PROSPECTIVE COHORT STUDY

First-trimester 3D Power Doppler of Uteroplacental Circulation and Placental Volume for the Prediction of Preeclampsia: A Prospective Cohort Study

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ABSTRACT

Aim and objective: To evaluate the role of first-trimester 3D power Doppler of placental circulation and placental volume in the prediction of poor pregnancy outcomes.

Materials and methods: This prospective cohort study included 375 pregnant women. 3D scans for the determination of placental volume and vascularization indices were performed. The primary outcome was the occurrence of preeclampsia (PE).

Results: Placental 3D power Doppler indices were significantly lower in women who developed PE [vascularization index (VI) = 3.13 ± 2.1 , flow index (FI) = 14.9 ± 9.3 , vascularization flow index (VFI) = 0.1 ± 0.9] and fetal growth restriction (FGR) (VI = 4.5 ± 2.4 , FI = 15.3 ± 7.9 , VFI = 0.3 ± 0.6) compared with those who did not (VI = 9.7 ± 1.9 , FI = 28.9 ± 4.6 , VFI = 1.8 ± 1.4) (VI = 10.9 ± 1.6 , FI = 30.9 ± 7.6 , VFI = 1.9 ± 0.9), respectively ($p < 0.001$). The cutoff values for the prediction of PE were VI ≤ 3.22 , FI ≤ 17.73 , and VFI ≤ 0.5 , while those for the prediction of intrauterine FGR were VI ≤ 4.12 , FI ≤ 15.93 , and VFI ≤ 0.3 .

Conclusion: First-trimester evaluation of placental bed vasculature with 3D power Doppler can be used as a good predictor of PE.

Clinical significance: First-trimester 3D power Doppler of placental bed vasculature can help early prediction of PE and FGR allowing early intervention giving opportunity for better pregnancy outcomes.

Keywords: Cohort studies, Doppler, Duplex, Imaging, Placenta, Preeclampsia, Three-dimensional, Ultrasonography.

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INTRODUCTION

Early prediction of many problematic pregnancy outcomes as preeclampsia (PE) and preterm labor (PTL) is very important allowing the early start of prophylactic treatment for women at risk.¹ Abnormal placental development is associated with many obstetrical adverse outcomes, such as fetal growth restriction (FGR), PTL, PE, fetal hypoxia, and death.² Developments in ultrasound technologies allowed three-dimension (3D) ultrasound and power Doppler to evaluate the whole placental vasculature instead of limited planes evaluated by 2D power Doppler.³ Three-dimension power Doppler evaluates placental vascularization using three vascular indices; vascularization index (VI), flow index (FI), and vascularization flow index (VFI).⁴

The role of first trimester placental 3D power Doppler in the prediction of poor pregnancy outcomes as PE, PTL, and FGR was investigated with promising results,^{5–7} also the measurement of placental volume using 3D ultrasound for the prediction of these conditions was investigated as well.^{3,8} Still, all these studies had different methodologies and a relatively limited number of participants.

This study was conducted over a period of 5 years to include a large number of participants aiming to evaluate the value of both first trimester 3D power Doppler vascular indices of the placenta and placental volume as possible predictors of PE.

MATERIALS AND METHODS

This study was conducted in Ain Shams University Maternity Hospitals during the period from April 2015 till April 2020 after approval of the

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institutional Ethics and Research Committee of Ain Shams University. The study recruited pregnant women attending for routine first-trimester ultrasound scan with the following criteria: age ≥ 18 years, single intrauterine pregnancy, normal fetal morphology, and visualization of the entire placenta. Women with fetal anomalies, multifetal pregnancy, active bleeding or threatened miscarriage, uterine malformation, or uterine myoma that could interfere with the placental volume measurement and patients with medical disorders with pregnancy like chronic hypertension, diabetes mellitus, or any other systemic disease were excluded from the study. Informed written consent was obtained from all participants.

Three-dimension scans were performed using a Voluson E6 Expert ultrasound machine (General Electric®, Fairfield, CT,

USA) equipped with a 5.0–7.0-MHz transabdominal probe and a combination of 3D/4D and power Doppler technology. Each woman was asked to hold her breath when the placenta is being scanned. Individual setting of the gain value was done depending on; thickness of adipose tissue, the placental location, and resultant imaging conditions.

The power Doppler settings were preadjusted 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. Manufacturer default settings were set for other ultrasound and Doppler settings.

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

Optimal zooming ($\times 1.5$ – 1.8) was achieved and a spherical volume biopsy with a 2 cm diameter was sampled. One pole was placed at the placenta and the other pole at the upper end of the uteroplacental circulation. The spherical volume was analyzed with the virtual organ computer-aided analysis program (VOCAL; GE) to determine the VI (the ratio between color voxels and total

voxels expressed in percentages), FI (the sum of the color voxels' signal intensity divided by the number of color voxels, quantified between 0 and 100), and VFI (the sum of color voxels' signal intensity divided by the total tissue voxels, quantified between 0 and 100) (Fig. 1).

The contour of the placenta was outlined and the image was rotated six times repeatedly by 30°. After completing the entire rotation, the placental volume was analyzed using the VOCAL imaging program (Fig. 2). Each of the previous measurements was done twice and an average of the two readings was obtained to avoid intraobserver variation.

Participants had regular antenatal care till the end of their pregnancies and after birth, their medical files were reviewed to obtain the outcome data and the occurrence of pregnancy-related complications. The primary outcome measure was an incidence of development of PE. Other secondary outcomes were the development of gestational hypertension (GHTN), FGR, placental abruption, PTL, and stillbirth.

A previous study showed that the overall accuracy of 3D power Doppler indices of the uteroplacental circulation measured in the first trimester in the prediction of hypertensive disorders in pregnancy ranged between 77.6% and 79.6%.⁹ Calculation according to these values to produce the minimal statistically acceptable figure produces a minimal sample size of 355 women. Assuming a dropout rate of 5%, 374 women are needed to be recruited in this study.

Fig. 1: 3D power Doppler indices (VI, FI, VFI) and placental volume using VOCAL

Fig. 2: 3D structure of the placenta at 12 weeks of gestation and measurement of placental volume using the VOCAL

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 17 (IBM® Corp., Armonk, NY, USA). Inferential analyzes were done for quantitative variables using an independent *t*-test in cases of two independent groups with parametric data and paired *t*-test in cases of two dependent groups with parametric data. Inferential analyzes were done for qualitative data using the Chi-square test for independent variables. Receiver-operating characteristic (ROC) analysis was done with cutoff value, sensitivity, specificity, and positive/negative likelihood ratio analysis.

RESULTS

A total of 400 pregnant women were recruited in the study, 355 were analyzed for outcomes after excluding women not fitting the inclusion criteria or refusing to participate in the study, women lost during follow-up, and women who experienced miscarriage (Flowchart 1). The demographic characteristics of the participants were as follows; age ranged from 18 to 41 years (27.7 ± 4.9), gestational age from 11 to 13 weeks + 4 days (11.8 ± 0.6), and body mass index 25.6 ± 2.7 kg/m². The incidence of adverse pregnancy outcomes were; GHTN 48 (13.5%), PTL 29 (8.17%), PE 22 (6.2%), small for gestational age/FGR 19 (5.35%), placental abruption 11 (3.1%), and intrauterine fetal death/stillbirth 2 (0.56%). Considering the overlap that occurred between different outcomes, a total of 62 (17.47%) women experienced adverse pregnancy outcomes.

Placental 3D power Doppler indices were significantly lower in women who developed PE ($VI = 3.13 \pm 2.1$, $FI = 14.9 \pm 9.3$,

Flowchart 1: Flow diagram of the study

$VFI = 0.1 \pm 0.9$) than for those who did not ($VI = 9.7 \pm 1.9$, $FI = 28.9 \pm 4.6$, $VFI = 1.8 \pm 1.4$) ($p < 0.001$). Also, these indices were much lower in who experienced FGR during pregnancy ($VI = 4.5 \pm 2.4$, $FI = 15.3 \pm 7.9$, $VFI = 0.3 \pm 0.6$) compared with those who did not ($VI = 10.9 \pm 1.6$, $FI = 30.9 \pm 7.6$, $VFI = 1.9 \pm 0.9$) ($p < 0.001$). Placental volume in spite being lower in both cases compared with normal women, yet, was statistically insignificant in both (PE; 69.3 ± 21.2 vs 92 ± 29.6 , $p = 0.09$) and (FGR; 97.3 ± 23.2 vs 121.4 ± 34.6 , $p = 0.06$).

The cutoff values for the prediction of PE were $VI \leq 3.22$, $FI \leq 17.73$, and $VFI \leq 0.5$ (Table 1), while, those for the prediction of FGR were $VI \leq 4.12$, $FI \leq 15.93$, and $VFI \leq 0.3$ (Table 2).

Neither placental 3D power Doppler indices nor placental volume showed a significant difference in women who developed the other studied adverse pregnancy outcomes (GHTN, placental abruption, PTL, and stillbirth) from those who did not (Table 3).

DISCUSSION

This study showed that mean vascular indices of placental vasculature measured in the late first trimester using 3D ultrasound were significantly lower in women developing PE and women suffering from FGR than women who did not experience either condition. The sensitivity of the calculated cutoff values was considerably satisfactory especially for FI reaching 94.8% for PE and 93% for FGR. Placental volume measurement did not show any value in the prediction of women prone for adverse pregnancy outcomes, neither was placental vascular indices measurement in studied adverse pregnancy outcomes other than PE and FGR.

The prediction of maternal and fetal complications related to placental pathology as PE and FGR has been the concern of many researchers for many years aiming to reach the best predictive methodology for the early commencement of prophylactic

Table 1: Receiver-operating characteristic (ROC) curve analysis for the prediction of preeclampsia using VI, FI, VFI, and placental volume

Variable	Predictor			
	VI	FI	VFI	Placental volume
AUROC	0.83	0.96	0.90	0.63
95% CI	0.7–0.9	0.9–1	0.79–1	0.45–0.8
<i>p</i> value (AUC = 0.5)	<0.001	<0.001	<0.001	0.167
Cutoff value	≤3.22	≤17.73	≤0.5	
Validity	Sensitivity (%)	82	94.8	92.3
	Specificity (%)	81.8	90.9	81.82
	PPV (%)	94.1	97.4	97.7
	NPV (%)	56.2	83.3	75
	Positive likelihood ratio	4.51	10.44	5.08
	Negative likelihood ratio	0.22	0.06	0.09

Table 2: Receiver-operating characteristic (ROC) curve analysis for the prediction of fetal growth restriction using VI, FI, VFI, and placental volume

Variable	Predictor			
	VI	FI	VFI	Placental volume
AUROC	0.86	0.92	0.83	0.66
95% CI	0.69–0.92	0.9–1	0.79–1	0.45–0.8
<i>p</i> value (AUC = 0.5)	<0.001	<0.001	<0.001	0.83
Cutoff value	≤4.12	≤15.93	≤0.3	
Validity	Sensitivity (%)	86	93.0	90.6
	Specificity (%)	84.2	88.1	89.42
	PPV (%)	90.4	94.2	93.2
	NPV (%)	39.1	73.4	65
	Positive likelihood ratio	3.81	7.55	4.06
	Negative likelihood ratio	0.29	0.04	0.04

Table 3: 3D power Doppler indices and placental volume in women who developed adverse pregnancy outcomes vs women who did not

	Women with gestational hypertension	Women without gestational hypertension	<i>p</i>
VI	11.1 ± 1.4	9.9 ± 1.8	0.1
FI	28.5 ± 8.3	34.9 ± 6.6	0.09
VFI	1.6 ± 0.6	2.0 ± 1.1	0.23
Placental volume	118.3 ± 21.2	126.4 ± 31.6	0.07
	Women with preterm labor	Women without preterm labor	
VI	10.3 ± 1.1	9.6 ± 2.8	0.5
FI	30.5 ± 6.3	35.9 ± 8.6	0.08
VFI	1.4 ± 0.7	2.2 ± 1.0	0.13
Placental volume	128.3 ± 25.4	116.4 ± 21.6	0.17
	Women with placental abruption	Women without placental abruption	
VI	10.5 ± 2.4	10.9 ± 1.5	0.3
FI	31.5 ± 8.8	33.9 ± 5.4	0.07
VFI	1.2 ± 0.3	0.9 ± 1.4	0.43
Placental volume	114.1 ± 29.2	136.1 ± 11.6	0.06
	Women with IUFD	Women without IUFD	
VI	14.6 ± 2.1	15.1 ± 1.5	0.4
FI	34.6 ± 7.3	31.3 ± 5.6	0.39
VFI	1.1 ± 0.4	1.5 ± 0.7	0.33
Placental volume	138.1 ± 11.2	136.4 ± 25.6	0.07

therapy for these morbidities. With the introduction of 3D ultrasound technology, many of these researches were directed to the evaluation of the value of 3D in the early prediction of these pathologies. Many previous studies investigated the value of placental volume and vascular indices for the prediction of PE and other pregnancy adverse outcomes,^{3,6,8–11} still, these studies reported conflicting results about the value of these indices in the prediction of adverse pregnancy outcomes especially concerning the value of placental volume. This conflict might be attributed to several reasons; different machine settings used, different methodologies used for placental volume measurement, also relatively sample sizes used in all these studies. It has been proved that the machine settings themselves can influence greatly the results obtained from 3D power Doppler about the placental vascular indices.^{12,13}

This study was conducted to follow-up pregnant women over a period of 2 years, thought to be a long period enough to recruit a sufficient sample of pregnant women to validate the value of both; 3D power Doppler placental vascular indices and placental volume for the prediction of these adverse pregnancy outcomes and specifically PE. A strong point of this study is being prospective, thus decreasing the possible bias of the results. Still, this study was not without limitations, including only low-risk population as evident by the exclusion criteria allowed studying several adverse outcomes, yet, recruiting women at high risk of developing one or two adverse outcomes only as PE and FGR might have increased the validity of the results for these specific diseases which should be an issue for further future research. The incidence of occurrence of poor outcomes might be slightly higher than expected for the low-risk population which could be explained by the fact that the hospital where the study was conducted is considered as a tertiary center that usually handles most of the high-risk cases in its area. Also, the VOCAL technique used in the study, despite seeming to be a good technique for obtaining reliable results, still comparing this technique to other used techniques may help to reach the best methods for using 3D ultrasound for the prediction of PE and FGR. Further larger multicenter studies are needed to validate this technique and prove its value in clinical practice.

CONCLUSION

Late first-trimester 3D power Doppler evaluation of placental bed vascular indices is a good predictor of PE and FGR with FI showing the highest predictive value.

CLINICAL SIGNIFICANCE

First-trimester 3D power Doppler of placental bed vasculature can help early prediction of PE and FGR allowing early intervention giving opportunity for better pregnancy outcomes.

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