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Predictive value of extremely low PAPP-A, free βhCG and extremely high mean uterine artery pulsatility index in the first trimester for fetal growth restriction

Prediktivna vrednost izuzetno niskih nivoa PAPP-A, slobodnog βhCG i izuzetno visokog srednjeg pulzatornog indeksa uterinih arterija u prvom trimestru trudnoće u proceni nastanka intrauterusnog zastoja u rastu ploda

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Abstract

Background/Aim. Adverse pregnancy outcomes such as preeclampsia (PE), placental abruption (PA), fetal intrauterine growth restriction (IUGR) and stillbirth could be recognized by prenatal screening. The objective of this study was to predict IUGR by using first-trimester extremely low pregnancy-associated plasma protein-A (PAPP-A), extremely low free beta-human chorionic gonadotropin (free βhCG) levels, and extremely high Pulsatility-index (PI) of uterine arteries, as single and combined predictors for IUGR development. **Methods.** This was a prospective first-trimester study analyzing singleton pregnancies at 11–13+6 weeks' gestation who underwent routine first-trimester screening at the Department of High Risk Pregnancy of the Clinic for Gynecology and Obstetrics „Narodni front“, University of Belgrade, Serbia. First-trimester screening for PAPP-A, free βhCG, and PI was performed in nulliparous, normotensive women with extremely low PAPP-A (PAPP-A ≤ 0.52 unit multiple of median – MoM) and/or extremely low free βhCG (free βhCG ≤ 0.56 MoM) and/or extremely high PI (PI ≥ 2.52). **Results.** Of 85 pregnant women included in the final analysis, 14 (16.5%) developed IUGR. PAPP-A ≤ 0.52 MoM and PI ≥ 2.52, as single categorical variables, found to be with high predictable values for IUGR development (odds ratio – OR = 3.064, 95% confidence interval – CI= 0.634-14.810, $p = 0.046$, and OR = 2.129, 95% CI = 0.449–10.713, $p = 0.021$, respectively). Furthermore, the receiver operating characteristic (ROC curve identified PAPP-A and PI as continuous variables to be significant predictors of IUGR (area under curve – AUC = 0.671, 95% CI = 0.521−0.820, $p = 0.045$, and AUC = 0.744, 95% CI = 0.587−0.902, $p = 0.004$, respectively). **Conclusion.** The present study suggests that the first trimester extremely low PAPP-A and increased Doppler-PI levels are single predictors of IUGR. Described model could be used in a routine daily clinical practice in resource limited settings where other parameters are not available for the prediction of IUGR development.

Key words:
pregnancy trimester, first; fetal growth retardation; ultrasonography, doppler, color; pregnancy-associated plasma protein-a; chorionic gonadotropin, beta subunit, human.

Apstrakt

Uvod/Cilj. Neželjeni ishodi trudnoće kao što su preeklampsija, abrupcija placente i zaostajanje rasta fetusa i mrtvorođenost mogu biti prepoznati u okvirima prenatalnog skrininga. Cilj ove studije bio je ispitati mogućnost predviđanja pojave intrauterusnog zastoja u rastu ploda (IUGR) pojedinačnom i kombinovanom upotrebom izuzetno niskih vrednosti plazma proteina A povezanog sa trudnoćom (PAPP-A), izuzetno niskih vrednosti slobodne beta subjedinice humanog horionskog gonadotropina (free βhCG), kao i ekstremno visokih srednjih vrednosti doplerskog pulsatilnog indeksa (PI) uterinih arterija u prvom trimestru trudnoće. **Metode.** Prospektivnom studijom analizirane su jednoplodne trudnoće starosti 11–13+6 nedelja gestacije u okviru rutinskog skrininga na Daunov sindrom. Studija je rađena na Odeljenju za visoko rizične trudnoće, univerzitetske Ginekološko-akušerske klinike

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„Narodni front“ u Beogradu, Srbija. Skrining prvog trimestra je obuhvatao analizu: PAPP-A, *free* βhCG i PI kod normotenzivnih nulipara, kod kojih su zabeležene ekstremno niske vrednosti PAPP-A (PAPP-A ≤ 0,52 *unit multiple of median* – MoM) i/ili ekstremno niske vrednosti *free* βhCG (*free* βhCG ≤ 0,56 MoM) i/ili ekstremno visoke vrednosti PI (PI ≥ 2,52). **Resultati.** Kod 85 trudnica uključenih u konačnu analizu, kod njih 14 (16,5 %) je zabeležena pojava IUGR ploda. PAPP-A ≤ 0,52 MoM i PI ≥ 2,52, kao pojedinačne kategorijske varijable, su prepoznate kao varijable sa visokim prediktivnim značajem za pojavu IUGR (*odds ratio* – OR = 3,064, 95% *confidence* interval – CI = 0,634 – 14,810, p = 0,046 i OR = 2,129, 95% CI = 0,449 – 10,713, p = 0,021). Daljom analizom, *receiver operating characteristic* (ROC) – kriva je identifikovala PAPP-A i PI, kao kontinualne varijable, koje su značajni prediktori za pojavu IUGR ploda (*area under the curve* – AUC = 0,671, 95% CI = 0,521 – 0,820, p = 0,045 i AUC = 0,744, 95% CI = 0,587 – 0,902, p = 0,004). **Zaključak.** Ova studija sugeriše da u prvom trimestru trudnoće ekstremno niske vrednosti PAPP-A i ekstremno visoke srednje vrednosti Doppler-PI uterinih arterija mogu biti značajni parametri za predviđanje pojave IUGR ploda. Opisani model bi mogao da se primeni u svakodnevnoj kliničkoj praksi u zemljama sa ograničenim mogućnostima, kada ostali parametri za predviđanje pojave IUGR ploda nisu dostupni.

Ključne reči:
trudnoća, prvi trimestar; fetus, zaostajanje u rastu; ultrasonografija, dopler kolor; plazma, protein a, udružen sa trudnoćom; horionski gonadotropin, beta subjedinica, humani.

Introduction

In the recent studies it has been shown that the placenta is a new field of prenatal screening and diagnosis. Adverse pregnancy outcomes such as preeclampsia (PE), placental abruption (PA), fetal growth restriction (IUGR) and stillbirth could be recognized by prenatal screening. Mentioned adverse pregnancy outcomes occur in 5% to 10% of pregnancies worldwide [1].

The function of the placenta is based on an adequate trophoblastic invasion into the maternal circulation during the first and second trimester. Aberrations of this invasion may lead to a high resistance vascularization, hypo-perfusion of placental and chorionic villi, deposition of fibrin and increased apoptosis process [2]. Histological characteristics of the placenta changes correspond with the appearance of the adverse pregnancy outcomes, thus decrease in placental function could also decrease production of pregnancy-associated plasma protein A (PAPP-A) [3–5]. On the other hand, impaired placental perfusion in pregnancies with PE, PA, IUGR and/or stillbirth has been provided by Doppler studies where pulsatility index (PI) of the uterine arteries were increased [6–8].

Since there are no currently recommended models for prediction of IUGR, our primary objective was to evaluate extremely low levels of maternal serum PAPP-A, extremely low levels of free βhCG and extremely high levels of mean Doppler uterine PI in the first trimester, as an independent single or combined predictors for development of IUGR.

Methods

This prospective, first-trimester study analyzed singleton pregnancies during 11–13+6 gestation weeks. The study was performed at the Department of High Risk Pregnancy of the Clinic of Gynecologyand Obstetrics «Narodni front», University of Belgrade, Serbia. Written consent was obtained from all participants and the study was approved by the Ethics Committee, Faculty of Medicine, University of Belgrade, Serbia.

General inclusion criteria

All pregnancies underwent routine first-trimester screening. Combined first-trimester screening comprised a combination of maternal age, fetal nuchat translucency (NT) thickness, maternal serum free ßhCG and PAPP-A in a single point of time [9–12]. The pregnancy was dated according to the last menstrual period. In the case that the date was uncertain or the estimated gestation by crown–rump length (CRL) was discordant by more than 7 days from the estimated gestation, the CRL was used to date the pregnancy.

Inclusion criteria in the study were following: all nulliparous, normotensive pregnant women with singleton pregnancy. Included subjects were routinely screened for Down syndrome and they were screened for ultrasound markers such as: fetal crown-rump length and nuchal translucency, as well as for maternal first trimester biochemistry analysis: PAPP-A and free βhCG. Only subjects with all mentioned parameters were included in the final analysis.

Exclusion criteria were following: multiparous women, women with multiple gestations and pregnancies with a major fetal chromosomal or structural anomaly. Pregnancies with no fetal abnormality findings at the 11–13 weeks scan and/or the 20–23 weeks scan which resulted in termination, miscarriage or stillbirth, as well as those lost to follow-up were also excluded.

In order to be included in a final analysis, besides fulfilling all general inclusion criteria, patients had to have at least one out of three following criteria: extremely low maternal serum PAPP-A levels, extremely low free βhCG levels and/or extremely high mean uterine artery PI index. Maternal serum samples for PAPP-A and free βhCG were assayed with the Kryptor software package analyzer and results were expressed in the multiple of the median (moM) unit, while the uterine artery mean PI measurements were performed by transabdominal ultrasound (US) with 3–7.5 MHz curvilinear transducers by the same experienced fetal medicine specialists. In order to do so, transabdominal US (e.g. Voluson 730 Expert series, GE Healthcare, Kretzttechnik, Zipf, Austria) was

performed to measure fetal crown rump lenght (CRL) and NT thickness. Pulsed wave Doppler was used with the sampling gate set at 2 mm to cover the whole vessel with angle of insonation was less than 30°. When three similar consecutive waveforms were obtained of the PI measurement, the mean PI of the right and left arteries was calculated [13]. In each pregnancy the mean uterine artery PI were expressed as a multiple of the expected median calculated from The Fetal Medicine Foundation's reference limits for singleton pregnancies after correction for maternal ethnicity, body mass index (BMI) and gestational age [14, 15]. The extreme PAPP-A, free βhCG and mean PI index cut-off values were as follows: first-trimester PAPP-A ≤ 0.52 MoM [16], first-trimester free βhCG ≤ 0.56 MoM [13] and mean PI ≥ 2.52 [13–15], respectively. All patients who fullfield inclusion criteria were followed by intensive antenatal care such as: growth scans, blood pressure measurements and biochemical analysis at 24, 28, 32 and 36 gestational weeks.

Maternal history

Patients were asked to complete a questionnaire about maternal age, ethnicity, smoking status during pregnancy, spontaneous or assisted conception such as usage of ovulation drugs and/or *in vitro* fertilization. Patients were also asked about their medical history, in particular about diabetes mellitus, antiphospholipid syndrome, trombophilia, human immuno-deficiency virus infection and sickle cell disease. They were also asked about concomitant medication usage of antidepressant, antiepileptic, anti-inflammatory drugs, aspirin, beta-mimetic, insulin and thyroxin. One part of the questionnaire was focused on parity (multiparous or nulliparous), obstetric history if any and family history (mother).

Outcome measure

In patients included in the final analysis, patients were followed-up until the end of pregnancy and data on pregnancy outcome were recorded, including adverse pregnancy outcomes such as PE, PA and IUGR. For this particular study we were focused only on pregnancies with IUGR outcome. IUGR was defined as an estimated weight ≤ 10th centile of a given population at the same gestational age [17].

Statistical analysis

Data were presented as numer (percentage) or mean ± SD, depending on the data type. Pearson's χ^2 or Fisher's exact tests were used for the comparison of categorical variables and Student's *t*-tests were used for continuous variables. Univariate analysis was initially performed to determine variables with a significant association with IUGR. Backward stepwise logistic regression was used to determine the combined prediction model for IUGR. Receiver operating characteristic (ROC) analysis was performed to assess cut-off values of markers that best predict adverse event in pregnancy. Defined level of significance was $p < 0.05$. Statistical analyses were performed using SPSS 20.0 (IBM Corporation) software package.

Results

The 11,326 singleton pregnancies underwent routine first trimester screening at 11–13+6 weeks of gestation. They comprised 9,944 pregnancies ending in a live birth without fetal abnormality, 1,030 pregnancies with abnormal fetuses (566 chromosomal abnormalities and 464 structural defects) and 354 pregnancies were lost to follow-up (Figure 1).

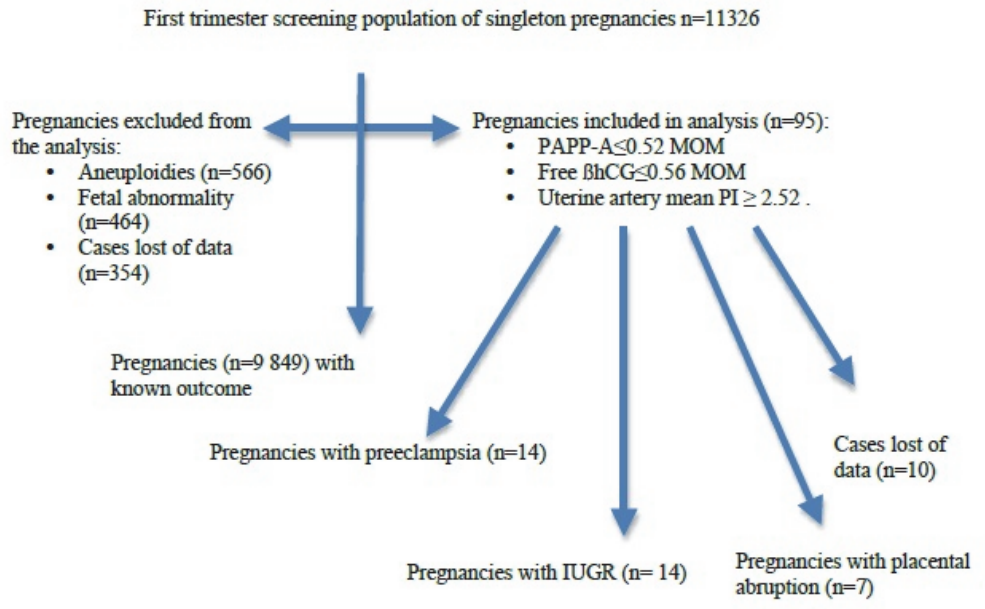

Fig. 1 – Flow-chart of the study population.

PAPP-A – pregnancy-associated plasma protein A; fβhCG – free beta-human chorionic gonadotropin; PI – pulsatility index; MoM – unit multiple of median; IUGR – intrauterine growth restriction.

In the final analysis 85 patients, all Caucasians, all normotensive, were included in the study. IUGR as an adverse pregnancy outcome, has been diagnosed in 14 (16.47%) patients. Baseline patients' characteristics are shown in Table 1.

Association between first trimester maternal parameters (PAPP-A, free-βHCG and uterine artery Doppler PI) using various thresholds for all three variables are shown in Table 2. Overall percentage of correctly classified data was between 81.2% and 85.9%. PAPP-A, as continuous variable, tended to be significantly associated with IUGR ($p = 0.060$), which was not a case with PAPP-A < 0.52 MoM, as categorical variable ($p = 0.164$). However, PI, as continuous variable, was not significantly associated with IUGR development ($p = 0.108$), with high odds ratio (OR) for development of IUGR. Also, PI ≥ 2.52 MoM, as a categorical variable, was also not found to be significantly associated with IUGR ($p = 0.332$). There was no statistically significant association between free βHCG either as continuous or categorical variable with IUGR across all defined thresholds ($p = 0.357$ and $p = 0.494$, respectively).

Backward stepwise logistic regression used to determine the combined prediction model including categorical variables PAPP-A ≤ 0.52 MoM together with PI ≥ 2.52 was found not to be significantly associated with IUGR development ($p = 0.224$) (Table 3). Overall percentage of correctly classified data was 83.5%.

Table 1

Baseline patient's characteristics

Characteristics	IUGR development		*p*
	Yes (n = 14)	No (n = 71)	
Maternal age (year), mean ± SD	31 ± 3.74	31.14 ± 4.33	0.910
BMI (kg/m^2), mean ± SD	29.95 ± 3.35	26.70 ± 4.34	< 0.01
Smoking, n (%)			
yes	9 (37.5)	15 (62.5)	< 0.01
no	5 (8.2)	56 (91.8)	
DM, n (%)			
yes	2 (33.3)	4 (66.7)	0.256
no	12 (15.2)	67 (84.8)	
IVF, n (%)			
yes	1 (25)	3 (75)	1.000
no	13 (16)	68 (84)	
PAPP-A (MoM), mean ± SD	0.44 ± 0.16	0.66 ± 0.42	< 0.05
PI, mean ± SD	2.56 ± 0.25	2.41 ± 0.30	< 0.01
free βHCG (MoM) , mean ± SD	0.51 ± 0.25	0.64 ± 0.47	0.141

IUGR – intrauterine growth restriction; BMI – body mass index; SD – standard deviation; DM – diabetes mellitus; IVF – *in vitro* fertilisation; PAPP-A –pregnancy-associated plasma protein-A; PI – pulsatility index; free βHCG – free beta-human-chorionic-gonadotropin; MoM – unit multiple of median.

Table 2

Univariate logistic regression analysis of the first-trimester biomarkers and uterine artery Doppler findings and their association with IUGR

Parameters	*p*	OR (95% CI)	R^2
PAPP-A	0.060	0.043 (0.002–1.138)	0.117
PAPP-A < 0.52 MoM	0.164	3.064 (0.634–14.810)	0.046
PI	0.108	13.765 (0.564–33.668)	0.075
PI ≥ 2.52	0.332	2.192 (0.449–10.713)	0.021
Free-βHCG	0.357	0.361 (0.041–3.156)	0.024
Free βHCG ≤ 0.56 MoM	0.494	1.745 (0.353–8.620)	0.010

IUGR – intrauterine growth restriction; PAPP-A – pregnancy-associated plasma protein-A; PI – Pulsatility index; βHCG – beta-human chorionic-gonadotropin; MoM – unit multiple of median; OR – odds ratio; CI – confidence interval.

Table 3

Backward stepwise logistic regression of combined first-trimester PAPP-A and uterine artery Doppler findings and their association with IUGR

Parameters	*p*	OR (95% CI)	R^2
PAPP-A ≤ 0.52 MoM + PI ≥ 2.52	0.224	2.171 (0.622–7.576)	0.031

PAPP-A – pregnancy-associated plasma protein-A; PI – Pulsatility index; IUGR – intrauterine growth restriction; OR – odds ratio; CI – confidence interval; MoM – unit multiple of median.

Area under curve (AUC) of the ROC curve was performed to assess cut-off value of studied variables that best predicts IUGR, as adverse pregnancy outcome. The model identified first- trimester PAPP-A [AUC = 0.671, 95% confidence interval (CI) = 0.521–0.820; $p = 0.045$) and PI (AUC = 0.744, 95% CI = 0.587–0.902; $p = 0.04$) to be significant predictors for IUGR development, and first trimester free βHCG (AUC = 0.375, 95% CI = 0.215–0.536; $p = 0.142$) to be a non-significant predictor for IUGR (Figure 2).

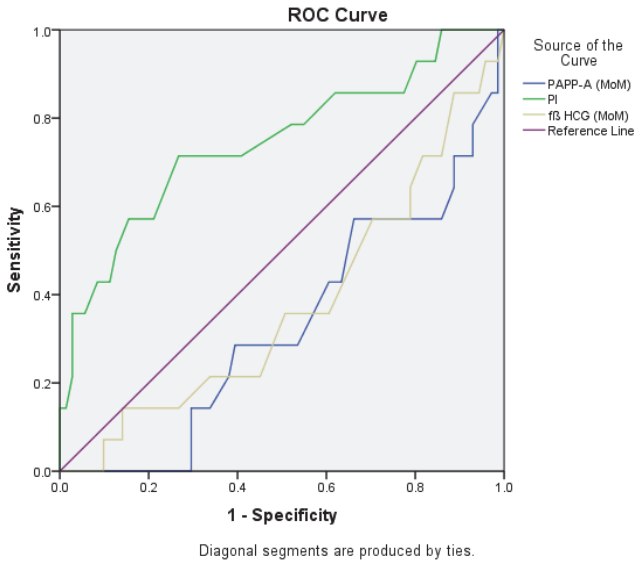

Fig. 2 – Receiver operating characteristic (ROC) curve for the prediction of IUGR using first- trimester PAPP-A, PI of uterine arteries and free βHCG.

IUGR – intrauterine growth restriction; PAPP-A – pregnancy associated plasma protein-A; PI – pulsatility index; fβHcg – free beta-human chorionic gonadotropin; MoM – unit multiple of median.

Discussion

The etiology of IUGR has not been completely understood. However, impaired trophoblastic invasion of spiral arteries and the lack of placentation are highly marked in pregnancies destined to develop IUGR [12]. It has been also shown that low levels of PAPP-A, which is a protease for insulin-like growth factor (IGF) binding protein-4 (IGFBP-4), are associated with higher IGFBP-4 and lower IGF [16]. Therefore, IGF influences trophoblast invasion and may have a role in PE as well as IUGR development [18].

The findings of this prospective study in nulliparous women with extreme levels of at least one out of three risk parameters for fetal IUGR have demonstrated that the first trimester low levels of maternal serum PAPP-A and first trimester high levels of uterine Doppler PI are associated with an increased risk for subsequent development of fetal IUGR. Our study also demonstrated no association between low levels of maternal serum free β-HCG and development of fetal IUGR. The same results were presented in several other studies [13, 18–21].

Our results are also consistent with the results of the FASTER Trial Research Consortium study which demonstrated that women with low first-trimester PAPP-A levels were at significantly increased risk for obstetric complications and consequently adverse obstetric outcomes such as fetal IUGR [19]. Low first-trimester PAPP-A levels used in the predictive model for detection of fetal IUGR without PE, had detection rate of 73% with false positive rate of 10% [20]. In addition, a significant increase in the relative risk of fetal IUGR development is associated with a further decline of PAPP-A [21].

Important evidence for impaired placental perfusion in pregnancies destined to develop fetal IUGR has been provided by Doppler studies of increased pulsatility index (PI) of uterine arteries in first trimester. A number of first trimester studies using single abnormal uterine artery Doppler PI high levels demonstrated an overall sensitivity of 25% for the prediction of IUGR improving to about 60% for its development [20–24]. In our study extremely high levels of mean uterine artery Doppler evaluation (e.g. PI ≥ 2.52), as a single predictor, showed a high relative risk for fetal IUGR development, even though with no statistical significance. First-trimester mean uterine artery Doppler PI, was found to be significantly associated with IUGR development [23]. Recently, Cruz-Lemini et al. [25] demonstrated a significant increase in the first-trimester uterine artery Doppler PI in patients who developed both early and late-onset preeclampsia compared to controls.

In our study, multivariate prediction model combining the first-trimester extremely high levels of mean uterine artery Doppler PI together with the first-trimester extremely low levels of PAPP-A significantly improve predictive capability and efficiency for IUGR. Single addition of above mentioned first- trimester maternal biochemical and hemodynamic markers could improve the prediction of IUGR, but limitation according to low sensitivity and specificity still exist.

While waiting for the specific predictive model for fetal IUGR development, alternative strategies could possibly focus on the early identification of high-risk pregnancies and undertaking of the necessary measures to improve placentation. Algorithms combining maternal characteristics and biophysical and biochemical tests at 11–13 weeks could identify most pregnancies delivering preterm IUGR neonates in the presence or absence of PE [20, 24].

This study has the limitation of being a single-center study with a small sample size. The important aspect of this study was to demonstrate the capability of extremely low levels of maternal serum PAPP-A and free βhCG used for Down syndrome screening in the first trimester, and extremely high levels of Doppler uterine PI in the first trimester, as a single and combined predictors for IUGR development. Evaluation of high-risk pregnant women for PE and/or IUGR as a part of a routine perinatology clinical practice in the first trimester by using maternal serum PAPP-A and uterine artery PI is efficient model with no additional costs, which might be important in the resource limited settings.

Conclusion

The present study suggests that the first-trimester extremely low levels of maternal serum PAPP-A and Doppler PI are single predictors of IUGR. Described model could be used in a routine daily clinical practice in resource limited settings where other parameters are not available for the prediction of IUGR development.

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