logistic regression for the combination of examined parameters) showed that the combination of PlGF and UtA-PI in the first trimester of high-risk pregnancies correctly classified 66.67% of pregnant women at a fixed rate of 5% FPR and 73.33% at a fixed rate of 10% FPR (Table 3).

The best screening performance was achieved by combining maternal factors with PlGF and UtA-PI, with a detection rate of 73.33% at a fixed rate of 5% FPR and 86.67% at a fixed rate of 10% FPR.

DISCUSSION

Our research approach closely resembles that used by many other studies aimed at identifying an optimal screening algorithm for the early detection of preeclampsia in pregnancy (24). The primary distinction of this study compared to others is that our cohort exclusively included high-risk pregnant women in their first trimester of gestation.

The results obtained align with those of previous studies (24,25), which have consistently indicated that serum PlGF levels are reduced not only during the clinical phase of preeclampsia but also in the first and second trimesters of pregnancies complicated by preeclampsia. While earlier studies attributed the discrepancies regarding the roles of pro- and anti-angiogenic markers in the first trimester of pregnancies to preeclampsia as a complication (25), recent research strongly supports the involvement of PlGF in the pathogenesis of preeclampsia and its potential as a biomarker for screening, particularly for early preeclampsia (25). It is evident that many studies consistently reported lower PlGF concentrations in the second and third trimesters of pregnancies complicated by preeclampsia, with a decreased PlGF level correlating with the severity of the condition (16,20,26). There is a significant re-

Table 2. Correlation analysis of placental growth factor (PlGF) and uterine artery pulsatility index (UtA-PI) with maternal factors (MF) in the control group of healthy pregnant women

	PLGF pg/mL		UtA-PI	
	rho	p	rho	p
Gestational age (weeks)	0.725	<0.05	-0.635	<0.05
CRL (mm)	0.887	<0.05	-0.762	<0.05
BMI (kg/m2)	-0.883	<0.05	0.746	<0.05
Cigarette consumption	0.671	<0.05	-0.566	<0.05

Rho, Spearman's correlation coefficient; p, significance level; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index; CRL, crown rump length; BMI, body mass index

Table 3. Performance of screening for pre-eclampsia by maternal factors (MF), placental growth factor (PlGF), uterine artery pulsatility index (UtA-PI) and by their combinations as shown by detection rate for the fixed false-positive rate (FPR) of 5% and 10% in screening

Screening test	DR (%) (95% CI))	
	FPR 5%	FPR 10%
Maternal factors*	48.67 (26.67–73.33)	59.56 (33.33–80.00)
PlGF MoM	64.24 (53.80–71.83)	70.25 (59.18–84.64)
UtA-PI MoM	29.67 (0.00–72.99)	70.67 (23.56–100.00)
PlGF MoM + UtA-PI MoM	66.67 (26.67–86.67)	73.33 (46.67–93.33)
MF+PlGF MoM+UtA-PI MoM	73.33 (40.00–93.33)	86.67 (60.00–100.00)

*Maternal factors: smoking, body mass index
DR; detection rate, 95% CI: 95% confidence intervals; MoM; multiples of the median

duction in PlGF concentrations during the second trimester of pregnancy (27–29). Furthermore, PlGF concentration reduction is also found to occur as early as the first trimester (25,30). The serum concentration of PlGF level gradually increases during gestation and is significantly higher in pregnant women who smoke cigarettes (25,31). Our study, indicated that foetal CRL, maternal weight, and cigarette smoking in the control group significantly influenced PlGF level. For the uterine artery PI, gestational age and foetal CRL were found to significantly impact its value.

The results of our study indicated reduced concentration of placental growth factor (PlGF) in pregnant women with increased BMI, which is in line with earlier findings (25). Additionally, the influence of factors such as gestational age, maternal weight, ethnicity, cigarette smoking, conception method, parity, and pre-existing diabetes on serum PlGF concentrations during the first trimester of pregnancy was described earlier (32,33) As gestational age increases, PI and resistance index (RI) of the uterine arteries decrease. This change is thought to occur due to a reduction in resistance within the uterine blood vessels, a result of trophoblastic invasion (34). Mean PI value of the uterine artery declined during the third trimester up to the 34th week (34). Conversely, various authors, have confirmed that PI values in the uterine arteries are influenced by ethnicity and tend to be higher in women with elevated BMI (32).

Doppler measurements of the uterine artery during the second trimester possess high sensitivity for predicting preeclampsia in low-risk population but, the positive predictive value is low (35). This low predictive value can complicate screening efforts within low-risk groups. Our research, which focused on a high-risk population for the development of preeclampsia (although it was a relatively small sample), indicated that Doppler measurements of the uterine artery yielded a slightly higher predictive value (29.67%) compared to low-risk population. However, the isolated use of PlGF for predicting preeclampsia is not effective, as it has a low sensitivity of 32% and a false positive rate of 5%. The outcome of preeclampsia screening studies vary; most were conducted in the first trimester and they are often limited by the small sample sizes (17,27,28). A combination of obstetric history, biophysical markers, and biochemical markers could detect approximately 91% of early preeclampsia cases with a fixed false positives rate of 5% (16).

The Fetal Medicine Foundation's screening model demonstrates detection rates of 90% for early preeclampsia and 75% for preterm preeclampsia, accompanied by a false-positive rate of 10%. This screening performance markedly surpasses that of traditional methods reliant solely on maternal risk factors (36).

Our research supports FMF triple test findings and demonstrates that the best screening performance for preeclampsia in high-risk pregnancies during the first trimester is attained by combining maternal factors with PlGF and uterine artery PI with a detection rate of 86.67%.

It is important to acknowledge several limitations inherent in our study, notably the moderate sample size constrained by limited resources and the single-centre design. The conventional approach to screening, which relies on a checklist of maternal risk factors, has demonstrated limited predictive accuracy and is no longer adequate for effectively forecasting preeclampsia.

Our research should help facilitate the establishment of a comprehensive screening program across health institutions in Bosnia and Herzegovina. This initiative is geared towards the early identification of high-risk pregnant women, ultimately enhancing the management and outcomes of pregnancies affected by preeclampsia.

AUTHOR CONTRIBUTIONS

Conceptualization, J.H., B.M., A.G. and E.B.Š.; Data curation, J.H. and A.G.; Formal analysis, J.H.; Funding acquisition, J.H.; Investigation, J.H., B.M., A.G., H.Š.H. and E.B.Š.; Methodology, J.H., B.M. and A.G.; Project administration, J.H.; Resources, J.H. and A.G.; Software, J.H.; Supervision, J.H. and B.M.; Validation, J.H.; Visualization, J.H. and A.G.; Writing – original draft, J.H., A.G. and H.Š.H.; Writing – review & editing, J.H. and A.G. All authors have read and agreed to the published version of the manuscript.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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