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The Use of Three-Dimensional Power Doppler Ultrasound in Assessment of Placental Blood Flow and Volume and Its Correlation with Severity of Preeclampsia

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ABSTRACT

Background: Hypertensive disorders in pregnancy, especially preeclampsia are among the commonest medical disorders encountered in pregnancy and major contributors to maternal & fetal morbidity and mortality.

Objective: Assessment of the efficacy of 3rd trimester three-dimensional power Doppler (3D PD) ultrasound of placental volume and vascular indices in determining the severity of preeclampsia.

Subjects and Methods: A cross-sectional analytic study involving 200 women from 18 to 35 years old, with singleton pregnancies in the third trimester complicated with preeclampsia. The subjects were further divided into two groups of 100 patients stratified by disease severity; severe group and non-severe group.

Results: The non-severe and severe preeclamptic groups had a significant decrease in placental volume. No significant correlation was found between gestational age and placental volume regarding severity of preeclampsia. The non-severe group had significantly higher values for each of the 3 indices: Vascularization index (VI), Flow index (FI), and Vascularization Flow index (VFI) (16.9 versus 8.5), (36 versus 26), and (4.9 versus 2.6), respectively, compared to the severe group. Both the non-severe and the severe groups had a significant negative correlation between gestational age (GA) and VFI. Additionally, neither the severe nor the non-severe groups showed any correlation between VI and GA, while FI showed a non-significant inverse correlation with GA. **Conclusion:** The 3D Power Doppler ultrasound may provide alternative methods for assessment of placental blood flow and provide insights on pathophysiology of placental disease. Additional studies are required for verification of its accuracy and applicability in clinical practice.

Keywords: Three-dimensional power Doppler, Placental vascular indices, Placental volume, Preeclampsia.

INTRODUCTION

Preeclampsia is among the commonest complications encountered in pregnancy with a range of consequences including intrauterine fetal growth restriction, eclampsia and reaching fetal and maternal mortality. The condition is associated with marked reduction of uteroplacental blood flow [(1)].

Preeclampsia is a disease unique to pregnancy and is marked by the presence of elevated blood pressure and significant proteinuria at or beyond the 20th week of pregnancy. The worldwide incidence is around 28%. The current view of hypertensive disorders complicating pregnancy (HDCP), including pre-eclampsia, is as a chronic placental pathology. Pathophysiology and subsequent pregnancy outcomes are significantly influenced by abnormal placental function and diminished vascular perfusion [(2)].

Gross pathological changes are most evident in placental specimens retrieved from cases of severe preeclampsia. Typical placental changes in preeclampsia are those reflecting placental ischemia, including diminished size and presence of infarctions. These findings are also often encountered in cases of fetal growth restriction (FGR) [(3)].

In conventional 2D sonography, blood flow assessment is done by application of Doppler to a single vessel of interest and measurement of vascular flow velocity and resistance indices. This technique is limited by the ability to examine only portions of an organ or tissue blood flow [(4)]. By assessment of the power Doppler signal within the desired organ as a whole as defined by the volume of interest, 3D ultrasonography, in contrast, allows examination and quantification of overall blood flow through an organ. Three indices are used to evaluate the vascular perfusion of the placenta, including the VI, which is the percentage of a target volume with detectable moving blood, the FI, which is the mobile blood's mean value in the target volume, and the VFI, which signifies the relative quantity of moving blood in the target volume [(5)]. Measurement of placental volume alone or combined with uterine artery Doppler has been suggested for early prediction of both preeclampsia and fetal growth restriction. The usage of 3D PD and VOCAL techniques to assess placental volume and vasculature can prove to be a useful modality for adequate identification of FGR pregnancies and evaluation of preeclampsia severity [(6)].

This study's goal was to examine the placental volume and placental vascularization using 3D power Doppler ultrasound (3DPD) in third-trimester pregnancies complicated by preeclampsia, combined with pathological examination of such placentae for signs of hypoperfusion.

PATIENTS AND METHODS

Patients:

A cross-sectional analytic investigation including 200 women aged from 18 to 35 years old with singleton

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pregnancies in the third trimester complicated by preeclampsia was conducted. The subjects were further divided into two groups of 100 patients stratified by disease severity; severe group and non-severe group. Our study was done at Kasr Al Ainy Obstetrics and Gynecology Hospital over a period of 18 months starting from June 2016 to December 2017. The first day of the last menstrual period (LMP) and a first trimester ultrasound were the main factors used to determine gestational age. We included pregnant patients aged 18-35 years (which weeks of pregnancy) with preeclampsia as defined by the American College of Obstetricians and Gynecologists (ACOG). According to the severity we divided the patients into 2 groups. The criteria of severity of preeclampsia were according to ACOG 2013.

Exclusion criteria:

We excluded: 1-Patients with high blood pressure first detected before 20 weeks gestation, 2- Fetal deformities and fetal chromosomal abnormalities, 3-Anomalies of the placenta, 4- Placenta previa, 5-Umbilical anomalies, 6- Gestational diabetes, 7-Systemic vascular or autoimmune disorders, 8- Rupture of amniotic membrane, 9- Women with history of Coagulopathy, and 10 transferred to other centres.

Ethical Approval:

All participant in the study gave their written consents after it had been approved by Cairo University's Ethics Board. This research was conducted in conformity with the Declaration of Helsinki, which is the World Medical Association's code of ethics for human subjects' studies.

Ultrasound examination:

3D PD ultrasound for placental volume and vasculature was done:

The best site for acquisition of 3D of the whole placenta has been discovered, following viability had been confirmed and placental position had been identified. The Power Doppler window was placed over the placenta, mapping the vascular tree from basal to chorionic plate.

With the use of the rotational technique, which involves repeatedly outlining the placenta's contour following rotating its image 6 times via 30 degrees, placental volume was determined employing the VOCAL (Virtual Organ Computer-aided Analysis) software. The software automatically calculates the volume following the complete rotation. The VOCAL software automatically calculated the vascularization indices on a histogram, including VI, FI, and VFI.

All scans were performed employing a Volusion E10 ultrasound machine (GE Healthcare, Chicago, Illinois, United States) equipped with a curvilinear three-dimensional abdominal probe with a frequency range of 4 to 8 MHz. Scans were performed by a single observer to avoid inter-observer bias. All patients were scanned in a semi-recumbent position and the previously preserved machine setup (low 1 wall motion filter, 0.9 kHz pulse repetition frequency, 3 dB PD gain). The use of the same settings for every patient is ensured by doing this.

Histopathological examination

The resultant placentas were washed in running tap water, tagged with patient's name and preserved in 10% formalin solution. Histopathological preparations were done in concordance with recommendations of Royal College of Pathologists UK [(7)]. Histopathological analysis of the placentae following delivery was performed in 50 of non-severe and 50 of severe preeclampsia patients. Coronal sections of placenta 5 µm thick were obtained by a microtome (Leica RM 2025, Germany), sections were placed on glass slides and examined under hematoxylin and eosin stains. Histopathological assessment was done at Pathology Department, Kasr El-Aini Faculty of Medicine. Placental lesions were recorded according to **Suranyi *et al*.** [(8)].

Statistical Analysis

Statistical analysis of data was demonstrated using mean ± standard deviation (SD). By utilizing the student *t* test for independent samples, a comparison of the research groups was established. The Spearman rank correlation equation was used to evaluate non-normal variables and non-linear monotonic relationships, and the Pearson' correlation equation was used to evaluate linear relationships between normally distributed variables. Statistical significance was defined as $p \leq 0.05$. Data were calculated by Windows release 22 of the IBM SPSS program (Statistical Package for Social Science, IBM Corp).

RESULTS

We approached 278 patients (153 with non-severe criteria and 125 with severe criteria). We excluded 78 patients (53 and 25 respectively) and finally analyzed 200 patients 100 in each group. (Figures 1 & 2). Maternal age and diastolic and systolic blood pressures were significantly different ($P < 0.05$) in both non-severe and severe preeclampsia. A non-significant difference ($P>0.05$) was noticed between GA in both groups (Table 1).

Table (1): Demographic data of the two groups of preeclampsia patients

	Non-severe	**Severe**	**P**
Maternal age (years)	25.2 ± 4.1	28 ± 5.3	<0.05
Blood pressure:			
Systolic	148.71 ±5.968	181.6 ±16.063	<0.05
Diastolic (mmHg)	105.9±14.509	113.5 ±4.633	<0.05
Gestational age (weeks)	33.39 ±3.629	33.42 ±3.774	>0.05

The mean placental volume in non-severe preeclampsia patients (268.9 ± 182.07) was significantly greater (P<0.05) compared to the severe group (190 ± 145). The mean placental VI in non-severe preeclampsia patients (16.89 ± 15.492) was significantly greater (P<0.05) compared to the severe group (8.547 ± 3.788). Regarding the FI, there was a significant decline (P<0.05) between the severe group (26.027 ± 8.22) and the non-severe group (36.018 ± 7.3). There was a significant decline (P<0.05) in the **V**FI between the severe (2.598 ± 1.19) and the non-severe group (4.489 ± 2.02) (Table 2).

Table (2): Comparison between non-severe and severe preeclampsia patients as regards volume, VI, FI and VFI.

	Group	N	Mean	Std. Deviation	Std. Error Mean	P value
Volume	Non-severe	100	268.92	182.076	18.208	0.001
	Severe	100	190.42	144.920	14.492	
VI	Non-severe	100	16.892	15.4928	1.5493	0.000
	Severe	100	8.541	3.7886	0.3789	
FI	Non-severe	100	36.018	7.3070	0.7307	0.000
	Severe	100	26.027	8.2240	0.8224	
VFI	Non-severe	100	4.489	2.0204	0.2020	0.000
	Severe	100	2.598	1.1907	0.1191	

When we correlated the gestational age to the placental volume and indices as shown in table (3) and table (4) we found that:

- There was a non-significant connection between volume and GA (r = 0.174, p= 0.084) as well as between VI and GA (r= 0.162, p= 0.108) in non-severe preeclampsia patients. There was a non-significant inverse connection between FI and GA (r= 0.-0.049, p= 0.0.627) in non-severe preeclampsia patients. There was a significant inverse correlation between VFI and GA (r= -0.227, p= 0.023) in non-severe preeclampsia patients (Table 3).

- There was a non-significant connection between volume and GA (r = 0.069, p= 0.493) in severe preeclampsia patients. There was a non-significant connection between VI and GA (r= 0.016, p= 0.876) in severe preeclampsia patients. There was a non-significant inverse connection between FI and GA (r= -0.056, p= 0.577) in severe preeclampsia patients. There was a significant inverse connection between GA and VFI (r= -0.432, p= 0.000) in severe preeclampsia patients (Table 4).

Table (3): Correlation between GA, placental volume, VI, FI, VFI non-severe group

		GA
Volume	Pearson Correlation	0.174
	P value	0.084
	Sample size	100
VI	Pearson Correlation	0.162
	P value	0.108
	Sample size	100
FI	Pearson Correlation	-0.049
	P value	0.627
	Sample size	100
VFI	Pearson Correlation	-0.227
	P value	0.023
	Sample size	100

Signifiant = P< 0.05, non signifiant = P >0.05

Table (4): Correlation between GA, placental volume, VI, FI, VFI in severe group

		GA
Volume	Pearson Correlation	0.069
	P value	0.493
	Sample size	100
VI	Pearson Correlation	0.016
	P value	0.876
	Sample size	100
FI	Pearson Correlation	-0.056
	P value	0.577
	Sample size	100
VFI	Pearson Correlation	-0.432
	P value	0.000
	Sample size	100

Signifiant = P< 0.05 , non signifiant = P >0.05

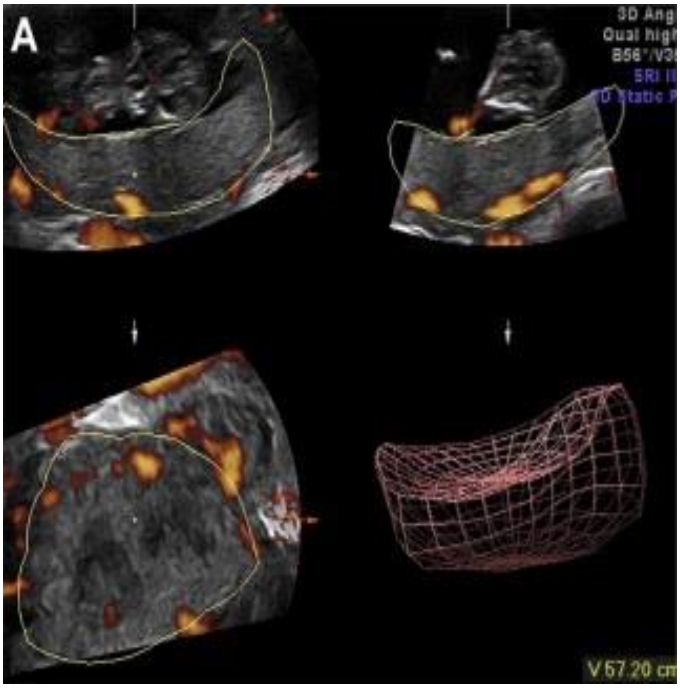

Figure (1): VOCAL analysis of placenta

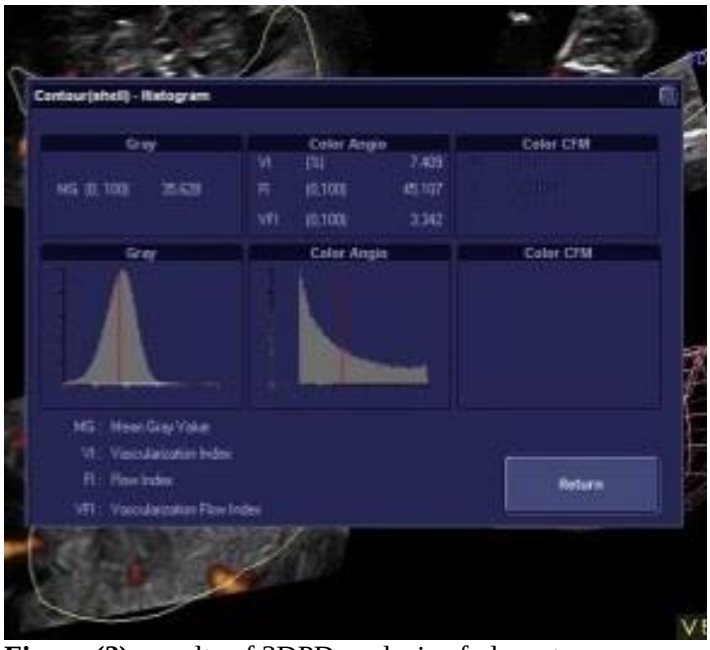

Figure (2): results of 3DPD analysis of placenta.

Regarding histopathological analysis, table (5 and Figures 3, 4 & 5) showed that only interstitial fibrosis, parenchymal hematoma, syncytial knots, calcification, and infarction were significantly greater among patients who had severe preeclampsia than those with non-severe forms.

Table (5): Histological characteristics of placenta in preeclampsia patients

Items	Non- severe group N=50	Severe group N=50	P value
- Neutrophil invasion	0	0	…
- Interstitial fibroses	20	30	0.047
-Vascularization: hypovascularization	50	50	…
- Parenchymal hematoma	10	20	0.030
- Fibrin deposits	50	50	…
- Syncytial knots	20	30	0.047
- Calcification	20	50	0.000
- Accelerated maturation	50	50	…
- Infarction	15	35	0.000

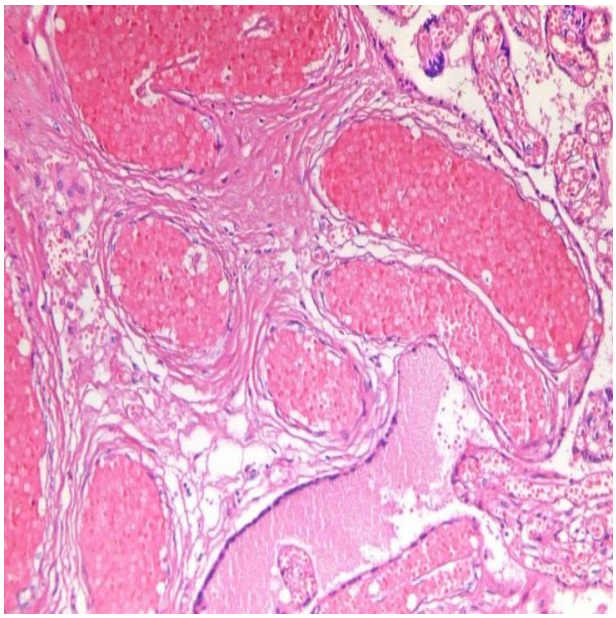

Figure (3): Decidual arteriopathy with fibrinoid necrosis of wall (H&E, 100x)

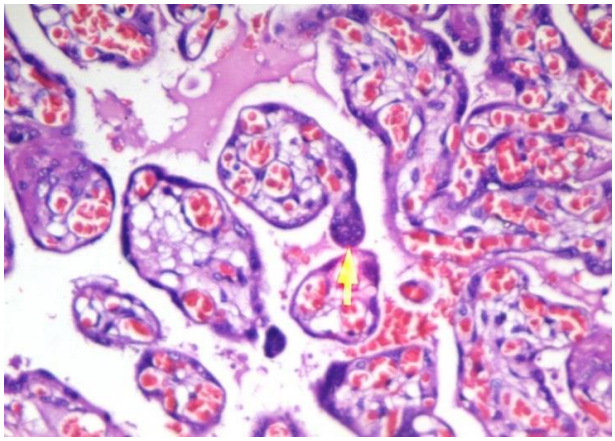

Figure (4): Interstitial hemorrhage (H&E, 100x) .

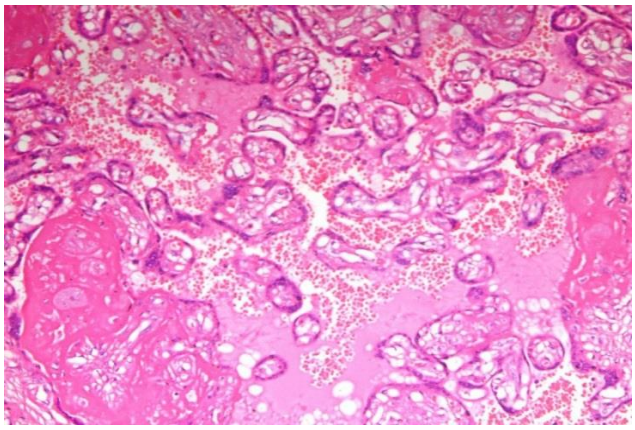

Figure (5): Syncytial knobs (H&E, 100x)

DISCUSSION

Placental perfusion and vascularization indices were calculated using 3D Power Doppler analysis, which theoretically correlates with uteroplacental and fetoplacental perfusion. Evaluation of the perfusion of in-vivo placentae is now achievable by assessment of vascular indices. Three-dimensional power Doppler (3DPD) is now on the frontline of research into placental pathology and fetal growth restriction. It surpasses 2D Doppler not only in accuracy but also in assessment of intraplacental vessel morphology as branching pattern and change in diameter [2,9].

In our study comparison of placental volume between non-severe and severe preeclampsia groups showed a significant decrease in severe group. **De Paula *et al*.** [10] results showed a constant distribution of all three indices (VI, VFI, FI) throughout pregnancy, this was demonstrated along with increase in placental volume as pregnancies progress.

In the present study, we found no significant connection (P>0.05) between gestational age and placental volume as regards to preeclampsia severity. In study of **Moran *et al*.** [11], there was no association between volume and gestational age among preeclampsia patients. However, it has also been shown that while preeclampsia is mainly associated with decreased placental volume, this is definitely not the rule [12]. Association of preeclampsia with a large placenta could be associated with the presence of infarction on histopathological study due to utero-placental insufficiency. Thus the applicability of placental volume assessment alone as an early predictor of preeclampsia severity of is limited benefit. In another study, **Abdallah *et al*.** [14] revealed that women who develop preeclampsia had a significantly lower placental volume than normotensive women. During the first trimester of the study mentioned above, the placental volume was estimated. On the contrary, the study conducted by **Fahim *et al*.** [15] during the first trimester concluded that the volume of the placenta did not differ statistically significantly between the pregnancies with adverse outcomes and those without. Other studies have shown that in small for gestational age/Fetal Growth Retardation pregnancies, placental volume decrease occurs during the second trimester rather than the first [16]. This could be due to underdevelopment of uteroplacental circulation with abnormal remodeling of placental vasculature which normally occur in 2nd trimester, which is consistent with our results.

In our research, we measured the placental vascularization throughout the third trimester of pregnancy and we evaluated its relation to preeclampsia severity. All indices (VI, FI, and VFI) showed significantly greater values in the non-severe group than in the severe group, with no significant correlation with the gestational age only in the case of VI and FI. VFI showed an inverse correlation with gestational age. In a study conducted by **Moran *et al*.** [11], VI and VFI were unaffected by GA, but FI showed higher values as pregnancy advanced. In contrast to our data, **Yuan *et al*.** [17] showed a significant relationship among all parameters and GA, but in the severe preeclampsia group, all indicators showed significantly lower levels, aligning with our results. Much like our data, **Chen *et al*.** [18] demonstrated significant reduction in all indices in severe preeclampsia compared to control and also showed that the utility of 3DPD indices for predicting severity of preeclampsia is very limited. **Mercé *et al*.** [19] showed higher values of all indices correlating to gestational age however, they only examined placental areas of high vessel density. This contradicts results by **Guiot *et al*.** [5], which showed significant reduction in all indices. In accordance with our data **Suranyi *et al*.** [8] demonstrated reduced values of VI in preeclamptic patients, however there was no significant correlation. In research conducted by **Guiot *et al*.** [5] and **Odeh *et al*.** [20], FI showed a significant reduction in preeclampsia. Preeclampsia is associated with dysfunctional placental perfusion, which coincides with lower VI and FI values. For those that later developed preeclampsia, **Odibo *et al*.** [22] found that the mean vascular indicators were decreased in the 1st trimester. According to **Eastwood *et al*.** [21] the three vascular indices were significantly lower across various studies of 1st trimesteric pregnancies eventually complicated by preeclampsia. Thus the three vascular indices appear to decrease throughout pregnancy not only in the third trimester according to our results. **Yuan *et al*.** [17] similar to our results demonstrated a significant reduction in VI and VFI in severe preeclampsia compared to non-severe preeclampsia cases. Their results demonstrated that intraplacental vascularisation was worse in women who experienced severe preeclampsia, while damage to placental vessels may be relatively mild in non-severe preeclampsia.

In preeclampsia, reduction in VI values can be explained by decrease in the number of placental vessels. A reduced VI values can be explained by defective trophoblastic invasion [23]. Reduction in VFI reflects diminished placental tree and vascular perfusion resulting in placental blood insufficiency. **Soliman *et al*.** [24] demonstrated significantly high VI and VFI in preeclampsia placentae compared to normal pregnancies, but showed no significant correlation as regards FI. **Ali *et al*.** showed lower values of all three indices in pregnancies complicated by preeclampsia, which is understandable due to dysfunctional placental circulation resulting in hypoperfusion of placenta [25].

As regards the results of the histopathological section, placental vessel damage could be relatively

mild in non-severe preeclampsia. Abnormal placental function and diminished blood perfusion [(26)] are the main contributors to pathophysiology of preeclampsia, and this is reflected in results of our histopathological examination of placentae. Examination showed dysplastic villi, villous fibrosis, narrowing of placental vessels and infarction reflecting placental ischaemia and hypoxia.

Hypovascularisation and accelerated maturation was noticed in our cases. Number of infarctions increases with increase in severity of preeclampsia denoting decreased placental perfusion. In accordance with the present work VI indices had a non-significant decrease compared to average limit in non-severe group of preeclampsia. This could be due to mild damage of placental blood vessels [(17)].

Although, 3DPD indices have been recently promoted in various fields, its use has several limitations like absence of standardized ultrasound settings [(28)] and differences in attenuation and gain settings [(29, 30)].

CONCLUSION

The placental volume and blood perfusion determined by three-dimensional power Doppler sonography in patients with severe preeclampsia are significantly lower than in non-severe preeclamptic patients. Consequently, 3DPD sonography can provide alternative avenues for evaluation of placental disease. Additional research is required to confirm the feasibility of its clinical application. The reliability and duplicability of this modality is still disputable. Furthermore, the lack of confirmed reference values confounds the problem of clinical applicability.

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