2015

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?

Karen E. Hannaford
Washington University School of Medicine in St. Louis

Methodius Tuuli
Washington University School of Medicine in St. Louis

Katherine R. Goetzinger
Washington University School of Medicine in St. Louis

Linda Odibo
Washington University School of Medicine in St. Louis

Alison G. Cahill
Washington University School of Medicine in St. Louis

See next page for additional authors

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?

Karen E. Hannaford, MD, Methodius Tuuli, MD, MPH, Katherine R. Goetzinger, MD, MSCI, Linda Odibo, RN, BSc, MN, Alison G. Cahill, MD, MSCI, George Macones, MD, MSCE, Anthony O. Odibo, MD, MSCE

Objectives—The purpose of this study was to compare the use of vascular indices derived from the whole placenta to those from the placental bed only for predicting preeclampsia and to determine whether the addition of pregnancy-associated plasma protein A (PAPP-A) and mean uterine artery Doppler values improves prediction.

Methods—We conducted a secondary analysis of a prospective cohort of women with singletons between 11 and 14 weeks' gestation undergoing sonography for aneuploidy screening. Placental vascularization indices from the whole placenta versus the placental bed were combined with first-trimester maternal serum PAPP-A levels, mean uterine artery Doppler values, or the combination of both to predict the development of preeclampsia or early preeclampsia (delivery <34 weeks). The predictive ability of each vascular index was calculated by using areas under receiver operating characteristic curves. The sensitivity of the model for predicting preeclampsia and early preeclampsia at fixed false-positive rates of 10% and 20% was calculated.

Results—Of 570 women, 48 (8.4%) had preeclampsia, and 10 (1.7%) had early preeclampsia. The area under the curve and sensitivity values for the prediction of preeclampsia or early preeclampsia were not different when evaluating the whole placenta versus the placental bed. Additionally, there was no significant improvement when adding PAPP-A, uterine artery Doppler values, or both. The variables in the model were more sensitive for the prediction of early preeclampsia than preeclampsia.

Conclusions—Although placental bed vascular indices are modestly predictive of preeclampsia, the addition of PAPP-A and uterine artery Doppler values to vascularization indices in the whole placenta or the placental bed did not significantly improve their predictive ability.

Key Words—first trimester; obstetric ultrasound; preeclampsia; 3-dimensional placental vascularization

Received June 12, 2014, from the Department of Obstetrics and Gynecology, Washington University, St Louis, Missouri USA. Revision requested July 9, 2014. Revised manuscript accepted for publication September 7, 2014.

This work was presented in part at the 2014 American Institute of Ultrasound in Medicine Annual Convention; April 1, 2014; Las Vegas, Nevada.

Address correspondence to Karen E. Hannaford, MD, Department of Obstetrics and Gynecology, Washington University, 660 S Euclid Ave, Campus 1Box 8064, St Louis, MO 63110 USA.

E-mail: hannafordk@wudosis.wustl.edu

Abbreviations

AUC, area under the curve; BMI, body mass index; FI, flow index; MoM, multiple of the median; PAPP-A, pregnancy-associated plasma protein A; 3D, 3-dimensional; VFI, vascularization-flow index; VI, vascularization index

doi:10.7863/ultra.34.6.965

Preeclampsia affects approximately 5% to 8% of pregnancies in the United States and is a leading cause of both maternal and perinatal morbidity and mortality, especially in severe forms, which often require premature delivery.[1] Although maternal characteristics and the pregnancy history can be helpful for identifying patients at high risk, there is still no reliable test to predict

which patients will ultimately develop preeclampsia. Many recent studies have evaluated serum or sonographic markers to further differentiate those at high risk with conflicting results.[2] Serum markers, including first-trimester placental protein 13, pregnancy-associated plasma protein A (PAPP-A), free β-human chorionic gonadotropin, and uterine artery Doppler values, have been studied for the prediction of poor pregnancy outcomes with some promising results.[3–9]

Three-dimensional (3D) power Doppler sonography has been used in various areas of obstetrics and gynecology to evaluate vascular indices in areas of interest. This technique serves as a noninvasive method to evaluate the placenta and has become a method of investigation to evaluate placental blood flow as early as the first trimester. Given the central role of the placenta in the pathogenesis of preeclampsia, specifically the abnormal invasion of trophoblastic cells and remodeling of maternal spiral arteries, there is a biologically plausible mechanism for evaluating the vascular indices of the placenta to identify pregnancies at risk for preeclampsia.[10,11] The indices of interest have been well described and include the vascularization index (VI), flow index (FI), and vascularization-flow index (VFI).[12]

Previous studies by our group and others have shown that placental vascularization indices derived from the whole placenta are lower in pregnancies that eventually develop preeclampsia.[13–15] However, the discriminatory ability of these indices alone for predicting preeclampsia is modest. A recent study suggests that these indices were superior at predicting preeclampsia when obtained from the placental bed only.[9] The findings from that study have yet to be validated by other investigators.

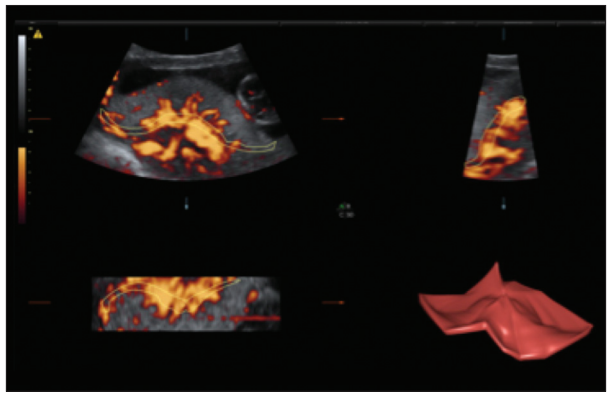
The purpose of this study was to compare the use of vascular indices derived from the whole placenta to those from the placental bed only for predicting preeclampsia and to determine whether the addition of PAPP-A and mean uterine artery Doppler values improves prediction. We hypothesized that evaluation of these vascularization indices at the placental bed may better predict the development of preeclampsia compared to the entire placenta.

Materials and Methods

We conducted a secondary analysis of a prospective cohort study evaluating the prediction of adverse pregnancy outcomes. Women were approached to participate at the time of first-trimester aneuploidy screening in the ultrasound unit at Washington University between December 2008 and April 2012. This study was approved by the Institutional Review Board. Dedicated research nurses enrolled patients between 11 and 14 weeks' gestation with singleton pregnancies after informed consent was obtained. Patients with fetal aneuploidy or anomalies identified on sonography were excluded from the study.

At the first sonographic examination, gestational age was calculated from the last menstrual period and confirmed by crown-rump length measurements. Three-dimensional scans were performed by experienced obstetric sonographers using Voluson 730 Expert ultrasound machines (GE Healthcare, Milwaukee, WI) equipped with 4–8-MHz transducers and an advanced software package capable of calculating the specific vascularization indices described above. The same preestablished instrument power settings were used in all cases (angio mode, cent; smooth, 4/5; frequency, low; quality, 16; density, 6; enhance, 16; balance, GO150; filter, 2; actual power, 2 dB; and pulse repetition frequency, 0.9). The entire view of the placenta was identified by 2-dimensional sonography; the volume box was adjusted to scan the entire placenta, and the sonograms were stored on a removable hard disk for future analysis. Evaluation of the whole placenta was performed by using a 4-dimensional computer software program. This process involved rotating the image at 30° intervals and outlining the contour of the placental 6 times. The placental volume and whole placenta VI, FI, and VFI were then calculated. To interrogate the placental bed only, the region of interest was traced as follows.[9] The caliper was used to trace the deciduo-myometrial junction with a maximal thickness of the traced area of 1 cm or less to account for the irregular shape of each placenta. The placenta was rotated at 30° intervals, and the contour of the placental bed was outlined 6 times (Figure 1). The placental bed VI, FI, and VFI were obtained from 4-dimensional power Doppler histograms. The reproducibility of obtaining these vascular indices was previously reported by our group.[3]

Figure 1. Sonogram for obtaining placental bed vascularization indices.



A Doppler examination of the uterine arteries was performed using transabdominal sonography with color flow mapping. A midsagittal view of the uterus was obtained, and the cervical canal was identified. The transducer was then rotated until the paracervical vessels were visualized. The uterine artery was isolated, and the pulsatility index was measured. The mean value was obtained by averaging the left and right values. An elevated mean uterine artery Doppler value was defined as a pulsatility index above the 75th percentile for each gestational age.

Trained research nurses extracted baseline maternal characteristics, medical and obstetric histories, as well as details of the current pregnancy and outcomes from the medical record. They also obtained results of PAPP-A levels, which were drawn in the first trimester and measured by a commercial laboratory. These levels were reported as multiples of the median (MoMs) adjusted for fetal number, gestational age, maternal age, maternal weight, diabetes status, history of pregnancy affected by Down syndrome, family history of open neural tube defects, and ethnicity.

The primary outcome of this study was to determine the ability of 3D power Doppler vascularization indices in the whole placenta compared to those in the placental bed to predict preeclampsia and early preeclampsia. Secondary outcomes were to determine whether the addition of PAPP-A and uterine artery Doppler values would improve the screening efficiency of the placental indices.

Preeclampsia was defined by using guidelines from the American College of Obstetricians and Gynecologists[1] and by the criteria proposed by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.[4] Mild preeclampsia was defined as blood pressures of 140/90 mm Hg or higher after 20 weeks' gestation in women with previously normal blood pressures and proteinuria of 300 mg of greater in a 24-hour period or at least 1+ on a urine dipstick. Severe preeclampsia was defined as any of the following criteria in a patient with preeclampsia: blood pressures of 160/110 or higher on 2 or more occasions at least 6 hours apart with at least 5 g of proteinuria in a 24-hour period or 3+ on a urine dipstick on 2 samples randomly taken at least 4 hours apart, elevated liver enzymes, visual disturbances, headache or other neurologic signs, persistent right upper quadrant pain or epigastric pain, oliguria with less than 500 mL of urine in a 24-hour period, oligohydramnios, and fetal growth restriction. Early preeclampsia was defined as preeclampsia requiring delivery before 34 weeks.

Baseline and delivery characteristics were compared between patients who developed preeclampsia or early preeclampsia and those who did not by using a Student *t* test for continuous variables and a Pearson χ^2 test for categorical variables. Logistic regression analysis was used to determine whether the vascularization indices from the whole placenta and placental bed made a significant contribution to the prediction of preeclampsia or early preeclampsia as well as to determine whether the addition of PAPP-A, uterine artery Doppler values, or both improved the prediction model. Confounders such as maternal body mass index (BMI), chronic hypertension, and African American race were controlled for in the regression model. The performance of the variables in a screening paradigm was determined by using receiver operating characteristic curves. The area under the curve (AUC) was used to estimate the overall predictive ability of each model. The AUCs for the screening models were compared by using nonparametric statistics.[16] The sensitivity of the model for predicting preeclampsia and early preeclampsia at false-positive rates of 10% and 20% was calculated.

Statistical analysis was performed with Stata version 11.0 software (StataCorp, College Station, TX). $P < .05$ was considered significant.

Results

Over the study period, 1200 women met inclusion criteria and underwent sonographic examinations. We excluded pregnancies in which placental vascularization indices were not obtained because they were scanned in a room that did not have an ultrasound machine equipped with the proper programming to calculate the indices. Twelve patients were lost to follow-up. The final study population included 570 patients with both whole-placenta and placental bed vascularization indices. There were 48 (8.4%) with preeclampsia, including 10 (1.7%) with early preeclampsia. Table 1 shows maternal demographic data and pregnancy outcomes for those women with preeclampsia and early preeclampsia compared to those without. Women who developed preeclampsia or early preeclampsia were more likely to be African American, have chronic hypertension, and have higher BMIs than those who had normal blood pressures. Neonates born to mothers with preeclampsia or early preeclampsia were more likely to be of an earlier gestational age and lower birth weight than those with normal blood pressures.

Three-dimensional power Doppler placental vascularization indices (for both the whole placenta and placental bed alone) were lower among those patients who developed preeclampsia or early preeclampsia. Pregnancy-associated plasma protein A MoM values were lower and

mean uterine artery Doppler values were higher in those who developed preeclampsia and early preeclampsia (Table 2).

There was no significant difference between the AUC for the prediction of preeclampsia or early preeclampsia when comparing vascularization indices from the whole placenta to the placental bed alone. However, prediction efficiency was improved for early preeclampsia compared to preeclampsia (Table 3).

The sensitivity (with fixed false positive rates of 10% and 20%) for the prediction of early preeclampsia was greater than that for preeclampsia when looking at the placental vascularization indices of the placental bed or whole placenta. There was not a significant increase in sensitivity when adding PAPP-A, elevated uterine artery Doppler values, or both (Table 3).

Discussion

In this study, we confirmed the finding of lower placental vascularization indices in those pregnancies with preeclampsia and early preeclampsia. The use of placental vascularization indices for the prediction of preeclampsia or early preeclampsia yields modest results and is not significantly improved with the use of the whole placenta versus the placental bed. We conclude that evaluation of the placental bed is not superior to evaluation of the entire placenta; however, it may become useful when evaluation of the entire placenta is not possible (eg, outside the first trimester). Finally, even though PAPP-A levels were found to be lower and mean uterine artery Doppler values were found to be higher in those pregnancies with preeclampsia, the addition of these markers did not improve the predictive ability of the

Table 1. Maternal Characteristics and Pregnancy Outcomes for Patients With Preeclampsia or Early Preeclampsia Versus No Preeclampsia

Characteristic	No PE (n = 512)	PE (n = 48)	*P* (PE)	Early PE (n = 10)	*P* (Early PE)
Age, y	31.4 ± 587	30.6 ± 6.1	.33	31.2 ± 6.8	.89
Gravidity	2.7 ± 1.7	3.2 ± 2.0	.22	2.3 ± 1.0	.41
Parity	1.0 ± 1.2	1.2 ± 1.4	.55	0.8 ± 1.1	.50
White race, %	57.0	35.4	<.01	20.0	.02
African American race, %	27.2	56.2	<.01	70.0	<.01
Tobacco use, %	8.2	12.7	.3	10.0	.8
Current BMI, kg/m^2	27.6 ± 6.8	32.8 ± 1.4	<.01	32.7 ± 8.0	.03
Chronic hypertension	6.6	41.7	<.01	70.0	<.01
Gestational age at delivery, wk	38.2 ± 3.9	35.7 ± 3.8	<.01	30.2 ± 4.7	<.01
Birth weight, g	3256 ± 713	2572 ± 813	<.01	1430 ± 737	<.01

Data are presented as mean ± SD where applicable. PE indicates preeclampsia.

Table 2. Serum Markers and Placental Vascularization Indices for Patients With Preeclampsia and Early Preeclampsia Versus No Preeclampsia

Parameter	No PE (n = 512)	PE (n = 48)	*P* (PE)	Early PE (n = 10)	*P* (Early PE)
PAPP-A, MoM	1.29 ± 1.0 (1.20–1.38)	0.95 ± 0.47 (0.82–1.09)	.02	0.98 ± 0.56 (0.58–1.38)	.34
High mean UAD	0.23 ± 0.42 (0.19–0.27)	0.25 ± 0.44 (0.13–0.38)	.70	0.4 ± 0.03 (0.03–0.77)	.20
Placental bed VI	51.0 ± 21.0 (49.2–52.9)	44.1 ± 19.0 (38.6–49.6)	.02	42.8 ± 18.7 (29.5–56.3)	.22
Placental bed FI	51.4 ± 11.0 (50.4–52.3)	47.6 ± 9.4 (44.8–50.3)	.02	45.8 ± 11.3 (37.8–54.0)	.12
Placental bed VFI	27.8 ± 14.7 (26.5–29.1)	21.9 ± 12.0 (18.4–25.4)	<.01	20.9 ± 12.1 (12.2–29.5)	.14
VI	17.0 ± 10.2 (16.1–17.9)	14.8 ± 7.6 (12.6–16.9)	.14	12.4 ± 6.5 (7.8–17.1)	.16
FI	44.4 ± 9.0 (43.6–45.1)	42.0 ± 7.8 (39.6–44.2)	.06	39.7 ± 9.5 (32.9–46.5)	.10
VFI	7.9 ± 5.6 (7.5–8.4)	6.4 ± 3.9 (5.2–7.5)	.06	5.4 ± 3.6 (2.8–8.0)	.15

Data are presented as mean ± SD (range). PE indicates preeclampsia; and UAD, uterine artery Doppler.

placental bed vascularization indices. The ability of preeclampsia prediction with either PAPP-A or mean uterine artery Doppler values does not appear to be different from that with placental bed vascularization indices alone.

In a similarly designed study, Hafner et al[9] evaluated placental bed vascularization indices in the first trimester using 3D power Doppler sonography for the prediction of preeclampsia, intrauterine growth restriction, and "severe pregnancy problems," which were defined as pregnancy-induced hypertension and preeclampsia plus birth weight at or below the 10th percentile or delivery at or before 34 weeks. That study included a low-risk population of more than 4000 women and found that placental bed vascularization performed better than other markers such as 3D placental volume, PAPP-A, and uterine artery Doppler values in the first and second trimesters. They found that the placental bed VI could detect 52% of all preeclampsia cases and 60% of severe preeclampsia cases. The authors concluded that the placental bed vascularization indices are superior to other first-trimester sonographic or biochemical markers and performs as well as second-trimester uterine artery measurements. They also suggested that previous studies evaluating vascularization indices in the whole placenta and placental vascular biopsies yielded poorer results for the prediction of adverse pregnancy problems due to decreased vascularity of the placenta in the first trimester secondary to immature development of fetal vessels in the placental villi. However, in our study, we did not find a difference in the predictive values of any of the vascularization indices for detection of preeclampsia, whether the whole placenta or, specifically, the placental bed was examined. Additionally, we did not find an improvement in the predictive ability when serum markers or other Doppler indices were added.

To our knowledge, a study performing a direct comparison between 3D power Doppler vascularization indices of the whole placenta and the placental bed alone has not been reported previously. Other strengths of our study included its prospective design and well-maintained database with a low loss to follow-up and comprehensive maternal histories and delivery outcomes.

However, our study was not without limitations, particularly its relatively small sample size. Consequently, we had only 10 patients with early preeclampsia. Our study may therefore have been underpowered to address this category of preeclampsia. However, the overall incidence of preeclampsia in our cohort was higher than that reported by Hafner et al[9] in the study evaluating placental bed vascularization noted above. Our small number of patients with early preeclampsia should be considered when interpreting our results, as previous studies have suggested that first-trimester screening paradigms are better at predicting early-onset preeclampsia.

Many other investigators are developing models with various combinations of maternal histories, serum markers, and other physical parameters to formulate prediction models for detection of preeclampsia and early preeclampsia. Crovetto et al[17] recently published a nested case-control study within a cohort of nearly 6000 pregnancies, including 28 cases of early preeclampsia. They looked at maternal characteristics, including mean arterial pressure, uterine artery Doppler parameters, and serum markers, including

Table 3. Area Under the Receiver Operating Characteristic Curve Values for the Prediction of Preeclampsia and Early Preeclampsia

Parameter	PE AUC	Sensitivity, %		Early PE AUC	Sensitivity, %	
		10% FPR	20% FPR		10% FPR	20% FP
Whole placenta VI alone	0.77 (0.69–0.84)	45	55	0.89 (0.78–1.00)	79	79
Placental bed VI alone	0.88 (0.77–0.98)	47	60	0.88 (0.76–0.99)	67	80
Placental bed VI + PAPP-A	0.79 (0.72–0.86)	54	54	0.89 (0.78–0.99)	68	80
Placental bed VI + high mean UAD	0.77 (0.69–0.85)	49	62	0.86 (0.71–1.00)	79	79
Placental bed VI + both	0.79 (0.72–0.86)	54	69	0.88 (0.77–1.00)	67	80
Whole placenta FI alone	0.75 (0.68–0.83)	44	56	0.85 (0.78–1.00)	79	79
Placental bed FI alone	0.76 (0.68–0.84)	44	60	0.85 (0.67–1.00)	67	80
Placental bed FI + PAPP-A	0.78 (0.70–0.85)	48	60	0.88 (0.75–1.00)	67	79
Placental bed FI + high mean UAD	0.76 (0.68–0.84)	45	64	0.82 (0.62–1.00)	79	79
Placental bed FI + both	0.78 (0.70–0.85)	48	59	0.87 (0.74–1.00)	68	80
Whole placenta VFI alone	0.77 (0.69–0.84)	44	57	0.89 (0.77–1.00)	79	79
Placental bed VFI alone	0.77 (0.70–0.85)	47	60	0.88 (0.76–1.00)	67	80
Placental bed VFI + PAPP-A	0.79 (0.73–0.86)	52	60	0.89 (0.79–0.99)	67	80
Placental bed VFI + high mean UAD	0.78 (0.70–0.85)	49	65	0.87 (0.73–1.00)	79	79
Placental bed VFI + both	0.79 (0.72–0.86)	53	59	0.89 (0.78–1.00)	68	80

Data were adjusted for maternal BMI, African American race, and chronic hypertension. Values in parentheses are 95% confidence intervals. FPR indicates false-positive rate; PE, preeclampsia; and UAD, uterine artery Doppler. $P < .05$ using nonparametric statistics.

vascular endothelial growth factor, placental growth factor, soluble Fms-like tyrosine kinase 1, and soluble endoglin. They found that for the prediction of early preeclampsia, significant contributors included a maternal history of chronic hypertension, a history of preeclampsia, mean arterial pressure, uterine artery Doppler parameters, placental growth factor, and soluble Fms-like tyrosine kinase 1. Models using these predictors achieved detection rates for early preeclampsia of 77.8% with a false-positive rate of 5% and 88.9% with a false-positive rate of 10% (AUC, 0.958; 95% confidence interval, 0.920–0.996).[17]

In a recent review by Poon and Nicolaides,[18] the effectiveness of screening for early preeclampsia by specific maternal risk factors alone or in combination with several biophysical and biochemical markers was evaluated. They included PAPP-A, placental growth factor, the uterine artery pulsatility index, and mean arterial pressure.[18] They reported a detection rate of 93% (95% confidence interval, 89%–96%) for early preeclampsia with a false-positive rate of 5% and 96% (95% confidence interval, 93%–98%) with a false-positive rate of 10% when these specific variables were used in a prediction model.

In conclusion, 3D power Doppler placental indices in the first trimester may serve a role in the prediction of preeclampsia. Although our data do not support the idea that the placental bed is superior to the whole placenta, we suspect that given our knowledge on the pathophysiologic characteristics of preeclampsia, evaluation of the placental bed may provide important insight. The use of these placental vascularization indices from both the placental bed and the whole placenta were able to predict early preeclampsia with greater sensitivity than preeclampsia. Although associations can be made between PAPP-A, uterine artery Doppler values, and preeclampsia, the exact combination of these markers to form the best prediction model for preeclampsia is yet to be determined. Additionally, larger prospective trials are needed to determine both the combination of these markers as well as the timing of their evaluation to best detect the development of preeclampsia, especially early-onset cases.

References

1. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin: diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol* 2002; 99:159–167.
2. Giguere Y, Charland M, Bujold E, et al. Combining biochemical and ultrasonographic markers in predicting preeclampsia: a systematic review. *Clin Chem* 2010; 56:361–375.
3. Huster KM, Haas K, Schoenborn J, McVean D, Odibo AO. Reproducibility of placental volume and vasculature indices obtained by 3-dimensional power Doppler sonography. *J Ultrasound Med* 2010; 29:911–916.
4. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000;183:S1–S22.
5. Plasencia W, Maiz N, Bonino S, Kaihura C, Nicolaides KH. Uterine artery Doppler at 11 + 0 to 13 + 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2007; 30:742–749.
6. Goetzinger KR, Singla A, Gerkowicz S, Dicke JM, Gray DL, Odibo AO. 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; 30:1138–1142.
7. Khalil A, Cowans NJ, Spencer K, Goichman S, Meiri H, Harrington K. First-trimester markers for the prediction of pre-eclampsia in women with a-priori high risk. *Ultrasound Obstet Gynecol* 2010; 35:671–679.
8. Spencer CA, Allen VM, Flowerdew G, Dooley K, Dodds L. Low levels of maternal serum PAPP-A in early pregnancy and the risk of adverse outcomes. *Prenat Diagn* 2008; 28:1029–1036.
9. 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; 34:892–898.
10. Espinoza J, Romero R, Mee Kim Y, et al. Normal and abnormal transformation of the spiral arteries during pregnancy. *J Perinat Med* 2006; 34:447–458.
11. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. *Biol Reprod* 2003; 69:1–7.
12. Alcázar JL. Three-dimensional power Doppler derived vascular indices: what are we measuring and how are we doing it? *Ultrasound Obstet Gynecol* 2008; 32:485–487.
13. Chen CY, Wang KG, Chen CP. Alteration of vascularization in preeclamptic placentas measured by three-dimensional power Doppler ultrasound. *J Matern Fetal Neonatal Med* 2013; 26:1616–1622.
14. Mihu CM, Drugan T, Mihu D. Contribution of 3D power Doppler ultrasound to the evaluation of placental circulation in normal pregnancies and pregnancies complicated by preeclampsia. *J Perinat Med* 2012; 40:359–364.
15. Odibo AO, Goetzinger KR, Huster KM, Christiansen JK, Odibo L, Tuuli MG. Placental volume and vascular flow assessed by 3D power Doppler and adverse pregnancy outcomes. *Placenta* 2011; 32:230–234.
16. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44:837–845.
17. Crovetto F, Figueras F, Triunfo S, et al. Added value of angiogenic factors for the prediction of early and late preeclampsia in the first trimester of pregnancy. *Fetal Diagn Ther* 2014; 35:258–266.
18. Poon LC, Nicolaides KH. First-trimester maternal factors and biomarker screening for preeclampsia. *Prenat Diagn* 2014; 34:618–627.