CEOG Clinical and Experimental Obstetrics & Gynecology

Prediction of preeclampsia using extreme first-trimester PAPP-A, free βhCG and uterine artery Doppler in resource limited settings

R. Lukic[1], M. Djukic[1], I. Soldatovic[2], N. Karadzov Orlic[1], D. Ardalic[1], G. Dragovic[3], Z. Mikovic[1]

[1] Gynecology and Obstetrics Clinic "Narodni Front", School of Medicine, University of Belgrade, Belgrade
[2] Institute for Biomedical Statistics, School of Medicine, University of Belgrade, Belgrade
[3] Institute for Pharmacology, Clinical Pharmacology and Toxicology, School of Medicine, University of Belgrade, Belgrade (Serbia)

Summary

Purpose of investigation: The objective of this study was to predict preeclampsia using extreme-low first-trimester pregnancy-associated-plasma-protein-A-(PAPP-A), extreme-low free-beta-human-chorionic-gonadotropin-(free-βhCG)-levels, and extreme-high pulsatility-index (PI) of uterine arteries, as single and combined predictors for preeclampsia development in resource-limited-settings. *Materials and Methods:* First-trimester screening for PAPPA, free-βhCG, and PI was performed between 11-13^{+6} gestation-weeks in nulliparous, normotensive women with singleton pregnancy with extremely-low PAPP-A (PAPP-A ≤ 0.52 MoM), extremely-low free-βhCG (free-βhCG ≤ 0.56 MoM) and extremely-high PI (≥ 2.52). *Results:* Of 85 pregnant women, 14 (16.5%) developed preeclampsia. PAPP-A ≤ 0.52 MoM and PI ≥ 2.52, as a single categorical variables, found to be with high OR for preeclampsia-development (OR = 7.07, 95% CI = 0.873−57.204, $p = 0.067$; OR = 5.098, 95% CI = 0.625−41.575, $p = 0.128$, respectively). The ROC-curve identified PAPP-A and PI as continuous variables to be significant predictors of preeclampsia (AUC = 0.864, 95% CI = 0.750−0.978, $p = 0.000$; AUC = 0.762, 95% CI = 0.598−0.925, $p = 0.002$, respectively). A prediction model for preeclampsia including PAPP-A ≤ 0.52 MoM + PI ≥ 2.52 was found to be significantly associated with preeclampsia ($p = 0.027$). *Conclusion:* The present study suggests that the first-trimester extreme low-PAPP-A and increased Doppler-PI levels have significant predictive capability for preeclampsia.

Key words: Preeclampsia prediction; First trimester; Resource limited settings.

Introduction

Preeclampsia is known as a major factor of perinatal morbidity and mortality worldwide. Given the high prevalence of preeclampsia, early identification of pregnant women at high risk for developing this disorder could improve antenatal surveillance and would enable use of preventive strategies [1]. Women at risk could be possibly identified for preeclampsia risk using clinical and history data, such as parity, body mass index, impaired glycoregulation, previous preeclampsia or chronic hypertension. However, the usage of mentioned screening model will detect only 30% of patients who will really develop preeclampsia [2].

Maternal serum pregnancy-associated plasma protein A (PAPP-A) levels and free beta human chorionic gonadotropin (free βhCG) levels, used for routine Down syndrome screening together with maternal age and other ultrasound parameters, have also been suggested as a part of the first-trimester predictive model of preeclampsia [3-4]. The association of first-trimester low levels of PAPP-A with preeclampsia have already been demonstrated in a number of studies [5-7], while correlation between the first-trimester, low levels of free βhCG with preeclampsia have been confirmed in a very few studies [5]. On the other hand, a number of first-trimester maternal serum hormones, such as placental growth factor (PlGF), placental protein 13 (PP13), inhibin A, ADAM 12, and many others have also been assessed as early predictors of preeclampsia [8-11]. In addition, the important evidence for impaired placental perfusion in pregnancies destined to develop preeclampsia was provided by Doppler studies of increased pulsatility index (PI) of uterine arteries in the first trimester [12]. Recently, Poon *et al.* created significant predictive model for development of preeclampsia combining maternal characteristics with first-trimester serum analytes (e.g. PAPP-A and PlGF), hemodynamic parameters (e.g. uterine Doppler PI) and mean arterial pressure (MAP) [13]. Due to the shortages, the majority middle-income countries, such as Serbia, cannot use a number of the suggested first-trimester biomarkers in order to provide similar preeclampsia risk-predictive model. Therefore, the objective of this study was to evaluate extreme low levels of maternal serum PAPP-A and free βhCG used for routine Down syndrome screening in first trimester and extreme high levels of Doppler uter-

Revised manuscript accepted for publication January 25, 2016

Table 1. — *Baseline patients characteristics.*

		Preeclampsia development		*p*-value
		Yes (n=14)	No (n=71)	
Maternal age (years)		32.14±3.42	30.92±4.35	0.322
BMI (kg/m^2)		31.28±3.56	26.44±4.06	<0.01
Smoking	Yes	4 (16.7%)	20 (83.3%)	1.000
	No	10 (16.4%)	51 (83.6%)	
DM	Yes	3 (21.43%)	3 (4.23%)	0.054
	No	11 (13.9%)	68 (86.1%)	
IVF	Yes	2 (50.0%)	2 (50.0%)	0.125
	No	12 (14.8%)	69 (85.2%)	
PAPP-A (MoM)		0.33±0.11	0.68±0.41	<0.001
PI		2.61±0.21	2.40±0.30	<0.001
Free βHCG (MoM)		0.61±0.35	0.62±0.46	0.708

*Data are presented as n (%) or mean±sd.

Table 2. — *Univariate logistic regression analysis of first trimester biomarkers and uterine artery Doppler findings and their association with pre-eclampsia.*

Parameters	*p*-value	OR (95% CI)	R^2
PAPP-A	<0.001	3.803E-7 (OE-7-0.0012)	0.470
PAPP-A<0.52 MoM	0.067	7.065 (0.873-57.204)	0.103
PI	0.051	345.9 (0.836-143153)	0.170
PI ≥ 2.52	0.128	5.098 (0.625-41.575)	0.067
Free βHCG	0.932	0.943 (0.246-.618)	0.001
Free βHCG ≤ 0.56 MoM	0.462	0.614 (0.168-2.250)	0.010

Table 3. — *Backward stepwise logistic regression of combined first trimester PAPP-A and uterine artery Doppler findings and their association with preeclampsia.*

Parameters	*p*-value	OR (95% CI)	R^2
PAPP-A ≤0.52 MoM + PI ≥2.52	0.027	5.83 (1.217-27.297)	0.125

ine PI in the first trimester, as an independent single and combined predictors for development of preeclampsia in resource limited settings.

Materials and Methods

This was a prospective study of pregnant women booked for the antenatal care from March 1st, 2012 to December 31st, 2014. First-trimester screening was performed between 11-13^{+6} weeks of gestation. All nulliparous, normotensive pregnant women, older than 18 years with singleton pregnancy routinely screened for Down syndrome (e.g. ultrasound markers: fetal crown-rump length, and nuchal translucency together with maternal biochemistry: PAPP-A and free βhCG) have been included in the study. Multiparous women, women with multiple gestations, and pregnancies with a major fetal chromosomal or structural anomaly, were excluded from further statistical analyses.

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 extremely high mean uterine artery PI index. The extreme PAPP-A, free βhCG, and mean PI index cut-off values were first-trimester PAPP-A ≤ 0.52 MoM [14], first-trimester free βhCG ≤ 0.56 MoM [15], and mean PI ≥ 2.52 [14, 16], respectively. Groups of 85 patients who fulfilled all inclusion criteria were followed for preeclampsia. Preeclampsia was defined as systolic blood pressure of >140 mmHg and/or diastolic blood pressure > 90 mmHg on two or more occasions four hours apart, developing with proteinuria of 0.3 mg or more in a 24-hour urine specimen occurring after 20 weeks of gestation in a woman with previously normal blood pressure [17].

At the time of inclusion in the final analysis, pregnant women answered a standardized questionnaire on maternal age, ethnic origin, smoking status during pregnancy, and other medical conditions (e.g. diabetes mellitus, blood pressure, etc.). The maternal weight and height were measured and BMI was calculated. Maternal serum samples for PAPP-A and free βhCG were assayed with the PRISCA software package analyzer and results were expressed as MOM, adjusted for gestational of age, ethnicity, maternal weight, insulin-dependent diabetes, smoking, and *in vitro* fertilization (IVF) history. Ultrasound (US) examinations were performed routinely at 11-13^{+6} weeks of gestation including standardized transabdominal ultrasound Doppler examination (REFF FMF) using 5.2 MHz curvilinear probe in all patients included in the study. Uterine artery mean PI measurements were performed by the same experienced fetal medicine specialists. Written consent for participation was obtained from all participants and the study was approved by the Ethics Committee, School of Medicine, University of Belgrade, Serbia.

Data are presented as count (percentage) or mean ± sd (min-max), depending on the data type. Pearson chi-squared 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 preeclampsia. Backward stepwise logistic regression was used to determine the combined prediction model for preeclampsia. ROC analysis was performed to assess cut-off values of markers that best predict adverse event in pregnancy. Statistical analyses were performed using SPSS 20.0 software package.

Results

There were 85 patients, all Caucasians, and all normotensive, included in the study. Preeclampsia as an outcome, was diagnosed in 14 patients (16.47 %). 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 83.5% and 88.2%.

PAPP-A, as continuous variable, was found to be significantly associated with preeclampsia ($p < 0.001$). While, PAPP-A ≤ 0.52 MoM, as categorical variable, was found to be very close to be significantly associated with preeclampsia ($p = 0.067$). While PI, as continuous variable, was found to be significantly associated with preeclampsia development ($p = 0.05$). In contrast with this, PI ≥ 2.52 MoM, as a categorical variable, with even higher OR for development of preeclampsia was not found to be significantly associated with preeclampsia ($p = 0.128$). There was no statistically significant association between free βhCG,

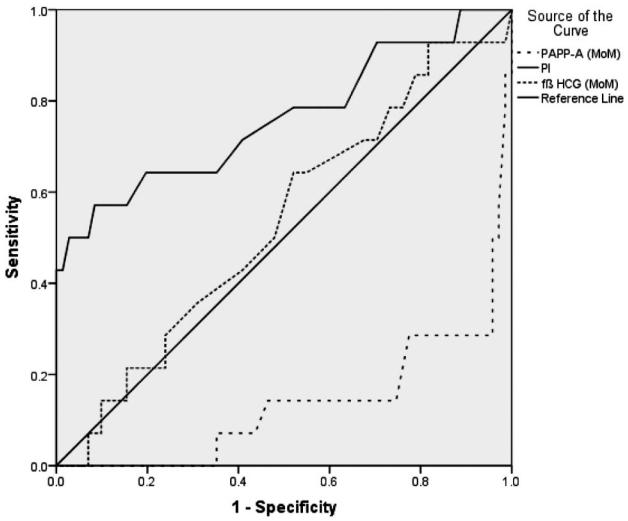

Figure 1. — ROC curve for the prediction of preeclampsia using first trimester PAPP-A, pulsatility index (PI) of uterine arteries and free βHCG.

either as continuous or categorical variable with preeclampsia across all defined thresholds ($p = 0.932$ and $p = 0.462$, 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 to be significantly associated with preeclampsia development ($p = 0.027$) (Table 3). Overall percentage of correctly classified data was between 83.5% and 87.1%.

AUC was performed to assess cut-off value of studied variables that best predicts preeclampsia as adverse pregnancy outcome. The model identified first-trimester PAPP-A (AUC = 0.864, 95% CI = 0.750−0.978; $p = 0.000$) and PI (AUC = 0.762, 95% CI = 0.598−0.925; $p = 0.002$) to be significant predictors for preeclampsia development, and first-trimester free βhCG (AUC = 0.532, 95% CI = 0.370−0.694; $p = 0.709$) to be a non-significant predictor for preeclampsia (Figure 1).

Discussion

The findings of this prospective study in nulliparous women with extreme levels of at least one out of three risk parameters for preeclampsia 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 preeclampsia. The same results were presented in several other studies [7, 12-14]. This study also demonstrated no association between low levels of maternal serum free βhCG and development of preeclampsia.

The etiology of preeclampsia is not completely understood, but impaired trophoblastic invasion of spiral arteries and the lack of placentation are highly marked in pregnancies destined to develop preeclampsia [18]. Since PAPP-A is a protease for insulin-like growth factor (IGF) binding protein-4 (IGFBP-4) and therefore low PAPP-A levels are associated with higher IGFBP-4 and lower IGF [19]. Therefore, IGF influence trophoblast invasion and may have a role in preeclampsia development [20]. The present study has shown that the first-trimester extreme low levels of PAPP-A, as a single independent predictor (e.g. ≤ 0.52 MoM), increased seven-fold the risk for preeclampsia development to be very close with statistical significance. This result is consistent with the results of another study which demonstrated that women with low first-trimester PAPP-A levels were significantly more likely to experience preeclampsia and pattern of increased risk was noted as the level of PAPP-A became more extreme [21]. In contrast to the present results, Pilalis *et al.* found low maternal levels of PAPP-A not to be significant independent predicting factor for preeclampsia [14]. In the present study, first-trimester maternal serum free βhCG, even in extreme low levels (e.g. ≤ 0.56 MoM) was not found to be associated with preeclampsia development. Dugoff *et al.* presented similar results [21].

Important evidence for impaired placental perfusion in pregnancies destined to develop preeclampsia has been provided by Doppler studies of increased 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 preeclampsia, improving to about 60% for early onset severe disease [22-24]. In the present study extreme high levels of mean uterine artery Doppler evaluation (e.g. PI ≥ 2.52), as a single predictor, have shown a high relative risk for preeclampsia development, although with no statistical significance. Furthermore, first-trimester mean uterine artery Doppler PI, was found to be significantly associated with preeclampsia. Recently, Parra-Cordero *et al.* 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 [25].

In the present study, multivariate prediction model combining extreme first-trimester high levels of mean uterine artery Doppler PI, together with extreme first-trimester low levels of PAPP-A, significantly improved predictive capability and efficiency for preeclampsia. Single addition of aforementioned first-trimester maternal biochemical and hemodynamic markers could improve the prediction of preeclampsia, but limitation according to low sensitivity and specificity still exist [26]. A review of screening tests for preeclampsia concluded that no single first-trimester marker is available to provide a complete sufficient diagnostic accuracy [27]. One of the significant first-trimester risk-predicting model for preeclampsia development was recently created and presented by Poon *et al.* using combining maternal characteristics with first-trimester serum

analytes (PAPP-A and PlGF) and hemodynamic parameters (uterine Doppler PI and MAP). This model presented a detection rate of 93% for early preeclampsia and 61% for late preeclampsia, at a 5% false positive rate [13]. Despite the mentioned finding, the majority of perinatal centers in middle income country, such as the present, generally cannot provide similar risk-predictive model for preeclampsia. This is because determination of maternal serum PlGF is not recognized by the National Health Care authorities, as a routine laboratory procedure. Furthermore, a single accuracy of PlGF is too poor to allow its routine use for prediction of preeclampsia [28]. Currently, there is not enough positive evidence-based data about its cost-effectiveness in order to support the implementation of PlGF and a number of other biomarkers to be a part of routine prenatal care programme in a resource limited setting, either of such a new screening strategy as a whole [29]. Also, limitation according to appropriate technology equipment and software package still exist. Therefore, the approach the present authors presented, could be possibly used in resource limited settings where three above described variables (e.g. first-trimester free βhCG, PAPP-A, and uterine artery PI) could be of possible clinical usage for the prediction of preeclampsia development on a daily basis. The present results generated an AUC indicating a significant efficiency for the prediction of preeclampsia.

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 extreme low levels of maternal serum PAPP-A and free βhCG used for Down syndrome screening in first trimester, and extreme high levels of Doppler uterine PI in first trimester, as a single as well as combined predictors for preeclampsia development as an alternative approach with a sufficient diagnostic accuracy and clinical usefulness. However, it has the advantage of evaluating high-risk pregnant women for preeclampsia as a part of a routine perinatology clinical practice with no additional recent risk-predictive model costs, which is of the great importance in the resource constrain settings.

Conclusion

The present study suggests that the first-trimester extreme low levels of maternal serum PAPP-A and Doppler PI significantly improved predictive capability for preeclampsia. Described model could be possibly used in a routine daily clinical practice in resource limited settings where other parameters are not available for the prediction of preeclampsia development.

Acknowledgements

The authors would like to thank all colleagues from Perinatology Unit of the Gynecology and Obstetrics Clinic "Narodni Front", Belgrade, Serbia.

References

[1] Sibai B., Dekker G., Kupferminc M.: "Pre-eclampsia". *Lancet*, 2005, *365*, 785.

[2] Yu C.K., Smith G.C., Papageorghiou A.T., Cacho A.M., Nicolaides K.H., Fetal Medicine Foundation Second Trimester Screening Group: "An integrated model for the prediction of pre-eclampsia using maternal factors and uterine artery Doppler velocimetry in unselected low-risk women". *Am. J. Obstet. Gynecol.*, 2006, *195*, 330.

[3] Krantz D., Goetzl L., Simpson J.L., Thom E., Zachary J., Hallahan T.W., *et al.*: "Association of extreme first-trimester free human chorionic gonadotropin-beta, pregnancy-associated plasma protein A, and nuchal translucency with intrauterine growth restriction and other adverse pregnancy outcomes". *Am. J. Obstet. Gynecol.*, 2004, *191*, 1452.

[4] Spencer K., Yu C.K., Cowans N.J., Otigbah C., Nicolaides K.H.: "Prediction of pregnancy complications by first-trimester maternal serum PAPP-A and free beta-hCG and with second-trimester uterine artery Doppler". *Prenat. Diagn.*, 2005, *25*, 949.

[5] Ong C.Y., Liao A.W., Spencer K., Munim S., Nicolaides K.H.: "First trimester maternal serum free beta human chorionic gonadotrophin and pregnancy associated plasma protein A as predictors of pregnancy complications". *BJOG*, 2000, *107*, 1265.

[6] Tul N., Pusenjak S., Osredkar J., Spencer K., Novak-Antolic Z.: "Predicting complications of pregnancy with first-trimester maternal serum free-betahCG, PAPP-A and inhibin-A". *Prenat. Diagn.*, 2003, *23*, 990.

[7] Spencer K., Cowans N.J., Nicolaides K.H.: "Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia". *Prenat. Diagn.*, 2008, *28*, 7.

[8] Akolekar R., Zaragoza E., Poon L.C., Pepes S., Nicolaides K.H.: "Maternal serum placental growth factor at 11 + 0 to 13 + 6 weeks of gestation in the prediction of pre-eclampsia". *Ultrasound Obstet. Gynecol.*, 2008, *32*, 732.

[9] Nicolaides K.H., Bindra R., Turan O.M., Chefetz I., Sammar M., Meiri H., *et al.*: "A novel approach to first-trimester screening for early pre-eclampsia combining serum PP-13 and Doppler ultrasound". *Ultrasound Obstet. Gynecol.*, 2006, *27*, 13.

[10] Salomon L.J., Benattar C., Audibert F., Fernandez H., Duyme M., Taieb J., *et al.*: "Severe preeclampsia is associated with high inhibin A levels and normal leptin levels at 7 to 13 weeks into pregnancy". *Am. J. Obstet. Gynecol.*, 2003, *189*, 1517.

[11] Spencer K., Cowans N.J., Stamatopoulou A.: "ADAM12s in maternal serum as a potential marker of pre-eclampsia". *Prenat. Diagn.*, 2008, *28*, 212.

[12] Plasencia W., Maiz N., Poon L., Yu C., Nicolaides K.H.: "Uterine artery Doppler at 11 + 0 to 13 + 6 weeks and 21 + 0 to 24 + 6 weeks in the prediction of pre-eclampsia". *Ultrasound Obstet. Gynecol.*, 2008, *32*, 138.

[13] Poon L.C., Nicolaides K.H.: "First-trimester maternal factors and biomarker screening for preeclampsia". *Prenat. Diagn.*, 2014, *34*, 618.

[14] Pilalis A., Souka A.P., Antsaklis P., Daskalakis G., Papantoniou N., Mesogitis S., *et al.*: "Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler and PAPP-A at 11-14 weeks' gestation". *Ultrasound Obstet. Gynecol.*, 2007, *29*, 135.

[15] Goetzinger K.R., Singla A., Gerkowicz S., Dicke J.M., Gray D.L., Odibo A.O.: "Predicting the risk of pre-eclampsia between 11 and 13 weeks' gestation by combining maternal characteristics and serum analytes, PAPP-A and free β-hCG". *Prenat. Diagn.*, 2010, *30*, 1138.

[16] Poon L.C., Staboulidou I., Maiz N., Plasencia W., Nicolaides K.H.: "Hypertensive disorders in pregnancy: screening by uterine artery Doppler at 11-13 weeks". *Ultrasound Obstet. Gynecol.*, 2009, *34*, 142.

[17] Brown M.A., Lindheimer M.D., de Swiet M., Van Assche A., Moutquin J.M.: "The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP)".

Hypertens. Pregnancy, 2001, *20*, IX-XIV.

[18] Guzin K., Tomruk S., Tuncay Y.A., Naki M., Sezginsoy S., Zemheri E., *et al.*: "The relation of increased uterine artery blood flow resistance and impaired trophoblast invasion in pre-eclamptic pregnancies". *Arch. Gynecol. Obstet.*, 2005, *272*, 283.

[19] Lawrence J.B., Oxvig C., Overgaard M.T., Sottrup-Jensen L., Gleich G.J., Hays L.G., *et al.*: "The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease secreted by human fibroblasts is pregnancy-associated plasma protein-A". *Proc. Natl. Acad. Sci. USA*, 1999, *96*, 3149.

[20] Irwin J.C., Suen L.F., Martina N.A., Mark S.P., Giudice L.C.: "Role of the IGF system in trophoblast invasion and pre-eclampsia". *Hum. Reprod.*, 1999, *14*, 90.

[21] Dugoff L., Hobbins J.C., Malone F.D., Porter T.F., Luthy D., Comstock C.H., *et al.*: "First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial)". *Am. J. Obstet. Gynecol.*, 2004, *191*, 1446.

[22] Martin A.M., Bindra R., Curcio P., Cicero S., Nicolaides K.H.: "Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation". *Ultrasound Obstet. Gynecol.*, 2001, *18*, 583.

[23] Parra M., Rodrigo R., Barja P., Bosco C., Fernández V., Muñoz H., *et al.*: "Screening test for preeclampsia through assessment of uteroplacental blood flow and biochemical markers of oxidative stress and endothelial dysfunction". *Am. J. Obstet. Gynecol.*, 2005, *193*, 1486.

[24] Gómez O., Martínez J.M., Figueras F., Del Río M., Borobio V., Puerto B., *et al.*: "Uterine artery Doppler at 11-14 weeks of gestation to screen for hypertensive disorders and associated complications in an unselected population". *Ultrasound Obstet. Gynecol.*, 2005, *26*, 490.

[25] Parra-Cordero M., Rodrigo R., Barja P., Bosco C., Rencoret G., Sepúlveda-Martinez A., *et al.*: "Prediction of early and late pre-eclampsia from maternal characteristics, uterine artery Doppler and markers of vasculogenesis during first-trimester of pregnancy". *Ultrasound Obstet. Gynecol.*, 2013, *41*, 538.

[26] Barrett S.L., Bower C., Hadlow N.C.: "Use of the combined first-trimester screen result and low PAPP-A to predict risk of adverse fetal outcomes". *Prenat. Diagn.*, 2008, *28*, 28.

[27] Conde-Agudelo A., Villar J., Lindheimer M.: "World Health Organization systematic review of screening tests for preeclampsia". *Obstet. Gynecol.*, 2004, *104*, 1367.

[28] Kleinrouweler C.E., Wiegerinck M.M., Ris-Stalpers C., Bossuyt P.M., van der Post J.A., von Dadelszen P., *et al.*: "Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis". *BJOG*, 2012, *119*, 778.

[29] Meads C.A., Cnossen J.S., Meher S., Juarez-Garcia A., ter Riet G., Duley L., *et al.*: "Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling". *Health Technol. Assess.*, 2008, *12*, 1.

Corresponding Author:
R. LUKIC, M.D.
Gynecology and Obstetrics Clinic "Narodni Front"
Kraljice Natalije 62
11000 Belgrade (Serbia)
e-mail: reljalu@gmail.com