IMAGING

First-trimester 3-dimensional power Doppler of the uteroplacental circulation space: a potential screening method for preeclampsia

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OBJECTIVE: The objective of the study was to compare 3-dimensional power Doppler (3DPD) of the uteroplacental circulation space (UPCS) in the first trimester between women who develop preeclampsia (PEC) and those who do not and to assess the 3DPD method as a screening tool for PEC.

STUDY DESIGN: This was a prospective observational study of singleton pregnancies at 10 weeks 4 days to 13 weeks 6 days. The 3DPD indices, vascularization index (VI), flow index (FI), and vascularization flow index (VFI), were determined on a UPSC sphere biopsy with the virtual organ computer-aided analysis (VOCAL) program.

RESULTS: Of 277 women enrolled, 24 developed PEC. The 3DPD indices were lower in women who developed PEC. The area under the receiver-operating characteristics curve for the prediction of PEC was 78.9%, 77.6%, and 79.6% for VI, FI, and VFI, respectively.

CONCLUSION: Patients who develop PEC have lower 3DPD indices of their UPCS during the first trimester. Our findings suggest that this ultrasonographic tool has the potential to predict the development of PEC.

Key words: 3-dimensional power Doppler, preeclampsia, screening tool, uteroplacental circulation space

Cite this article as: Dar P, Gebb J, Reimers L, et al. First-trimester 3-dimensional power Doppler of the uteroplacental circulation space: a potential screening method for preeclampsia. Am J Obstet Gynecol 2010;203:238.e1-7.

Normal development of the intervillous space during the first trimester is crucial to proper fetal-maternal interaction.[1] Pivotal to this is the trophoblast-mediated modification of the small-caliber spiral arteries into wide-caliber uteroplacental vessels that deliver blood to the intervillous space[2] and ultimately to the placenta at low pressure. Inadequate modification of the spiral arteries resulting in decreased blood flow to the placenta has been implicated in the pathophysiology of preeclampsia.[3]

Advances in both ultrasound and the knowledge of the pathophysiology of preeclampsia have revived attempts at finding a screening method for the disorder with the focus shifted to identifying a screening program for the first trimester. Current imaging methods, including first trimester uterine artery pulsatility index (UAPI)[4] or resistive index[5] and placental volume,[6] have low detection rates for preeclampsia and are improved only if detection of severe cases requiring early delivery are the focus. This may be because these methods represent an indirect assessment of the abnormal placentation process.

The addition of maternal serum markers such as placental protein 13[7] and pregnancy-associated plasma protein A (PAPP-A),[8] which are likely to better reflect the placentation process, are predicted to significantly improve screening sensitivity.[9,10]

The introduction of 3-dimensional (3D) ultrasound technologies, with the option of imaging vascular volumes,[11-13] has created an excellent opportunity to study early changes in the uteroplacental circulation space (UPCS), which includes the maternal spiral arteries and the intervillous space.

This technology may therefore allow a more direct evaluation of the abnormal placentation process that occurs with preeclampsia and particular findings that may herald the development of preeclampsia. In this study, we sought to: (1) compare first-trimester 3D power Doppler (3DPD) indices of the UPCS in patients who developed preeclampsia and those who did not; and (2) evaluate 3DPD of the UPCS as a potential first-trimester screening method for preeclampsia.

Materials and Methods

We conducted a prospective observational study in singleton pregnancies. All patients, 18 years old and older, who were attending our center for routine screening for chromosomal abnormalities by measurement of fetal nuchal translucency (NT) thickness and maternal serum-free beta-human chorionic gonadotropin and PAPP-A at a gestation of 10 weeks 4 days to 13 weeks 6 days were invited to participate.

The study was approved by our institutional review board, and written informed consent was obtained from all participants. Patients with multiple gestations or anomalous fetuses were ex-

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Received July 26, 2009; revised Nov. 2, 2009; accepted June 7, 2010.

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This study was supported in part by a grant from the Federico Foundation.

doi: 10.1016/j.ajog.2010.06.006

cluded. Patients' demographic data were extracted from their prenatal electronic records. This included maternal age; parity; ethnicity; medical history (including chronic hypertension, diabetes mellitus, antiphospholipid syndrome, thrombophilia, and sickle cell disease); obstetrical history (including previous pregnancy with preeclampsia); and medications (including antihypertensive medications). Maternal weight and height were measured and the body mass index (BMI) was calculated.

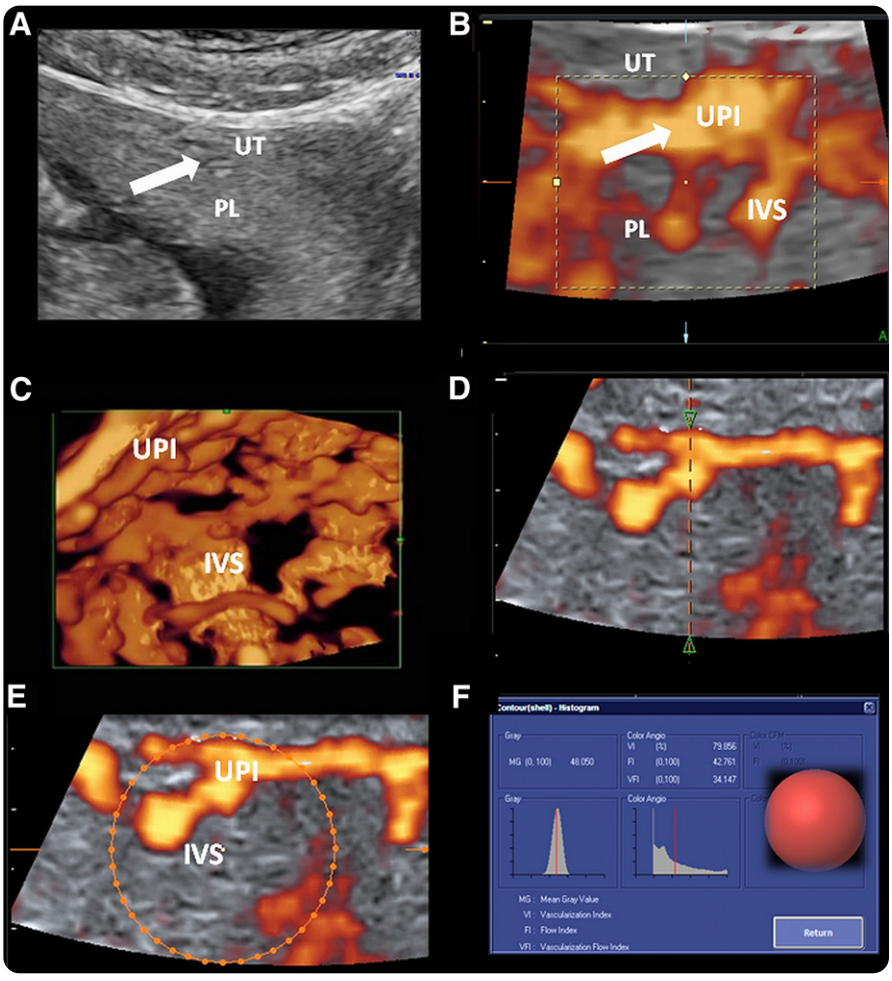
A single researcher (P.D.) performed all the ultrasound scans and the 3DPD analysis using Voluson 730 Expert (GE, Milwaukee, WI). Following transabdominal measurements of the crown-rump length (CRL) and NT, the uteroplacental interface was identified, and power Doppler was applied avoiding the fetus. The power Doppler settings were preadjusted on all machines to allow capture of weak signals that are common in the intervillous space, in addition to spiral arteries, and settings were maintained constant for all cases: image quality at high 1, color gain at 1.6, pulse repetition frequency at 0.6 kHz, and wall motion filter at 50 Hz. All other Doppler and sonographic settings were at the manufacturer default settings.

The 3D volume box was placed to contain, in addition to the uteroplacental interface, the placenta and the myometrium. After asking the patient to hold her breath and remain still for 10 seconds, a sweeping angle of 50° was used while the 3D volume was acquired. In the multiplanar view, the A plane was adjusted using the Z-axis knob to bring the uteroplacental interface axis to a transverse position in the center of the screen with the myometrium above and placenta below that axis.

Optimal zooming (×1.5-1.8) was achieved and a spherical volume biopsy with a diameter of 2 cm was sampled. One pole was placed at the upper end of the uteroplacental circulation and the other pole at the placenta (Figure 1). The spherical volume was then analyzed with the virtual organ computer-aided analysis program (VOCAL; GE) to determine the vascularization index (VI; the ratio between color voxels and total voxels expressed in percentages), flow index (FI; the sum of the color voxels' signal intensity divided by the number of color voxels, quantified between 0 and 100), and vascularization flow index (VFI; the sum of color voxels' signal intensity divided by the total tissue voxels, quantified between 0 and 100).

The uterine arteries were then identified and the pulsatility index was measured bilaterally. Because many placentas at this stage of pregnancy may appear to have both anterior and posterior implantation sites, the placental location was recorded according to sphere location. For example, if a placenta appeared to extend from the anterior to the posterior uterine wall and the volume was rendered from the posterior part, the placenta was recorded as posterior. Maternal serum was sent for PAPP-A as part of the aneuploidy screening program.

FIGURE 1
Steps for the 3DPD indices of the UPCS in first trimester



The required steps to acquire the 3-dimensional power Doppler indices of the UPCS in first trimester. The uteroplacental interface (UPI, *arrow*) is identified between the uterus (UT) and the placenta (PL) on **A,** gray scale and **B,** power Doppler views. The intervillous space (IVS) can be seen within the placenta. **C,** The 3DPD rendered view of the UPI and IVS. After activation of the virtual organ computer-aided analysis option (GE, Milwaukee, WI) the sphere sampling method is chosen. **D,** One pole is placed at the uterine side of the uteroplacental interface and the other at the fetal edge of the placenta. **E,** Sphere sampling is then activated, and **F,** the 3DPD indices are automatically calculated from the sphere biopsy.

3DPD, 3-dimensional power Doppler; *UPCS*, uteroplacental circulation space.

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Patients were followed up to the end of their pregnancies and outcome data were compiled. The primary outcome data were whether patients developed preeclampsia, defined by criteria outlined by the American College of Obstetrics and Gynecology. Briefly, patients had to have systolic blood pressures of 140 mm Hg or diastolic blood pressures of 90 mm Hg or higher occurring after 20 weeks of gestation with proteinuria, defined as urinary excretion of 0.3 g protein or higher in a 24-hour urine specimen.[14] The results of the 3D Doppler studies were not shared with the patients or their providers and did not affect the management of their pregnancies.

Statistical analysis

SAS version 9.1.3 (SAS Institute, Cary, NC) was used for statistical analysis. Maternal demographic characteristics for both the preeclampsia and control group were compared using the Student *t* test, Wilcoxon test, and Fisher's exact tests. The distribution of VI, FI, and VFI was analyzed with the Kolmogorov-Smirnov test. The indices were plotted against CRL and correlation was evaluated by the Pearson's correlation test.

The 3DPD indices were compared between patients who developed preeclampsia and unaffected patients. Multivariate logistic regression analysis was used to determine which 3DPD indices significantly predicted preeclampsia, adjusting for the maternal and gestational characteristics. Screening accuracy for each index was assessed through receiver-operating characteristics (ROC) curves. Overall accuracy was estimated with the area under the ROC curve and associated 95% confidence interval (CI). $P < .05$ was considered statistically significant.

RESULTS

Two hundred seventy-seven patients were enrolled. Eight patients (2.9%) had second-trimester spontaneous abortions, 1 patient (0.4%) had a voluntary termination, and 10 patients (3.6%) were lost to follow-up. Of the remaining 258 patients, 24 (9.3%) developed preeclampsia and 234 (90.7%) patients did not. Among those with preeclampsia, 12 (50%) had severe preeclampsia.[14] Three of these had preeclampsia requiring delivery prior to 34 weeks, 9 had severe preeclampsia after 34 weeks' gestation, and 2 patients of the latter group had eclampsia. Two patients with preeclampsia (8.3%) had a small-for-gestational-age (SGA) newborn defined as birthweight under the 10th percentile[15] and 14 patients (6.0%) had an SGA newborn without preeclampsia.

The demographic characteristics and pregnancy-related data of the group with preeclampsia and the unaffected group are compared in the Table. Patients who developed preeclampsia had a significantly higher rate of risk factors by history and a higher BMI in the first trimester. There was a larger proportion of African American and Hispanic patients in the preeclampsia group (96%) as compared with the control group (82%), but the difference was not statistically significant. As expected, gestational age at delivery and mean birthweight were significantly lower in the preeclampsia group.

All 3DPD indices fit a Gaussian distribution. A weak positive correlation was noted between placental flow indices and

TABLE
Comparison of maternal and gestational characteristics in pregnancies with preeclampsia and unaffected controls

Characteristic	Unaffected (n = 234)	Preeclampsia (n = 24)	*P* value
Maternal age, y, mean (range)[a]	28.0 (18–45)	26.3 (18–38)	NS
Ethnicity, n (%)[b]			NS
Caucasian	26 (11)	1 (4)	
African American	77 (33)	10 (42)	
Hispanic	115 (49)	13 (54)	
Asian/South Asian	14 (6)	0 (0)	
Other	2 (1)	0 (0)	
African American plus Hispanic	192 (82)	23 (96)	
Risk factors for preeclampsia by history, n (%)[b,c]			
Prior history of preeclampsia	13 (6)	5 (21)	< .05
Chronic hypertension	9 (4)	6 (25)	< .05
Diabetes mellitus	1 (0.4)	2 (8)	< .05
Sickle cell disease	1 (0.4)	0 (0)	NS
Chronic renal disease	0 (0)	1 (4)	NS
Systemic lupus erythematosus	1 (0.4)	0 (0)	NS
Nulliparity, n (%)[b]	78 (33)	15 (62.5)	< .05
Mean BMI, kg/m^2[a]	27.0 (15-45)	31.0 (10-49)	< .05
BMI >30,[b] kg/m^2	51 (23%)	10 (42%)	< .05
CRL at first screen, mm[d]	63.4 (43.7-84)	63.0 (50.5-79.7)	NS
Placental location (posterior)[b]	121 (52%)	17 (71%)	NS
Mean gestational age at delivery, wks[a]	39.1 (28.3-41.4)	37.3 (30.4-40.9)	< .05
Mean birthweight, g (range)[a]	3300 (794–4625)	2813 (954–4600)	< .05
Birthweight centile, n (range)[a]	43.2 (1–100)	32.8 (5–94)	< .05

BMI, body mass index; *CRL*, crown-rump length; *NS*, not significant.

[a] Wilcoxon test; [b] Fisher's exact test; [c] Neither group had patients with antiphospholipid antibody syndrome or thrombophilia; [d] Student *t* test.

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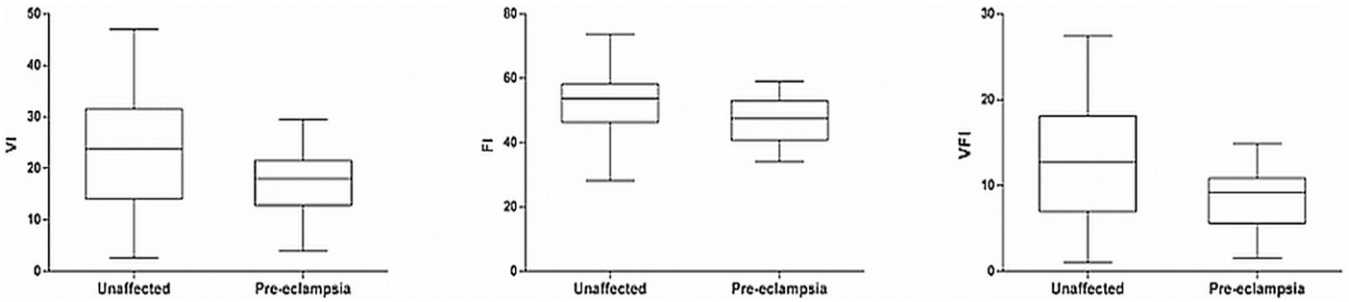
FIGURE 2
VI, FI, and VFI in preeclampsia and unaffected controls



Box and whisker plot of VI, FI, and VFI in patients who subsequently developed preeclampsia and unaffected controls. The *box* represents the interquartile range and the whisker represents the variables range.

FI, flow index; *VFI*, vascularization flow index; *VI*, vascularization index.

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CRL, but the correlations did not reach statistical significance (VI, r = 0.098; FI, r = 0.110; VFI, r = 0.113, *P* = NS). All first-trimester 3DPD flow indices were significantly lower in patients who subsequently developed preeclampsia as compared with unaffected pregnancies (mean ± SD, preeclampsia VI = 17.0 ± 7.2 vs no preeclampsia VI = 23.7 ± 10.6, *P* < .001; preeclampsia FI = 47.0 ± 6.9 vs no preeclampsia FI = 52.6 ± 8.3, *P* = .001; preeclampsia VFI = 8.3 ± 3.8 vs no preeclampsia VFI = 12.9 ± 7.1, *P* = .002). Figure 2 illustrates the median, interquartile range, and range of VI, FI, and VFI in the preeclampsia and unaffected groups.

First-trimester PAPP-A and UAPI were not found to be significantly different between patients who developed preeclampsia and those who did not (1.22 multiple of the medians [MOM]; range, 0.26–3.13 vs 1.33 MOM; range, 0.26–5.05; *P* = .443 for PAPP-A and 1.86 MOM; range, 0.13–3.84 vs 1.78 MOM; range, 0.1–9.37; *P* = .331 for UAPI).

The following regression equations were developed for each, adjusted for ethnicity, BMI, and placental location to predict preeclampsia.

Risk of preeclampsia using VI

$Y = -Y = -3.9932 - 0.0507 \times FI + 0.9236 \times$ (1 if race is African American or Hispanic; 0 if any other race) + $0.0985 \times$ BMI − $0.4399 \times$ (1 if anterior; 0 if other placental location) + 1.3925 (1 if nulliparous; 0 if none); $R^2 = 0.2075$, $P = 0.004$.

Risk of preeclampsia using FI

$Y = -5.7049 - 0.0458 \times VFI + 0.9952 \times$ (1 if race is African American or Hispanic; 0 if any other race) + $0.1085 \times$ BMI − $0.7944 \times$ (1 if anterior; 0 if other placental location) + 1.2387(1 if nulliparous; 0 if none); $R^2 = 0.1956$, $P = .0002$.

Risk of preeclampsia using VFI

$Y = -5.6145 - 0.0853 \times VI + 0.9506 \times$ (1 if race is African American or Hispanic; 0 if any other race) + $0.1040 \times$ BMI − $0.7197 \times$ (1 if anterior; 0 if other placental location) + 1.2472*(1 if nulliparous; 0 if none); $R^2 = 0.2120$, $P = .0002$.

PAPP-A and UAPI were assessed in the logistic regression models, and the prediction of preeclampsia was not improved by including these variables in the model.

Figure 3 shows the ROC curves for the prediction of preeclampsia by each of the flow parameters. The area under curve (AUC) for VI, FI, and VFI was 78.9% (95% CI, 70.2–87.4%), 77.6% (95% CI, 68.1–87.0%), and 79.6% (95% CI, 71.2–87.9%), respectively. In comparison, the AUC for PAPP-A and UAPI was 75.5% (95% CI, 64.7–86.2%) and 74.5% (95% CI, 63.0–85.9%), respectively.

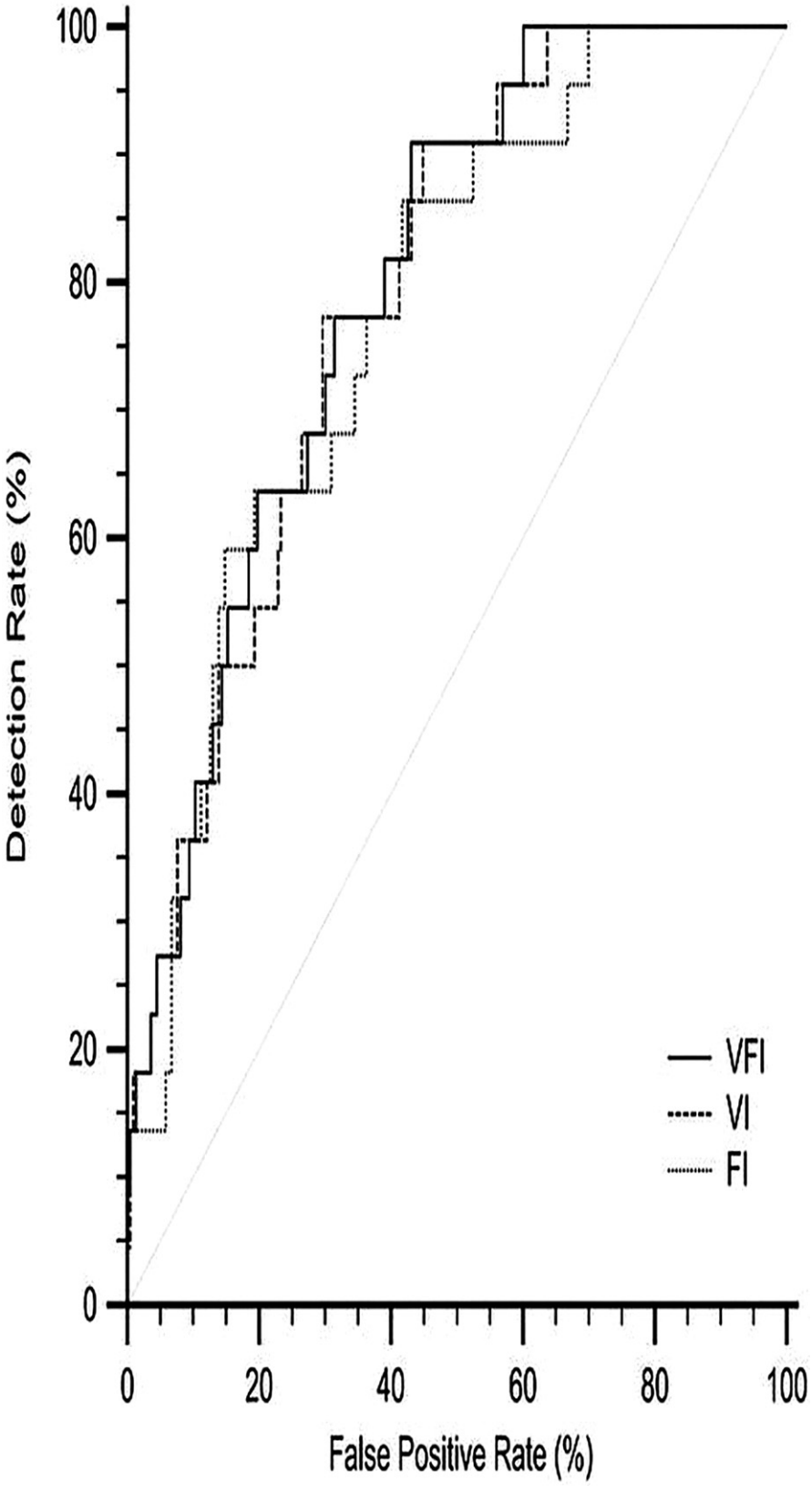
For a 10% false-positive rate, the detection rates for all cases of preeclampsia would have been 36.4% for VI (95% CI, 17.24–59.3%), 20.8% for FI (95% CI, 5.2–40.3%) and 36.4% for VFI (95% CI, 17.2–59.3%). In comparison, the detection rates of PAPP-A and UAPI for the same false-positive rate would have been 40.9% and 40.0%, respectively.

In the 12 women who subsequently developed severe preeclampsia, the first-trimester 3DPD indices were significantly lower than in those who did not (mean ± SD, 14.66 ± 7.42 vs 23.77 ± 11.58 for VI, *P* = .0021; 44.65 ± 6.96 vs 52.65 ± 8.33 for FI, *P* = .0013; and 6.93 ± 4.30 vs 12.91 ± 7.12 for VFI, *P* = .0005). The ROC AUC for VI, FI, and VFI for the prediction of severe preeclampsia was 83.2% (95% CI, 77.9–87.7%), 80.0% (95% CI, 74.5–84.9%), and 83.4% (95% CI, 78.1–87.8%), respectively. Although the ROC AUC appears to be greater for all indices for severe preeclampsia as compared with all cases of preeclampsia, the differences were not statistically significant.

COMMENT

Preeclampsia complicates approximately 2-7% of pregnancies and is a leading cause of maternal death worldwide.[16] The pathophysiological processes that occur in the UPCS and lead to the disorder begin early in pregnancy. Therefore, it is imperative that any screening or potentially prophylactic intervention should be aimed at the first trimester. In this study, we explored a novel ultrasonographic tool to investigate the UPCS in the first trimester. Our findings

FIGURE 3
ROC curves for VI, FI, and VFI



ROC curves for VI (*dashed line*; AUC, 78.9%) FI (*dotted line*; AUC, 77.6%) and VFI (*solid line*; AUC, 79.6%) for the prediction of preeclampsia.

AUC, area under the curve; *FI*, flow index; *ROC*, receiver operating characteristic; *VFI*, vascularization flow index; *VI*, vascularization index.

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demonstrate that in women who subsequently develop preeclampsia, 3DPD indices at 10 weeks 4 days to 13 weeks 6 days of gestation are significantly lower than in unaffected pregnancies.

These data are consistent with the current knowledge of the pathophysiology of the disorder. 3DPD indices were suggested by Pairleitner et al[11] to correlate with hemovascular parameters. VI was postulated to represent vascular density, FI to represent corpuscle volume within the blood vessels, and VFI to represent corpuscle volume within a tissue.

These assumptions were supported by correlating the flow indices with immunohistological assessment of the vasculature in different tissues.[17,18] Although the intervillous space is not comprised of blood vessels but blood-filled lacunae, the 3DPD technology when set up to capture low velocity flow will probably perceive the significant lacunae in the intervillous space as a vascular space. Nonetheless, in a recent elegant in vitro study, Raine-Fenning et al[19] showed that although a linear correlation exists between VI/VFI and vascularity and between FI and corpuscle volume, these correlations are more complex than previously suggested.

Our findings further suggest that measurement of VI, FI, and VFI in early pregnancy may provide an effective first-trimester screening method for this pregnancy-associated disorder. The AUCs for all 3 parameters in the current study were greater than previously reported findings on uterine artery pulsatility[4,20] or resistive[5] indexes and PAPP-A[8] as predictors for all cases of preeclampsia and comparable with the predictive value of PAPP-A and UAPI in the current study.

The main advantage of the 3DPD approach lies in its direct but noninvasive

ability to study hemovascular differences in a key area for the development of preeclampsia. The uterine artery pulsatility index, the most commonly studied sonographic tool for the prediction of preeclampsia, is an indirect tool and likely to be useful in the prediction of severe and early preeclampsia requiring delivery prior to 34 weeks' gestation. Although the latter approach is expected to capture most of the severe cases, there is no doubt that significant maternal and fetal morbidity can occur beyond 34 weeks' gestation.[21-23] Therefore, we believe that screening methods that identify a broader group of patients at risk for preeclampsia, such as patients with severe preeclampsia at any gestational age, should be searched for.

Our findings indicate that the sensitivity of the 3DPD approach for early screening for preeclampsia is too low to provide a single-marker prediction model. Nevertheless, this method carries the potential to contribute to a prediction model in combinations with other selected ultrasonographic and biochemical markers. Such an integrated model remains to be investigated.

The current study has several limitations. The first is a lack of universal standardization of volume sampling approach and equipment settings. We chose to use a sphere biopsy modality for 3DPD volume sampling. Other investigators, studying the uteroplacental and intervillous space between 5 and 12 weeks' gestation, used either free-hand volume sampling[24] or the sphere biopsy approach.[25] Both methods were demonstrated to be reproducible with good intra- and interobserver agreement.[24,25]

In our experience, the sphere biopsy modality is simpler to perform when scanning placentas between 11 and 14 weeks' gestation and allows for maintaining similar sample volumes between patients. Although recent in vitro studies have made advancements in determining the effects of different gain, power, pulse repetition frequencies, and wall motion filter settings on the power Doppler signal,[26,27] to date there are no in vivo data to support optimized settings for the study of the UPCS and particularly of the intervillous component. Nevertheless, it is our impression, also supported by others,[12,24,25] that as long as the same settings are maintained between patients and between studies, reproducibility of the results will be possible.

Second, it is recognized that the power Doppler intensity decreases as the distance between the transducer and the target object increases, a phenomenon called attenuation. As a result, variables such as abdominal girth and placental location may impact the 3DPD measurements. In this study, we used logistic regression to adjust the 3DPD indices for BMI and placental location. It is possible, however, that other approaches like the actual distance between the probe and the spherical center will prove to be a better adjustment variable than BMI and placental location. This aspect was not investigated in this study, and future studies are needed to substantiate its significance.

Finally, there is a concern that exists with the use of power Doppler imaging in the first trimester. Yet, with the suggested methodology, the sound waves are not directed toward the fetus. Furthermore, the application of the power Doppler with the volume acquisition does not exceed 10-15 seconds.

In summary, 3DPD emerges as a valuable noninvasive tool to study physiological changes that occur in the UPCS early in pregnancy. It appears that during the first trimester, patients who subsequently develop preeclampsia have lower 3DPD indices in this key space. Using this methodology has the potential to improve screening for preeclampsia in the future, possibly in a combination of selected predictive markers. ■

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