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FIRST TRIMESTER PREDICTION OF PREECLAMPSIA BASED ON MATERNAL FACTORS, BIOMARKERS AND 3D POWER DOPPLER OF PLACENTAL BED VASCULARIZATION

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Objective. *To develop the best screening model for preeclampsia (PE) based on maternal characteristics, biomarkers with 3D power Doppler of placental bed vascularization.*

Materials and methods. *A prospective non-interventional cohort study of patients who presented for combined screening at 11+0 - 13+6 weeks gestation was conducted. Maternal characteristics, mean arterial blood pressure (MAP), uterine artery Doppler pulsatility indices (UtA-PI), 3D power Doppler of placental bed vascularization indices (PB-VI) and VOCAL technology, maternal serum placental growth factor (PlGF) were estimated. Logistic regression analysis was used to predict PE.*

Results. *We screened 5157 pregnant women, 3424 (66,4%) of whom were eligible for analysis. In all, 102 (3,0%) developed PE, with 29 (0,9%) having early-onset PE and 73 (2,1%) having late-onset PE. The best model for early PE (n=29) and late PE (n=73) included maternal risk factors, MAP, PlGF and PB-VI achieving detection rates of 89,7% (AUC 0,941; CI: 0,944-0,978) and 50,7% (AUC 0,833; 95% CI: 0,800-0,863) for 10% of false-positive rates. There was no significant improvement when adding PAPP-A, uterine artery Doppler values, or both.*

Conclusions. *Preeclampsia can be predicted with high accuracy in low risk population by combined algorithms with vascularization indices of placental bed using 3D power Doppler angiography. Among Doppler parameters, PB-VI and UtA-PI improve the prediction for early and late PE; and PB-VI vs UtA-PI detects significantly higher rates of early PE. The data need confirmation in larger studies.*

Keywords: *preeclampsia, first trimester screening, prediction, three-dimensional power Doppler, uterine artery Doppler, placental bed.*

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Conflict of interest. *Authors declare lack of the possible conflicts of interests.*

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Preeclampsia (PE) complicates 2-8% of pregnancies. Being a multisystem disorder, it is the leading cause of maternal and perinatal morbidity and mortality worldwide [1, 2]. The etiology of PE remains unclear, but it is recognized that impaired growth and development of placental villi and accompanying this process vascularization play an important role in the pathogenesis of the disease [3]. PE is characterized by deteriorated physiological transformation of uterine spiral arteries and chronic utero-placental hypoperfusion [4]. PE can be represented by two main phenotypes with early and late manifestation of the disease. Early placental insufficiency is mainly associated with early PE [4].

Early detection of women at risk of PE development is a key objective of antenatal care. Significant resources are currently focused on the development and improvement of screening tests of the first trimester, as this approach will allow us to benefit from the start of preventive therapy and improve the quality of monitoring patients [5]. There is a wide range of effectiveness of available prognostic tests and markers, which include maternal risk factors, biophysical and/or biochemical factors alone or combined together. Combination of basic maternal risk with biophysical parameters such as maternal blood pressure (BP) and uterine artery dopplerometry (UtA) allows to achieve an early PE detection rate of 44-80% and 28-40% for late PE with 10% of false-positive result (FPR) rate [6, 7]. Doppler parameters of uterine arteries blood flow, abnormalities of which indirectly reflect the process of inadequate trophoblast invasion in maternal spiral arteries, are combined with biochemical markers, thus leading to better characterization of the process of placentation [8]. Biochemical markers that include PAPP-A, circulating angiogenic factors, such as placental growth factor (PlGF), may improve prognostic algorithms, the detection rate of which in this case varies from 47 to 96% [9, 10]. The search for new biomarkers and their optimal combinations in order to improve the efficiency of PE prediction still continues [8].

Three-dimensional (3D) echography technologies with the ability of visualization of vascular volumes make it possible to directly assess early changes in the utero-

placental circulatory space (placental bed), including the maternal spiral arteries and the intervillous space [11, 12]. The use of 3D echographic parameters as risk factors for PE has not been sufficiently studied, giving ambiguous results according to published data. In our recent work we have confirmed the results of a number of authors that women with PE have significantly lower indices of volumetric blood flow in the placental bed and placenta in the first trimester [13]. However, there is a dramatic lack of studies of 3D power Doppler assessment of placental bed vascularization in combined screening models with biomarkers, including serum angiogenesis markers.

The aim of this study was to develop the best predictive model for early and late PE of the first trimester based on the combined assessment of clinical and anamnestic factors, biomarkers, and 3D-power Doppler assessment of placental bed vascularization. Individualized and combined value of the vascularization of the placental bed (PB-VI) was analyzed when added to predictive algorithms for early and late PE of the first trimester.

Materials and methods

This was a prospective non-interventional cohort study of 5157 women with singleton pregnancies presenting to the National Medical Research Center for Obstetrics, Gynecology and Perinatology of the Ministry of Health of Russia (Moscow) in August, 2013 – December, 2016, for combined screening of the first trimester. Local ethics committee approved the study protocol and each patient signed an informed consent.

Women with singleton pregnancy, combined first trimester aneuploidy screening, and subsequent delivery of a phenotypically normal live baby or antenatal death at ⩾22 weeks gestation were eligible for inclusion. The exclusion criteria were fetus with aneuploidy and large fetal abnormalities, as well as termination of pregnancy, cases of miscarriage or fetal death up to 22 weeks of pregnancy.

Examination of patients at 11+0 - 13+6 weeks of pregnancy included: 1) collection of data on maternal risk factors and medical history; 2) ultrasound measurement of fetal crown-rump length (CRL), nuchal translucency, diagnosis of malformations; uterine artery Doppler and 3D-power Doppler angiography of the placental bed (see below); 3) measurement of average BP using a calibrated automatic device OMRON HEM 907 (Omron Healthcare, Japan) according to the standardized protocol [14]; 5) measurement of serum β-hCG, PAPP-A, PlGF levels (DELFIA Xpress system, Wallac Oy, Turku, Finland). The raw data were converted into multiples of the median (MoM), calculated according to the term of pregnancy (based on CRL), weight, age, ethnicity, smoking status, and method of conception. For risk assessment Astraia v23.4 software was used (Astraia Software Gmbh, Germany). Term of gestation was adjusted to CRL values at ultrasound examination in the first trimester (11+0 – 13+6 weeks; range of CRL values of 45-84 mm).

Echographic study was performed as a part of first trimester aneuploidy screening with expert class devices Voluson E8 (GE Medical Systems), equipped with 3D/4D convex probe RAB4-8-D with a frequency of 4-8 MHz. Doppler examination of uterine arteries in the first trimester was performed transabdominally, according to the previously described protocol [14]. Pulsatility indices of uterine arteries (UtA-PI) were automatically measured and mean value of UtA-PI was calculated. In the mode of 3D power Doppler angiography a three-dimensional volume of the placenta was evaluated as well as of adjacent decidua and myometrium. Doppler measurements were performed in the quality mode 'normal', the pulse repetition frequency was 0.9 KHz, the object motion filter was used at the 'low1' level. The angle of gray-scale images was 70°, magnification - 1.6, focus area - 1, XbeamCRI 1, SI 3, ATI normal, harmonic frequency: high. The volume frame of same resolution was located identically to the position of the color frame, and the recording process began in the maximum quality settings mode, followed by saving the data. Measurements were recorded at the same velocity in all patients (10 s). When artifacts occurred during recording due to fetal movements or intestinal loops, volume assessment was performed until sufficient quality of records was achieved. The VOCAL mode was used to consistently evaluate six sections of the placenta, each with an offset angle of 30 degrees from the previous position, rotated horizontally in both plane A and plane B. Contour of the placental bed (subplacental myometrium, uterine-placental intervillous space) was manually delineated in each of the six sections. Subplacental volume of the myometrium was restricted to 1 cm below the placenta [15]. Vascularization indices of the placental bed were automatically calculated using 4DView software (GE Healthcare).

Preeclampsia was diagnosed according to the recommendations of the International Society for the Study of Hypertension in Pregnancy and the Russian Society of Obstetricians and Gynecologists [16, 17]. Early-onset PE was defined as a condition requiring delivery before 34 weeks of pregnancy, whereas late-onset PE - after 34 weeks of pregnancy. Newborns were considered to be small for gestational age if the birth weight was below the 10th percentile [18]. Adverse perinatal outcomes included fetal/neonatal death during the perinatal period or presence of metabolic acidosis at birth, defined as umbilical artery pH ⩽7.15 and/or base excess >12 mEq/L at birth.

The Mann-Whitney U-test and Pearson $\chi 2$-test were used for one-dimensional comparisons of quantitative and qualitative variables between the groups with early, late PE and uncomplicated pregnancy, respectively. Multivariate logistic regression analysis was used to assess the independent and combined contribution of variables in early and late PE prediction and the additional contribution of the placental bed vascularization index to the improvement of existing first trimester predictive models of PE. All regression models used step-by-step algorithms to select variables at thresholds $p=0.05$. Patient-specific risk for early and late PE was calculated according to the formula: Risk = $e^y/(1 + e^y)$. The Y-value for early and late PE was derived from the inverse stepwise multivariate logistic regression analysis of the log value (or MoM) of each of the biomarkers, the log of transformed a priori risk for the state based on

maternal risk factors only. Conformity of models to the aim of prediction was done by calculating the coefficient of determination R^2 (Nagelkerke R^2). The efficiency of the model was also described by the area under the ROC-curve (AUC). The sensitivity (detection rate) of the model was calculated by predicting early and late PE with a false positive results rate of 10%. A pack of statistical software IBM SPSS 21.0 (New York, USA) was used for statistical analysis, graphics were built with the help of application MedCalc 18.5 (Mariakerke, Belgium)

Results

The study included 5157 women with singleton pregnancy. Out of them, 1733 (33.6%) women were excluded from the study because of the presence of chromosomal anomalies, major malformations, miscarriage before 22 weeks, the lack of data on the outcomes of pregnancy, on the results of uterine arteries Doppler (UtA-PI), on the placental bed vascularization (PB-VI) due to technical reasons related to the characteristics of the equipment used to perform an ultrasound. Of the 3424 (66.4%) cases included in the analysis, PE developed in 102 (3.0%) cases, with early-onset PE developing in 29 (0.9%) women and late-onset PE - in 73 (2.1%). Uncomplicated pregnancy was observed in 3322 (97.0%) patients who represented the control group.

The data on maternal characteristics, obstetric and neonatal outcomes of each of the study groups are displayed in Table 1. The data are presented separately for early and late PE. The biophysical and biochemical variables estimated in the first trimester are shown in Table 2.

According to multivariate analysis, MAP MoM, PB-VI and UtA-PI MoM were significantly higher in women with early-onset PE ($p<0.001$) and late-onset PE group ($p<0.001$) compared to control. Moreover, these parameters were also significantly higher in early PE compared to late PE ($p<0.001$).

PAPP-A MoM and β-hCG MoM were statistically non-significant for both groups with PE. PlGF MoM values were significantly lower in early-onset PE group ($p<0.001$) compared to control and late-onset PE group ($p<0.001$).

The following models were the most accurate in predicting early-onset PE:

[a priori and a posteriori risk = $e^y / (1+e^y)$]:

Risk (a priori) =-5.250+ (1.329 if there is PE in previous pregnancy) + (1.88697 if there is PE in family history) + (1.739 if chronic hypertension) + (1.92220 if diabetes mellitus); $R^2 = 11.9\%$; $p<0.0001$.

Risk (biophysical markers) =-3.651 + (0.62275×log a priori risk) + (7.418×log MAP MoM) – (0.148×log PB-VI); $R^2=46.8\%$; $p<0.0001$.

Risk (biophysical and biochemical markers) =1.74156 + (0.85468×log of a priori risk) + (7.198×log MAP MoM) – (0.1456×log PB-VI) – (5.381×log PlGF MoM); $R^2=63.2\%$; $p<0.0001$.

The following models were the most precise in predicting late-onset PE:

[a priori and a posteriori risk = $e^y / (1+e^y)$]:

Risk (a priori) =-6.047 - (0.541 if multipara) + (1.757 if having autoimmune disease, i.e. AFS, SLE) + (1.82498 if chronic hypertension) + (0.0946×BMI); $^R2$ = 9.7%; $p<0.0001$.

Risk (biophysical markers) =-5.011 + (0.751× log a priori risk) + (7.150×log MAP MoM) – (0.047×log PB-VI); $R^2=28.2\%$; $p<0.0001$.

Risk (biophysical and biochemical markers) =-2.92636 + (0.85468×log a priori risk) + (6.662×log MAP MoM) – (0.044×log PB-VI) – (1.599×log PlGF MoM); $R^2=33.1\%$; $p<0.0001$.

The detection rate of PE with a 10% FPR rate is presented in Table 3. ROC-curves for multifactor model, including data on the PB-VI and UtA-PI, are shown in Figure 1. Using this algorithm for the previously described population [14], we achieved the detection rate of early- and late-onset PE with maternal risk a priori 48.3 and 42.5%; when adding biophysical markers (MAP and PB-VI) 75.9 and 45.2%; when adding PlGF to biophysical markers (MAP and PB-VI) 89.7 and 50.7%, respectively, with a FPR rate of 10%. We observed no significant increase in sensitivity when PAPP-A, UtA-PI data were added to the model separately or together.

Discussion

The principal findings of the study

This study evaluated a new approach to PE prediction in the first trimester. The results confirm the theory that the data on placental bed vascularization (PB-VI) when included in the combined screening models improve the prediction of PE in the first trimester. The combination of maternal characteristics, biophysical parameters (MAP, PB-VI), levels of angiogenic factors (PlGF) allowed to reach the detection rate of early- and late-onset PE of 89.7 and 50.7%, respectively, with 10% FPR rate. Adding vascularization index PB-VI improved the detection rate of early-onset PE by 14% and late-onset PE by 3% comparing to the efficiency achieved by using the basic factors, MAP, and PlGF. Obtained data shows that PB-VI may play an independent role in improving the detection rate of both early- and late-onset PE. Although the level of PAPP-A was lower and UtA-PI was higher in women with PE, adding these markers did not improve the predictive value of vascularization indices of the placental bed.

Comparison with available studies

A number of authors studied vascularization of the placenta [19-21] and/or placental bed in first trimester in order to predict PE [12, 15, 22, 23], as well as the volume of the placenta [19, 23-25]. We focused on the analysis of placental bed with evaluation of the vascularization index.

To study the uteroplacental and interventricular spaces at 5 to 12 weeks of pregnancy, both the method of manual tracing of the region of interest [26] and the approach based on sphere echobiopsy [11, 23] can be used. Both methods demonstrated good reproducibility among one or several researchers [26]. We used method of manual tracing to mark out the analyzed volume.

Our results are consistent with a bulk of previous studies reporting lower indices of placental bed

vascularization in the first trimester in women who subsequently developed PE, especially in patients with early onset of the disease [12, 15, 27].

There are few publications concerning evaluation of the effectiveness of combined models of PE prognosis in the first trimester using the method of 3D power Doppler and evaluation of placenta and/or placental bed vascularization. These were mostly models that combined placental volume data, biophysical parameters (UtA-PI, MAP), biochemical markers (PAPP-A), data on medical history [21, 24, 25, 28]. Hannaford et al. (2015) attempted to analyze models that comprised indices of placenta/placental bed vascularization, uterine artery Doppler and PAPP-A in predicting PE

Table 1. Epidemiological, clinical characteristics and outcomes of the study population according to the study groups

Characteristics	Early PE	Late PE	Unaffected
	n=29	n=73	n=3322
Maternal factors			
Age, years	32,1 (27,0 - 36,5)	32,8 (28,0 - 35,5)	31,8 (28,0 – 34,0)
BMI, kg/m^2	22,6 (19,45 - 24,4)	23,7 (20,7 - 27,35)$^+$	21,65 (20,1 - 23,98)
Ethnicity			
White	28 (96,5)	72 (98,6)	3259 (98,1)
Other	1 (3,5)	1 (1,4)	63 (1,9)
Smoking status			
Non smoking	29 (100,0)	68 (93,1)	3123 (94,0)
Smoking	0 (0,0)	3 (4,1)	73 (2,2)
Stopped smoking	0 (0,0)	2 (2,7)	126 (3,8)
Medical history			
Chronic hypertension	8 (27,6)$^\#$	16 (21,9)$^+$	140 (4,2)
Diabetes mellitus	1 (3,4)$^\#$	1 (1,4)	27 (0,8)
Renal disease	2 (6,9)	2 (2,7)	113 (3,4)
Autoimmune disease (SLE, APS)	1 (3,4)	4 (5,5)	53 (1,6)
Coagulation disorders	6 (20,7)$^\#$	8 (11,0)	342 (10,3)
Conception			
Spontaneous	28 (96,6)	59 (80,8)	2927 (88,1)
Ovulation induction	0 (0,0)	4 (5,5%)	27 (0,8)
IVF/IUI/egg donor	1 (3,4)	10 (13,7)	369 (11,1)
Obstetric history			
Nulliparity	17 (58,6)	49 (67,1)	1857 (55,9)
Previous PE	6 (20,7)$^\#$	5 (6,8)$^+$	70 (2,1)
Previous SGA	16 (55,2)$^{\#,*}$	11 (15,1)$^+$	0 (0,0)
Maternal outcome			
GA at diagnosis of PE, weeks	30,2 (27,4-31,2)*	37.4 (36.5-38.2)	
PE latency, days from diagnosis to delivery	7 (8,5)*	1.6 (3.2)	
Eclampsia	0	1 (1,3)	0
HELLP syndrome	1 (3,4)#*	13 (5.3)+	0
Gestational diabetes mellitus	0	7 (9,5)+*	169 (5.1)
Placental abruptio	1 (3,4) #	2 (2,7)+	63 (1,9)
Mode of delivery			
Induction of labor or elective cesarean section	29 (100)#*	59 (80,8)+	724 (21,8)
Vaginal delivery	2 (6,8)#*	19 (26,0)+	1990 (59,9)
Operative vaginal delivery	1 (3,4)#	10 (13,7)+	691 (20,8)
Cesarean section	26 (89,8)#*	44 (60,3)+	638 (19,2)
Neonatal outcome			
GA at delivery, weeks	31.5 (28.6-32.0)#*	37.9 (36.5-39.6)+	40.3 (39-41.3)
Birth weight, g	1460 (1342-1912)#*	3000 (2710-3448)+	3400 (3168-3680)
Birth weight percentile	2,5 (0,8-18,7)#*	22,4 (8,5-52,8)+	45.1 (26.5-66.9)
Small for gestational age	18 (62,1) #*	19 (26,0)+	468 (14,1)
Apgar 5 minutes	6 (6-7)#*	8 (7-8)+	9 (9 - 9)
pH umbilical artery	7.20 (7.16-7.27)#*	7.24 (7.17-7.28)	7.24 (7.19-7.29)
Neonatal metabolic acidosis	7 (24,1)#	11 (15,1)+	322 (9,7)
Perinatal death, weeks	1 (3,4)#*	0 (0)	13 (0.4)

PE: Preeclampsia; SGA: small for gestational age; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; IVF: in-vitro fertilization; IUI: intrauterine insemination.
Statistically significance between early PE and unaffected (#); late PE and unaffected ($^+$); early and late PE (*).
Data are expressed as median (IQR) or n (%).

in the first trimester. The detection rate of early PE was 79% for the model that included PB-VI and UtA-PI, while as for overall PE detection rate accounted for 54% for the model that included PB-VI, UtA-PI, PAPP-A with 10% of FPR rate[12]. In our study combination of PB-VI and UtA-PI did not lead to improved model sensitivity. Moreover, PB-VI had a higher prognostic value compared to UtA-PI, which allowed to improve the efficiency of PE prediction, achieving detection rate of early-onset PE as high as 90% not including UtA-PI.

Strengths and limitations

As far as we know, a combination of 3D power Doppler assessment of placental bed vascularization with serum angiogenesis markers and a wide range of other markers and clinical and anamnestic factors has not been previously

Table 2. Biophysical and biochemical predicting variables of the study population according to the study groups

Characteristics	Early PE	Late PE	Unaffected
	n=29	n=73	n=3322
Maternal Blood pressure			
MAP, mm Hg	94,9 (87,3 - 100,5) #,*	94,7 (87,6 - 101,9) +	85,3 (80,8 - 91,5)
MAP, MoM	1.14 (1.04-1.2) #,*	1.13 (1,03-1,21) +	1.00 (0.96-1.08)
Biochemical parameters			
β-hCG, ng/mL	58,0 (31.5 – 72.3)	64,0 (36,1-94.1)	64.1 (41,2-98,0)
β-hCG, MoM	1,14 (1,04 – 1,20)	1,13 (1,03 – 1,21)	1,19 (0,97 – 1,81)
PAPP-A, mU/mL	2,960 (0,510-3,013) #	2,549 (0,312-3,282) +	3,317 (0,463-3,729)
PAPP-A, MoM	1,09 (0,69–1,53) #	1,07 (0,66–1,52) +	1,2 (0,87–1,73)
PlGF, pg/mL	11,3 (8,8 – 18,5) #,*	21,2 (12,4 – 26,9) +	26,6 (19,0 – 32,7)
PlGF, MoM	0,51 (0,38 – 18,45) #,*	0,85 (0,60 – 1,04) +	1,01 (0,80 – 1,33)
Uterine Artery Doppler			
UtA-PI	1,7 (1,36 - 2,35) #	1,65 (1,35 - 2,09) +	1,54 (1,26 - 1,82)
UtA-PI MoM	1,09 (0,86 - 1,42) #	1,01 (0,82 - 1,22) +	0.98 (0,81 – 1,16)
Placental Bed 3D Power Doppler			
PB-VI	19,3 (12,4 - 26,32) #,*	26,37 (18,74 - 41,35) +	39,71 (27,63 - 51,45)

PE: Preeclampsia; MAP: Mean arterial pressure; MoM: Multiple of the expected median; PAPP-A: Pregnancy-associated plasma protein A; β-hCG: β-human chorionic gonadotropin; PlGF: Placental growth factor; UtA-PI: Uterine artery Pulsatility index; PB-VI: 3D power Doppler vascularization indices of placental bed
Statistically significance between early PE and unaffected (#); late PE and unaffected (+); early and late PE (*).
Data are expressed as median (IQR) or n (%).

Table 3. Predictive values of screening for early and late preeclampsia

Screening method	Early PE		Late PE	
	AUC (CI 95%)	DR (% (95% CI) for a FPR of 10%	AUC (CI 95%)	DR (% (95% CI) for a FPR of 10%
History	0,711 (0,696 - 0,726)	48,28 (29,4 - 67,5)	0,688 (0,672 - 0,703)	42,47 (31,0 - 54,6)
UtA-PI	0,794 (0,780 - 0,808)	37,93 (20,7 - 57,7)	0,77 (0,734 - 0,803)	19,18 (10,9 - 30,1)
MAP	0,819 (0,805 - 0,832)	48,28 (29,4 - 67,5)	0,781 (0,767 - 0,795)	43,84 (32,2 - 55,9)
PlGF	0,867 (0,848 - 0,884)	55,17 (35,7 - 73,6)	0,791 (0,757 - 0,823)	20,55 (12,0 - 31,6)
PB-VI	0,854 (0,823 - 0,881)	58,62 (38,9 - 76,5)	0,676 (0,637 - 0,713)	30,14 (19,9 - 42,0)
History+**UtA-PI**	0,636 (0,619 - 0,652)	55,17 (35,7 - 73,6)	0,581 (0,564 - 0,597)	41,1 (29,7 - 53,2)
History+MAP	0,754 (0,739 - 0,768)	55,17 (35,7 - 73,6)	0,729 (0,713 - 0,744)	45,21 (33,5 - 57,3)
History+PlGF	0,814 (0,793 - 0,834)	68,97 (49,2 - 84,7)	0,838 (0,807 - 0,867)	44,83 (26,4 - 64,3)
History+**PB-VI**	0,882 (0,854 - 0,907)	62,07 (42,3 - 79,3)	0,725 (0,688 - 0,760)	42,47 (31,0 - 54,6)
History+MAP+**UtA-PI**	0,843 (0,830 - 0,855)	65,52 (45,7 - 82,1)	0,707 (0,692 - 0,723)	38,36 (27,2 - 50,5)
History+**UtA-PI**+**PB-VI**	0,892 (0,865-0,916)	68,97 (49,2-84,7)	0,707 (0,692-0,723)	38,36 (27,2-50,5)
History+MAP+**PB-VI**	0,924 (0,898 - 0,945)	75,86 (56,5 – 89,7)	0,814 (0,779 - 0,844)	45,21 (33,5 – 57,3)
History+MAP+PlGF	0,886 (0,868 - 0,902)	75,86 (56,5 - 89,7)	0,775 (0,753 - 0,796)	47,95 (36,1 - 60,0)
History+MAP+PlGF+**UtA-PI**	0,896 (0,879 - 0,911)	79,31 (60,3 - 92,0)	0,781 (0,759 - 0,802)	46,58 (34,8 - 58,6)
History+MAP+PlGF +**PB-VI**	0,964 (0,944 - 0,978)	89,66 (72,6 – 97,8)	0,833 (0,800 - 0,863)	50.68 (38,7 – 62,6)
History+MAP+PlGF +**UtA-PI**+**PB-VI**	0,941 (0,919-0,958)	86,21 (68,3-96,1)	0,807 (0,773-0,837)	47,95 (36,1-60,0)

PE: preeclampsia: AUC: Area under the curve; CI: Confidence interval; DR: Detection rate; FPR: False positive rate; History: maternal characteristics; MAP: Mean arterial pressure; UtA: Uterine artery; PI: Pulsatility index; MoM: Multiple of the expected normal median; PlGF: Placental growth factor; PB-VI: 3D power Doppler vascularization index of placental bed. Data are expressed as median (IQR).

reported. Another strength of our study is its prospective design and well-organized database with detailed registration of maternal history and obstetric outcomes. One of the advantages of the study is that the evaluation of biophysical markers was carried out in a strict accordance with the FMF protocol or our internal protocols.

Limitations of this study are relatively small sample size, as well as a lack of external validation of the developed model, which should be evaluated in general obstetric population.

A number of authors believe that the use of 3D power Doppler angiography for screening in the first trimester is currently not acceptable in clinical practice [29]. According to our data, method of 3D power Doppler angiography is a highly reproducible technique and can easily be performed during the screening in the first trimester while measuring nuchal translucency. The acceptability and reproducibility of quantitative evaluation of Doppler signals with calculation of vascularization index, flow index, and vascularization flow index were found to be satisfactory both in vivo and in vitro [30].

Time required to obtain the analyzed volume is approximately 2-3 minutes when scanning at 11-13 weeks of pregnancy. However, one should admit that additional time will be required to manually trace the contour of the placental bed (uteroplacental circulatory space, deciduo-myometrium). In this context, uterine artery Doppler is a relatively simple and less time-consuming method. However, the obtained results suggest a higher prognostic value of PB-VI compared to UtA-PI, which allows to increase the efficiency of PE prognosis achieving the detection rate of 90% for early PE in combined models not including UtA-PI in the model.

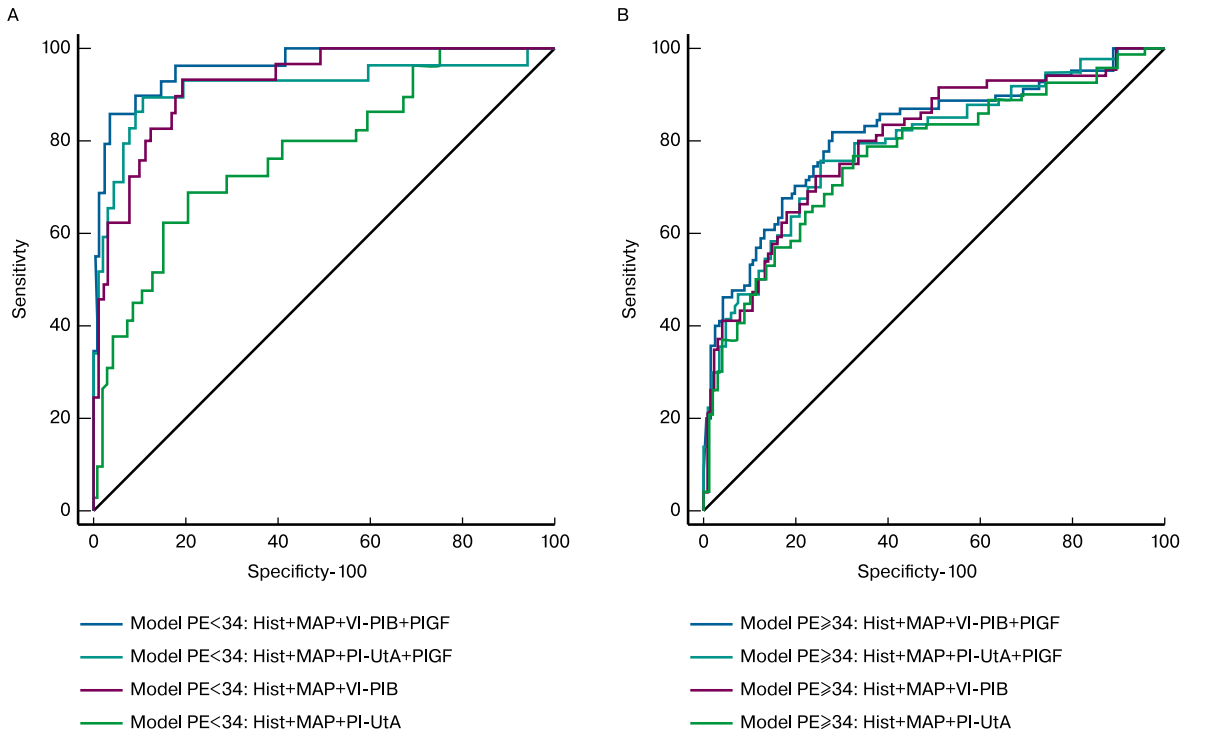
Clinical interpretation

These data show that as for PE screening in the first trimester, test is more accurate in predicting disease with an early rather than late onset. This is particularly important because the purpose of early screening is to identify a high-risk group that could benefit from therapeutic interventions in order to reduce the prevalence of PE. Prophylactic administration of low dose aspirin before 16 weeks of pregnancy is particularly effective since these measures reduce the incidence of complications in this group by 82% [5]. Meanwhile disturbances of vascularization in the region of deciduomyometrium in the first trimester in women who subsequently developed early- or late-onset PE were revealed with 3D power angiography. There are still ongoing discussions on whether early- and late-onset PE are different diseases. Based on the results of the study, there seems to be a positive correlation between the level of placental bed vascularization and the term of delivery. Thus, it is possible that PE is a single pathophysiological state with a wide range of severity, which depends on the term of pregnancy at the time of delivery. More accurate identification of high-risk group will allow us to assess new methods of decreasing the rate of PE, such as metformin or statins, more efficiently and in a smaller sample.

Conclusions

This study proves that prediction of PE in the first trimester is effective and assessment of placental bed vascularization (PB-VI) can be a valuable predictor of PE

Figure 1. ROC-curves for the detection of A) early preeclampsia (<34 weeks of gestation), B) late preeclampsia (≥34 weeks of gestation) using a logistic regression models which includes different combinations first trimester a-priori risk factors (Hist), mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), 3D power Doppler vascularization index of placental bed (PB-VI), placental growth factor (PIGF)



in combined screening models. Among the echographic markers, both UtA-PI and PB-VI demonstrate the ability to improve the efficiency of early- and late-onset PE prediction, and models with PB-VI in comparison with UtA-PI demonstrate a significantly higher rate of early-onset PE detection. The detection rate of early and late PE in combined screening comprising maternal characteristics, mean arterial blood pressure, PB-VI, and PlGF reached 89.7 and 50.7%, respectively. Further studies are needed to confirm these findings.

References

1. *Lisonkova S., Sabr Y., Mayer C., Young C., Skoll A., Joseph K.S.* Maternal morbidity associated with early-onset and late-onset preeclampsia. Obstet. Gynecol. 2014; 124(4): 771-81.
2. *Sidorova I.S., Nikitina N.A., Unanyan A.L.* Preeclampsia and lower maternal mortality in Russia. Akusherstvo i Ginekologiya/Obstetrics and Gynecology. 2018; (1): 107-12. (in Russian) https://dx.doi.org/10.18565/aig.2018.1. 107-112
3. *Brosens I., Pijnenborg R., Vercruysse L., Romero R.* The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am. J. Obstet. Gynecol. 2011; 204(3): 193-201.
4. *Chaiworapongsa T., Chaemsaithong P., Yeo L., Romero R.* Pre-eclampsia part 1: current understanding of its pathophysiology. Nat. Rev. Nephrol. 2014; 10(8): 466-80.
5. *Rolnik D.L., Wright D., Poon L.C., O'Gorman N., Syngelaki A., de Paco Matallana C.* et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N. Engl. J. Med. 2017; 377(7): 613-22.
6. *O'Gorman N., Wright D., Syngelaki A., Akolekar R., Wright A., Poon L.C., Nicolaides K.H.* Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. Am. J. Obstet. Gynecol. 2016; 214(1): 103. e101-3. e112.
7. *Scazzocchio E., Figueras F., Crispi F., Meler E., Masoller N., Mula R., Gratacos E.* Performance of a first-trimester screening of preeclampsia in a routine care low-risk setting. Am. J. Obstet. Gynecol. 2013; 208(3): 203. e1-203. e10.
8. *D'Silva A., Fyfe R., Hyett J.* First trimester prediction and prevention of adverse pregnancy outcomes related to poor placentation. Curr. Opin. Obstet. Gynecol. 2017; 29(6): 367-74.
9. *Crovetto F., Figueras F., Triunfo S., Crispi F., Rodriguez-Sureda V., Dominguez C.* et al. First trimester screening for early and late preeclampsia based on maternal characteristics, biophysical parameters, and angiogenic factors. Prenat. Diagn. 2015; 35(2): 183-91.
10. *O'Gorman N., Wright D., Poon L.C., Rolnik D.L., Syngelaki A., de Alvarado M.* et al. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. Ultrasound Obstet. Gynecol. 2017; 49(6): 756-60.
11. *Gebb J., Dar P.* Colour Doppler ultrasound of spiral artery blood flow in the prediction of pre-eclampsia and intrauterine growth restriction. Best Pract. Res. Clin. Obstet. Gynaecol. 2011; 25(3): 355-66.
12. *Hannaford K.E., Tuuli M., Goetzinger K.R., Odibo L., Cahill A.G., Macones G., Odibo A.O.* First-trimester 3-dimensional power Doppler placental vascularization indices from the whole placenta versus the placental bed to predict preeclampsia: does pregnancy-associated plasma protein a or uterine artery Doppler sonography help? J. Ultrasound Med. 2015; 34(6): 965-70.
13. *Kholin A.M., Khodzhaeva Z.S., Gus A.I.* 3D power doppler placental bed vascularization in the first trimester prediction of preeclampsia. Akusherstvo i Ginekologiya/Obstetrics and Gynecology. 2018; (2): 36-43. (in Russian) https://dx.doi.org/10.18565/aig.2018.2.36-43
14. *Kholin A.M., Muminova K.T., Balashov I.S., Khodzhaeva Z.S., Borovikov P.I., Ivanets T.Yu., Gus A.I.* First-trimester prediction of preeclampsia: Validation of screening algorithms in a Russian population. Akusherstvo i Ginekologiya/Obstetrics and Gynecology. 2017; (8): 74-84. (in Russian) http://dx.doi.org/10.18565/aig.2017.8.74-84
15. *Hafner E., Metzenbauer M., Stumpflen I., Waldhor T.* Measurement of placental bed vascularization in the first trimester, using 3D-power-Doppler, for the detection of pregnancies at-risk for fetal and maternal complications. Placenta. 2013; 34(10): 892-8.
16. *Tranquilli A.L.* Introduction to ISSHP new classification of preeclampsia. Pregnancy Hypertens. 2013; 3(2): 57-61.
17. ROAG, AAAR. Hypertensive disorders during pregnancy, during childbirth and the puerperium. Preeclampsia. Eclampsia. Clinical recommendations (protocol of treatment). Moscow: Ministry of Health of Russia; 2016. (in Russian)
18. *Figueras F., Gratacos E.* An integrated approach to fetal growth restriction. Best Pract. Res. Clin. Obstet. Gynaecol. 2017; 38: 48-58.
19. *Odeh M., Ophir E., Maximovsky O., Grinin V., Bornstein J.* Placental volume and three-dimensional power Doppler analysis in prediction of pre-eclampsia and small for gestational age between Week 11 and 13 weeks and 6 days of gestation. Prenat. Diagn. 2011; 31(4): 367-71.
20. *Plasencia W., Gonzalez-Davila E., Gonzalez Lorenzo A., Armas-Gonzalez M., Padron E., Gonzalez-Gonzalez N.L.* First trimester placental volume and vascular indices in pregnancies complicated by preeclampsia. Prenat. Diagn. 2015; 35(12): 1247-54.
21. *Rizzo G., Capponi A., Cavicchioni O., Vendola M., Arduini D.* First trimester uterine Doppler and three-dimensional ultrasound placental volume calculation in predicting pre-eclampsia. Eur. J. Obstet. Gynecol. Reprod. Biol. 2008; 138(2): 147-51.
22. *Hafner E., Metzenbauer M., Stumpflen I., Waldhor T., Philipp K.* First trimester placental and myometrial blood perfusion measured by 3D power Doppler in normal and unfavourable outcome pregnancies. Placenta. 2010; 31(9): 756-63.
23. *Demers S., Girard M., Roberge S., Tetu A., Giguere Y., Forest J.C., Bujold E.* First-trimester placental and myometrial blood perfusion measured by three-dimensional power Doppler in preeclampsia. Am. J. Perinatol. 2015; 32(10): 920-6.
24. *Gonzalez-Gonzalez N.L., Gonzalez Davila E., Padron E., Armas Gonzalez M., Plasencia W.* Value of placental volume and vascular flow indices as predictors of early and late preeclampsia at first trimester. Fetal Diagn. Ther. 2018; Jan 23.
25. *Sonek J., Krantz D., Carmichael J., Downing C., Jessup K., Haidar Z.* et al. First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume. Am. J. Obstet. Gynecol. 2018; 218(1): 126. e121-6. e113.
26. *Merce L.T., Barco M.J., Alcazar J.L., Sabatel R., Troyano J.* Intervillous and uteroplacental circulation in normal early pregnancy and early pregnancy loss assessed by 3-dimensional power Doppler angiography. Am. J. Obstet. Gynecol. 2009; 200(3): 315. e311-8.
27. *Eastwood K.A., Patterson C., Hunter A.J., McCance D.R., Young I.S., Holmes V.A.* Evaluation of the predictive value of placental vascularisation indices derived from 3-Dimensional power Doppler whole placental volume scanning for prediction of pre-eclampsia: A systematic review and meta-analysis. Placenta. 2017; 51: 89-97.
28. *Arakaki T., Hasegawa J., Nakamura M., Hamada S., Muramoto M., Takita H.* et al. Prediction of early- and late-onset pregnancy-induced hypertension using placental volume on three-dimensional ultrasound and uterine artery Doppler. Ultrasound Obstet. Gynecol. 2015; 45(5): 539-43.
29. *Poon L.* Re: Prediction of early- and late-onset pregnancy-induced hypertension using placental volume on three-dimensional ultrasound and uterine artery Doppler. T. Arakaki, J. Hasegawa, M. Nakamura, S. Hamada, M. Muramoto, H. Takita, K. Ichizuka and A. Sekizawa. Ultrasound Obstet. Gynecol. 2015; 45: 539-543. Ultrasound Obstet. Gynecol. 2015; 45(5): 513.
30. *Morel O., Grange G., Fresson J., Schaaps J.P., Foidart J.M., Cabrol D., Tsatsaris V.* Vascularization of the placenta and the sub-placental myometrium: feasibility and reproducibility of a three-dimensional power Doppler ultrasound quantification technique. A pilot study. J Matern. Fetal Neonatal Med. 2011; 24(2): 284-90.

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