THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/jog.14781 J. Obstet. Gynaecol. Res. Vol. 47, No. 6: 2051–2058, June 2021

Combination of three-dimensional placental vascular indices and volume and uterine artery pulsatility index at 10–13 weeks of gestation could improve the prediction of adverse pregnancy outcomes

In Yang Park, Jeong ha Wie, Ji Hyun Park and Ji Young Kwon

Department of Obstetrics and Gynecology, The Catholic University of Korea, Seoul, South Korea

Abstract

Aim: To evaluate whether three-dimensional (3D) placental vascular indices and volumes during the first trimester of pregnancy can be used as predictors of subsequent adverse outcomes.

Methods: This was a prospective cohort study including women with singleton pregnancies between 10 and 13 weeks. 3D placental volume and vascular indices and uterine artery pulsatility index (UtA-PI) were measured. Adverse outcomes were defined whether there was any of the following complications: small for gestational age pregnancy, preterm delivery, and preeclampsia. The serum pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG) levels were also compared. We analyzed the screening performances of these parameters for prediction of any of adverse outcomes.

Results: Of 348 women screened, 300 women were completed follow-up. Overall, 57 (19.0%) of 300 women developed any of adverse pregnancy outcomes.
Multiple logistic regression analysis demonstrated that gestational age—adjusted *z*-scores of $\log_{10}$ placental volume (odds ratio [OR], 0.572; 95% confidence interval [CI], 0.416–0.788), $\log_{10}$ placental vascularization flow index (VFI; OR, 0.676; 95% CI, 0.496–0.921), and $\log_{10}$ UtA-PI (OR, 1.910; 95% CI, 1.335–2.731) were significantly associated adverse pregnancy outcomes. The multivariate model combining placental VFI, placental volume, UtA-PI, and underweight or obese body mass index exhibited the highest screening performances (AUC = 0.77) and PAPP-A and β-hCG did not add any significance to multivariate model.

Conclusions: Placental volume and vascular indices at 10–13 weeks of gestation are significantly associated with adverse pregnancy outcomes. Combination of these placental indices and UtA-PI could improve the screening performance for adverse outcomes.

Key words: adverse pregnancy outcomes, early pregnancy placental volume, placental vascular indices, uterine artery pulsatility index.

Introduction

Preterm birth, preeclampsia, and small for gestational age (SGA) pregnancy are major pregnancy complications that contribute to perinatal morbidity and mortality. Therefore, early identification of pregnancies at risk to develop these complications is very critical. Several studies have developed first trimester screening models using biochemical markers including pregnancy-associated plasma protein A (PAPP-A),

Received: November 16 2020.
Accepted: March 20 2021.
Correspondence: Ji Young Kwon, Department of Obstetrics and Gynecology, College of Medicine, The Catholic University of Korea, 1021, Tongil-ro, Eunpyeong-gu, Eunpyeong St. Mary's Hospital, Seoul, South Korea.
Email: jiyoungk@catholic.ac.kr

free beta-human chorionic gonadotropin (β-hCG), and sonographic indices such as uterine artery pulsatility index (UtA-PI) and shown varying results.[1–8]

Recent advances in three-dimensional (3D) ultrasound have made it possible to objectively assess vascularization as well as to measure placental volume.[9] The vascular indices of interest included vascular density (vascularization index, VI), blood flow intensity (flow index, FI), and blood perfusion (vascularization flow index, VFI). Many attempts have been made to determine whether these ultrasound indices can be used as predictors of subsequent adverse pregnancy outcomes.[9–11] However, studies using placental vascular indices have focused primarily on preeclampsia and SGA pregnancy.[10–16] There is little research on relevance of the risks of preterm labor with or without membrane rupture. Although the development of preterm labor involves several complex pathologies, defective placentation appears to be the starting point for the issues.[17,18] Recently, it was suggested that many complicated pregnancies are not discrete entities but, rather, a syndrome that begins at impaired placentation,[19] it seems clinically useful to see whether changes in placental sonographic indices in early pregnancy can be used to predict the occurrence of complicated pregnancies of all kinds.

Therefore, in this study, we investigated whether 3D placental vascular indices and placental volumes during the first trimester of pregnancy can be used as predictors of adverse outcomes including SGA, preeclampsia, and preterm delivery. In addition, serum PAPP-A and β-hCG levels and UtA-PI were measured in the first trimester of pregnancy to analyze whether multivariate models can be used to improve the screening performances for adverse pregnancy outcomes.

Materials and Methods

Study design

This prospective cohort study was conducted including all pregnant women who underwent antenatal sonogram at 10–13 weeks of gestation at a university hospital in Korea between January 2017 and December 2017. The study was approved by our institution's Institutional Review Board (XC160IM10006K), and written informed consent was obtained from every patient. Exclusion criteria included multiple pregnancies; uncertain data of last menstrual period; positive smoking status; and comorbidities such as chronic hypertension, diabetes, immunologic disease, cardiovascular disease, and renal disease. Women who did not deliver at our hospital were also excluded in the final analysis.

Ultrasound study

Placenta volume and placental vascular indices were assessed between 10 and 13 weeks of gestation using a W580A with Elite (Samsung Medison, Seoul, Korea) ultrasound device equipped with a 3D abdominal probe (4–8 MHz). The following settings were used: 3D scan quality, high; 3D sweep angle, 85°. The volume box was positioned over the entire placenta, and after the 3D sweep, the information regarding placenta volume was stored on a removable hard disk for subsequent analysis. Every measurement was done offline after the scan by the one operator who was blinded to maternal characteristics and obstetric outcomes. Using the rotational technique in the VOCAL (Virtual Organ Computer-aided Analysis) software, each section of the placenta rotated at 18° intervals was manually delineated 10 times. Next, the final volume was automatically calculated, and placental vascular indices including VI, FI, and VFI were obtained from the power Doppler histogram.

The uterine artery Doppler was examined transabdominally. A midsagittal view of the uterus and the cervical canal was identified. The transducer was then rotated until each uterine artery was visualized at the level of the internal os with the color Doppler. The PI was measured with pulsed wave Doppler ensuring an angle of insonation <30°. The mean value was obtained by averaging the left and right values. All sonograms were performed by one of three sonographers with at least 3 years of experience in measuring uterine artery PI.

Maternal characteristics

Gestational age was determined by the last menstrual period if the cycle had been a regular 28 ± 2 day cycle and confirmed by ultrasound using crown-rump length. If ultrasound dating differed by more than 4 days from menstrual dating, gestational age was changed to correspond with the ultrasound dating. The participants' history of previous pregnancy was obtained by questionnaire at the first visit. The baseline and obstetric data included maternal age, parity, body mass index (BMI) at pre-pregnancy, and birthweight of newborn.

Biochemical markers

Serum PAPP-A and β-hCG levels were recruited from the report of the dual marker test for Down syndrome, which were measured and converted to multiples of the median (MoM) values at a commercial laboratory. MoM values were calculated after adjusting for fetal number, gestational age, maternal age, maternal weight, smoking status, diabetes status, type of conception, and ethnicity.

Outcome measures and definitions

Preeclampsia was defined as elevated blood pressure above 140/90 mmHg that develops after 20 weeks of gestation combined with proteinuria or the new development of decreased blood platelets, renal insufficiency, liver involvement, cerebral symptom, or pulmonary edema.[20] SGA pregnancy was defined as newborn weight below the 10th percentile for gestational age by the Korean gender-specific reference percentiles of birth weight at each gestational age.[21] Preterm delivery was defined as spontaneous birth before 37 weeks of gestation with or without prerupture of membrane. Adverse outcomes were defined if there was any of the following complication: SGA pregnancy, preterm delivery, and preeclampsia. Gestational diabetics was not classified into the group of complicated pregnancy as this condition was not directly associated with inadequate placentation. Abnormal BMI at pre-pregnancy was defined as BMI less than 18.5 kg/m^2 or above 25 kg/m^2.

Statistical methods

Baseline characteristics were compared between women with complicated pregnancy and women with unaffected pregnancy by Student's *t*-test for continuous variables and chi-square test for categorical variables.

The distribution of the continuous parameters was assessed using histograms, probability plots, and Shapiro–Wilk W-test, and all the sonographic factors and serum PAPP-A and β-hCG were made Gaussian after logarithmic$_{10}$ transformation. To control for the effects of gestational age, the gestational age-related reference range for placenta volume, placental vascular indices, and UtA-PI was constructed using data from the uncomplicated pregnancy group according to methodology suggested by Royston and Wright.[22] In brief, for each parameter, the mean for each gestational age were derived from the regression of $\log_{10}$ parameter against gestational age (days). The correlation coefficient, *R*-squared (R^2), was used as a model selection criteria.

Then the absolute residuals were regressed against gestational ages to determine the SD. The fitted values of this regression model were multiplied by $\sqrt{(\pi/2)}$ to give gestation-specific SD. The normality of the *z*-scores was evaluated with the Shapiro–Wilk W-test and a normal plot. Residual statistics was used out to identify outliers that have significant impact on the regression model. It there were outliers, we rechecked the placental volume and indices from stored 3D volume data. Finally, all the sonographic parameters were expressed as *z*-scores, which were calculated using the expected mean and SD at each gestational age.

Gestational age-adjusted *z*-scores for placental volume, placental 3D vascular indices, and UtA-PI were compared between women with adverse pregnancy outcomes and the control group using Student's *t*-test. Log_{10} MoM PAPPA-A and $\log_{10}$ MoM free β-hCG were also compared between both groups. Multivariate logistic regression analysis was performed to determine which of the factors among *z*-scores of $\log_{10}$ sonographic parameters, $\log_{10}$ PAPP–A, and abnormal BMI were significantly associated with the adverse pregnancy outcomes. And then, we performed multiple logistic regression with backward elimination to construct predictive models using significant parameters. As placental vascular indices are strongly correlated each other, only VFI on behalf of placental vascular indices was included in the multivariate analysis. A separate receiver operation characteristics (ROC) curve was assessed for five models: the placental volume alone, placental VFI alone, UtA-PI alone, and multivariate models with or without abnormal BMI. The screening performance of logit models for the prediction of adverse outcomes, as well as detection rates (DR) with 5% and 10% false-positive rate (FPR), was determined by ROC curve. The AUCs of each model were analyzed by pairwise comparison. SPSS (version 12.0; SPSS Inc., Chicago, IL) was used for statistical analysis. All reported *p* values are two-sided, and a *p* value of <0.05 was considered statistically significant.

Results

In total, 348 pregnant women who met the inclusion criteria were enrolled in this study. Of these women, 1 woman suffered a miscarriage and 47 women

Table 1 Baseline characteristics according to obstetric outcomes

Characteristics	Complicated pregnancy				Unaffected pregnancy	
	SGA without preeclampsia (n = 17)	Preterm without preeclampsia (n = 33)	Preeclampsia (n = 7)	Total (n = 57)	(N = 243)	p value[a]
Maternal age (years)	33.6 ± 3.5	33.8 ± 3.4	34.6 ± 3.4	33.5 ± 3.3	33.7 ± 3.6	0.730
Advanced age (≥35 years)	6 (35.3%)	13 (39.4%)	2 (28.6%)	21 (36.8%)	97 (39.9%)	0.393
Nullipara	7 (41.2%)	15 (45.5%)	2 (28.6%)	24 (42.1%)	102 (42.0%)	1.000
Height	161.6 ± 4.6	161.5 ± 4.5	163.0 ± 2.7	161.8 ± 4.4	162.0 ± 5.2	0.759
Weight at pre-pregnancy (kg)	52.5 ± 8.5	56.3 ± 10.6	60.3 ± 7.5	55.9 ± 10.2	55.0 ± 7.1	0.420
BMI at pre-pregnancy (kg/m^2)	20.0 ± 2.5	21.6 ± 4.4	22.7 ± 3.2	21.4 ± 3.9	21.0 ± 2.5	0.442
Underweight	4 (23.5%)	8 (24.2%)	0 (0.0%)	12 (21.1%)	24 (9.9%)	0.039[a]
Obese	1 (5.9%)	3 (8.1%)	2 (28.6%)	6 (10.5%)	17 (7.0%)	0.405
Underweight or obese	5 (29.4%)	11 (32.3%)	2 (28.6%)	18 (31.6%)	41 (16.9%)	0.016[a]
History of preterm delivery	1 (5.9%)	8 (24.2%)	2 (28.6%)	11 (19.3%)	12 (4.9%)	0.687
History of preeclampsia	0 (0.0%)	1 (3.0%)	1 (14.3%)	2 (3.5%)	2 (0.8%)	0.112
Gestational age at sonogram (weeks)	11.1 ± 0.9	11.4 ± 1.0	11.1 ± 0.9	11.2 ± 0.9	11.0 ± 0.9	0.337
Gestational age at delivery (weeks)	38 [37–39]	34 [32–35]	37 [35–39]	35.3 ± 3.4	38.5 ± 1.5	<0.001[a]
Birth weight (kg)	2.5 [2.3–2.6]	2.3 [1.7–2.6]	2.6 [2.4–2.9]	2.3 ± 0.6	3.2 ± 0.4	<0.001[a]

Note. All values are expressed as mean ± SD, number (%), or median [IQR] where applicable.; Abbreviations: BMI, body mass index; SGA: small for gestational age. [a]Student's t test between complicated pregnancy and unaffected pregnancy.

including 2 women with fetal aneuploidy were lost to follow-up. Finally, 300 women were eligible for analysis. Of 300 women, 120 (40%) women were aged 35 or older and 27 (9%) women had a previous history of preterm birth or preeclampsia. Seventeen (5.6%) of the 300 women had an SGA pregnancy without preeclampsia and 33 women (11.0%) developed preterm delivery without preeclampsia and 7 women (2.3%) had a preeclampsia. Overall, 57 women (19.0%) developed adverse pregnancy outcomes.

Table 1 shows the demographic features and pregnancy outcomes of the study's subgroups. There were no statistically significant intergroup differences in maternal age, parity, height, weight, and mean BMI at pre-pregnancy and history of preterm delivery and preeclampsia between the groups. Underweight women had significantly developed adverse pregnancy outcomes (p = 0.039).

In the unaffected pregnancies, log-transformed placenta volume, VI, FI, VFI, and UtA-PI were satisfactorily fitted to the gestational age in days with a linear model. The corresponding regression equations and their R^2 values are shown in Table 2. Spearman's correlation analysis showed that all the sonographic indices were not significantly related to maternal weight, height, BMI, and age.

The measured sonographic parameters in both groups were transformed into gestational age-adjusted z-scores and compared (Table 3). The z-$\log_{10}$ placental volume in women with adverse outcomes was significantly smaller than that in women without adverse outcomes ($p < 0.001$). The z-$\log_{10}$ placental vascular indices including VI, FI, and VFI were all significantly lower than those in women without adverse outcomes (p = 0.001, 0.005, and 0.001, respectively). In addition, z-$\log_{10}$ UtA-PI was significantly higher in women with adverse outcomes compared with control women ($p < 0.001$). Women with adverse pregnancy outcomes had significantly lower serum PAPP-A than unaffected women (p = 0.028). β-hCG was not significantly different between the two groups (p = 0.786) (Table 4).

Multiple logistic regression analysis demonstrated that z-$\log_{10}$ placental volume (odds ratio [OR], 0.572; 95% confidence interval [CI], 0.416–0.788, P = 0.001), z-$\log_{10}$ placental VFI (OR, 0.676; 95% CI, 0.496–0.921, P = 0.013), and z-$\log_{10}$ UtA-PI (OR, 1.910; 95% CI, 1.335–2.731, $P < 0.001$) were significantly associated with adverse pregnancy outcomes (Table 5).

Table 2 Regression equations and their correlation coefficients (R^2) for all sonographic variables as a function of gestational age at measurement

Variables	Constant	$A \times$ GA	R^2
Log_{10} placental volume	−0.3612	0.0239	0.385
Log_{10} placental VI	0.4797	0.0080	0.025
Log_{10} placental FI	1.3496	0.0048	0.036
Log_{10} placental VFI	−0.1588	0.0128	0.035
Log_{10} UtA-PI	0.3503	−0.0035	0.012

Abbreviations: A, coefficient for linear component; GA, gestational age (days); UtA-PI, uterine artery pulsatility index; VFI, vascularization flow index.

Table 3 Comparison of sonographic parameters according to obstetric outcomes

Variables (*z*-values)	Complicated pregnancy (*N* = 57)	Unaffected pregnancy (*N* = 243)	*p* value
Log_{10} placental volume	−0.729 ± 1.154	−0.009 ± 0.991	<0.001
Log_{10} placental VI	−0.475 ± 1.114	0.013 ± 0.954	0.001
Log_{10} placental FI	−0.423 ± 1.110	0.006 ± 1.012	0.005
Log_{10} placental VFI	−0.517 ± 1.098	−0.010 ± 0.961	0.001
Log_{10} UtA-PI	0.550 ± 0.771	0.018 ± 0.959	<0.001

Note. All values are expressed as mean ± SD. Abbreviations; FI, flow index; UtA-PI, uterine artery pulsatility index; VFI, vascularization flow index; VI, vascularization index.

Table 4 Comparison of serum PAPP-A and free β-hCG according to obstetric outcomes

Variables	Complicated pregnancy (*N* = 57)	Unaffected pregnancy (*N* = 243)	*p* value
Log_{10} MoM PAPP-A	−0.029 ± 0.220	0.045 ± 0.223	0.028
Log_{10} MoM free β-hCG	0.019 ± 0.164	0.026 ± 0.168	0.786

Note. All values are expressed as mean ± SD. Abbreviations: β-hCG, beta human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein A.

The screening performance of each sonographic factor and multivariate model is shown in Table 6. The AUCs of single separate parameters were between 0.6 and 0.7 (0.65 for *z*-log_{10} UtA-PI and *z*-log_{10} placental volume, and 0.62 for *z*-log_{10} placental VFI, respectively), and the AUCs of multivariate models were above 0.7. The highest AUC was from the multivariate model combining UtA-PI, placental VFL, placenta volume, and abnormal BMI. This combination model significantly improved screening performance in predicting adverse outcomes compared with those of single parameter alone.

Discussion

Pregnancy begins with fetoplacental adaptation of the placenta. The disturbance of this initial process leads to inadequate coordination of vascular and inflammatory processes between mother and fetus, which can cause SGA pregnancy, preterm delivery, and a hypertensive disorder as various other factors are added during pregnancy.[19] This prospective study explored whether first trimester placental sonographic indices can predict development of any of these complications of pregnancy. In addition, we attempted to develop screening model including all significant sonographic parameters and maternal characteristics for prediction of subsequent adverse outcomes.

Table 5 Multiple logistic regression analysis for the prediction of adverse outcomes

Variables	OR (95% CI)*	*p* value
Log_{10} placenta volume (*z*-score)	0.572 (0.416–0.788)	0.001
Log_{10} placental VFI (*z*-score)	0.676 (0.496–0.921)	0.013
Log_{10} UtA-PI (*z*-score)	1.910 (1.335–2.731)	<0.001
Log_{10} MoM PAPP-A	0.368 (0.087–1.555)	0.174
Maternal BMI (<18.5 or ≥25 (kg/m^2)	2.873 (1.355–6.090)	0.006

Abbreviations: CI, confidence interval; OR, odds ratio; UtA-PI, uterine artery pulsatility index; PAPP-A, pregnancy-associated plasma protein A; VFI, vascularization flow index.

In this study, placental volume and placental vascular indices were decreased in pregnant women at risk of developing SGA pregnancy, preterm delivery, or preeclampsia. In addition, this study confirmed that high UtA-PI was associated with subsequent adverse pregnancy outcomes. The screening performances for prediction of adverse outcomes of each predictor, placental volume, placental vascular indices, and UtA-PI alone showed relatively poor discriminatory ability with the AUC of 0.6–0.7, but the combination of placental volume, placental VFI, and UtA-PI could improve the AUC of up to 0.74. Especially, the addition of maternal BMI to the combination of placental sonographic indices and UtA-PI exhibited the highest screening performances (AUC = 0.77). PAPP-A and β-hCG were not significantly predictors in final model.

This study suggested that all 3D placental vascular indices and volume at 11–13 weeks of gestation were lower in women at high risk of subsequent adverse outcomes compared with unaffected women. Several

Table 6 Detection rates of adverse pregnancy outcomes at different FPR and comparison of screening performance of placental volume, placental VFI, UtA-PI, maternal BMI, and their combinations

Variables	Detection rate %		AUC (95% CI)	p value[a]
	5% FPR	10% FPR		
z-$\log_{10}$ placental volume, z-$\log_{10}$ VFI, z-$\log_{10}$ UtA-PI, abnormal BMI[b]	36.8	49.2	0.77 (0.72–0.81)	–
z-$\log_{10}$ placental volume, z-$\log_{10}$ VFI, z-$\log_{10}$ UtA-PI	28.1	33.3	0.74 (0.70–0.79)	0.200
z-$\log_{10}$ placental volume	21.1	26.3	0.65 (0.60–0.70)	0.014
z-$\log_{10}$ placental VFI	15.8	24.6	0.62 (0.56–0.68)	0.002
z-$\log_{10}$ UtA-PI	8.7	15.8	0.65 (0.60–0.71)	0.028

Abbreviations: AUC, area under the receiver operation characteristics (ROC) curve; BMI, body mass index; CI, confidence interval; FPR, false positive rate; UtA-PI, uterine artery pulsatility index; VFI, vascularization flow index.
[a]Pairwise comparison of ROC curves with combined model including placental volume, placental VFI, UtA-PI, and abnormal BMI.
[b]Abnormal BMI < 18.5 or ≥25 kg/m^2.

studies have demonstrated that low placental volume in the first trimester was associated with the development of severe preeclampsia[12,14,15] or SGA pregnancy.[12,13,15] However, other studies have found that placental volumes were not significantly different in pregnancies resulting in SGA pregnancy[10,11,23] and preeclampsia.[10,11,24] Regarding placental vascular indices, all indices measured at first trimester were significantly decreased in pregnancies with adverse outcomes in this study. These findings are consistent with those of Plasencia et al.[13] while Odeh et al.[10] found that only VI significantly decreased in pregnancy resulting in preeclampsia and Odibo et al.[11] found that all placental indices were significantly low in the pregnancies that developed preeclampsia but all indices were not significantly associated with SGA pregnancy.

Currently, Doppler examination of the uterine artery is used as a method of evaluating inadequate placentation. UtA-PI can represent placentation through spiral artery invasion, with high resistance reflecting inadequate uteroplacental circulation. High UtA-PI in the second and third trimesters of pregnancy is related to the risk of preeclampsia and SGA.[3] In the first trimester, the accuracy of UtA-PI for prediction of preeclampsia is reportedly controversial.[4–8] Demers et al.[5] and Melchiorre et al.[4] reported that the first trimester UtA-PI was associated with the risk of preterm preeclampsia but not with the risk of term preeclampsia. Since UtA-PI cannot assess the placental circulation in real time, it seems to show significant changes only after at least two-thirds of the placental vascularization is affected.[25] In this study, UtA-PI in the first trimester of pregnancy was significantly increased in the pregnancy at risk of adverse outcomes, but the screening performance of UtA-PI alone was moderate.

PAPP-A and β-hCG are currently measured for screening of Down syndrome at 11–14 weeks of pregnancy.[26] In particular, PAPP-A activates the mitogenic function of insulin like growth factor, which plays an important role in placental growth and development.[27] Several studies have shown that low PAPP-A is associated with the development of preeclampsia.[2,3] However, it appears to be primarily useful for predicting early-onset severe preeclampsia. In this study, PAPP-A was not a significant predictor of adverse pregnancy outcomes in the multivariate analysis.

Unlike the previous studies examining their effects on each complication separately, our study evaluated the performance of placental sonographic indices for predicting the overall complications. Early screening for pregnancy complications is not limited to preeclampsia or SGA but include all of the pregnancy complications. This can help counseling during antenatal care using the pregnancy risk assessment.

In addition, few previous studies have analyzed the association of placental sonographic indices with the risk of subsequent preterm birth. In this study, we analyzed adverse pregnancy outcomes by adding preterm birth to preeclampsia and SGA pregnancy. In the case of preterm birth, various multiple pathophysiology practices, such as uterine infection, overdistension, and maternal or fetal stress, have been the focus; however, recently, defective placentation has been reported to be associated with preterm labor.[18] Brosen et al.[19] demonstrated with placental biopsy that preterm labor, preterm premature rupture of the membrane, fetal growth restriction, and preeclampsia were associated with defective deep placentation. All major pregnancy complications seem to be interrelated diseases caused by defective placentation.

The main result of the study suggested the usefulness of placental volume, placental vascularization, and the UtA-PI in the first trimester in predicting adverse obstetric outcomes. However, the heterogeneity of the different software, the lack of standardization of normality values, and the time required to perform these measurements make it difficult establishing a screening method with these parameters.

Compared with the measurement of placental 3D volume, placental vascular indices could be used for a quick and reliable assessment of placental development.[28] Considering that there are some limitations on clinical use of volume calculation because it takes time to draw manual outline of the target organ on several planes, 3D placental vascular indices are likely to be a practical alternative.

Our study has some limitations. First, this study had small sample size and could be inevitably subject to selection bias. Second, it might be argued that the complication rate of 19% appears to be high. This might be explained by a high proportion of women with preterm delivery, preeclampsia, or advanced maternal age enrolled in the study. Alternatively, since the study was conducted in a tertiary care center, high-risk women were more likely to be included, whereas unaffected pregnant women were often lost to follow-up.

In conclusion, this study confirms that placental volume and placental 3D Doppler vascular index can reflect the adequacy of placentation at 11–14 weeks of pregnancy, and thus can ultimately be used to predict the development of pregnancy complications such as preterm birth, SGA pregnancy, or preeclampsia. Combinations of these placental indices and UtA-PI could achieve better screening performance than does either parameter alone in the early prediction of adverse pregnancy outcomes.

Disclosure

This study was supported by a research grant from Samsung Medison Co., Ltd.

References

1. Ong CYT, Liao AW, Spencer K, Munim S, Nicolaides KH. First trimester maternal serum free β human chorionic gonadotrophin and pregnancy associated plasma protein a as predictors of pregnancy complications. *Br J Obstet Gynaecol*. 2000;**107**:1265–70.
2. Smith GCS, Stenhouse EJ, Crossley JA, Aitken DA, Cameron AD, Connor JM. Early pregnancy levels of pregnancy-associated plasma protein A and the risk of intrauterine growth restriction, premature birth, preeclampsia, and stillbirth. *J Clin Endocrinol Metabol*. 2002;**87**:1762–7.
3. Cnossen JS, Morris RK, ter Riet G, van der Post JAM, Coomarasamy A, Zwinderman AH, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *Can Med Assoc J*. 2008;**178**:701–11.
4. Melchiorre K, Wormald B, Leslie K, Bhide A, Thilaganathan B. First trimester uterine artery Doppler indices in term and preterm preeclampsia. *Ultrasound Obstet Gynecol*. 2008;**32**:133–7.
5. Demers S, Boutin A, Gasse C, Drouin O, Girard M, Bujold E. First-trimester uterine artery Doppler for the prediction of preeclampsia in nulliparous women: the great obstetrical syndrome study. *Am J Perinatol*. 2019;**36**:930–5.
6. Rizzo G, Capponi A, Cavicchioni O, Vendola M, Arduini D. First trimester uterine Doppler and three-dimensional ultrasound placental volume calculation in predicting preeclampsia. *Eur J Obstet Gynecol Reprod Biol*. 2008;**138**:147–51.
7. Audibert F, Boucoiran I, An N, Aleksandrov N, Delvin E, Bujold E, et al. Screening for preeclampsia using first-trimester serum markers and uterine artery Doppler in nulliparous women. *Am J Obstet Gynecol*. 2010;**203**:383.e1–8.
8. Poon LC, Staboulidou I, Maiz N, Plasencia W, Nicolaides KH. Hypertensive disorders in pregnancy: screening by uterine artery Doppler at 11-13 weeks. *Ultrasound Obstet Gynecol*. 2009;**34**:141–8.
9. Pairleitner H, Steiner H, Hasenoehrl G, Staudach A. Three-dimensional power Doppler sonography: imaging and quantifying blood flow and vascularization. *Ultrasound Obstet Gynecol*. 1999;**14**:139–43.
10. 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**:367–71.
11. 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**:230–4.
12. Papastefanou I, Chrelias C, Siristatidis C, Kappou D, Eleftheriades M, Kassanos D. Placental volume at 11 to 14 gestational weeks in pregnancies complicated with fetal growth restriction and preeclampsia. *Prenat Diagn*. 2018;**38**:928–35.
13. Plasencia W, Akolekar R, Dagklis T, Veduta A, Nicolaides KH. Placental volume at 11-13 weeks' gestation in the prediction of birth weight percentile. *Fetal Diagn Ther*. 2011;**30**:23–8.
14. González-González NL, González Dávila E, Padrón 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;**44**:256–63.
15. González-González NL, González-Dávila E, González Marrero L, Padrón E, Castro-Conde JR, Plasencia W. Value of placental volume and vascular flow indices as predictors of intrauterine growth retardation. *Eur J Obstet Gynecol Reprod Biol*. 2017;**212**:13–9.

16. Plasencia W, González-Dávila E, González Lorenzo A, Armas-González M, Padrón E, González-González NL. First trimester placental volume and vascular indices in pregnancies complicated by preeclampsia. *Prenat Diagn*. 2015;**35**:1247–54.
17. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Science*. 2014;**345**:760–5.
18. Kim YM, Bujold E, Chaiworapongsa T, Gomez R, Yoon BH, Thaler HT, et al. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. *Am J Obstet Gynecol*. 2003;**189**:1063–9.
19. 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**:193–201.
20. Practice Bulletin No ACOG. 202: gestational hypertension and preeclampsia. *Obstet Gynecol*. 2019;**133**:e1–e25.
21. Lee JK, Jang HL, Kang BH, Lee KS, Choi YS, Shim KS, et al. Percentile distributions of birth weight according to gestational ages in Korea (2010-2012). *J Korean Med Sci*. 2016;**31**: 939–49.
22. Royston P, Wright EM. How to construct 'normal ranges' for fetal variables. *Ultrasound Obstet Gynecol*. 1998;**11**:30–8.
23. Schermuly S, Abele H, Zubke W, Kagan KO. First trimester pregnancy volumes and subsequent small for gestational age fetuses. *Arch Gynecol Obstet*. 2014;**290**:41–6.
24. Effendi M, Demers S, Giguère Y, Forest JC, Brassard N, Girard M, et al. Association between first-trimester placental volume and birth weight. *Placenta*. 2014;**35**:99–102.
25. Sebire NJ. Umbilical artery Doppler revisited: pathophysiology of changes in intrauterine growth restriction revealed. *Ultrasound Obstet Gynecol*. 2003;**21**:419–22.
26. Baer RJ, Flessel MC, Jelliffe-Pawlowski LL, Goldman S, Hudgins L, Hull AD, et al. Detection rates for aneuploidy by first-trimester and sequential screening. *Obstet Gynecol*. 2015; **126**:753–9.
27. Lawrence JB, Oxvig C, Overgaard MT, Sottrup-Jensen L, Gleich GJ, Hays LG, 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 U S A*. 1999;**96**:3149–53.
28. Mercé LT, Barco MJ, Bau S. Reproducibility of the study of placental vascularization by three-dimensional power Doppler. *J Perinat Med*. 2004;**32**:228–33.