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Research Article

Combined 3D Power Doppler Placental Volume and Vascular Flow Indices in the First Trimester of Pregnancy could be a specific screening toll in the Early Prediction of preeclampsia?

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Abstract

Background: placental maldevelopment plays a crucial role in the pathogenesis of many pregnancy complications. Power Doppler Placental Volume and Vascular Flow Indices are of value to assess early pregnancy problems.

Aim of the study: To estimate the specificity of first-trimester 3D-placental volume and vascular flow indices as a screening tool in the prediction of preeclampsia.

Patients and Methods: 200 women at risk factor for preeclampsia were enrolled in this prospective cohort study in Tanta University hospital, Obstetrics and Gynecology Department, in the period from August 2016 to December 2017. Included women were chosen as regards to specific inclusion and exclusion criteria. They were subjected to Full history taking, General Examination, Abdominal and Local examination, routine laboratory investigations and abdominal ultrasonography. Females included in this study were subjected to transabdominal Doppler ultrasonography for assessment of placental volume measurements, pulsatility index (PI) and resistivity index (RI) in both uterine arteries, and assessment of the placental volume and its vascular indices (VI, FI, VFI).

Results: 4 cases were excluded because they had abortion, 44 cases developed preeclampsia, The results revealed that Placental volume (PV), Vascularization flow index (VFI), Vascularization index (VI), Flow index (FI) and was significantly (P≤ 0.05 and 0.01) lower in Preeclampsia group than the normal pregnancy group. Also, the results indicated that pulsatility index (PI) and Resistance index (RI), were significantly (P≤ 0.01) higher in pre-eclamptic group of women than the normal pregnancy women.

Conclusion: A significant differences was found between preeclampsia patients and normal pregnancy as regard uterine artery Doppler indices and the placental volume and its vascular indices in first trimester so 3D power Doppler can be used for early prediction of adverse pregnancy outcomes and complications of uteroplacental insufficiency.

Introduction

Preeclampsia is defined as hypertension and proteinuria after 20 weeks of gestation, Preeclampsia affects approximately 2-8% of pregnant women and may lead to severe neonatal and maternal complications [1]. The uterine artery Doppler measurements indicated that impedance to flow in the urine arteries decreases with gestational age in normal pregnancies [2]; that impedance to flow is increased in established intrauterine growth restriction. Additionally, in normal pregnancy there is a doubling in placental volume between 11 and 14 weeks of gestation, which is resulted in a simultaneous doubling in fetal size and gestational sac volume [3]. Three-dimensional (3D) power Doppler sonography has been widely used in various areas of obstetrics and gynecology to evaluate vascular indices. 3D power Doppler technique serves as a noninvasive method for assessment of the placenta and has become a method of investigation to evaluate placental blood flow as early as the 1st trimester [4]. By the role of the placenta in preeclampsia pathogenesis, there is a biologically mechanism for assessing the vascular indices of the placenta to determine pregnancies at risk for preeclampsia [5]. The vascular indices include vascularization index (VI), flow index (FI), and vascularization-flow index (VFI) [6]. Some studies have suggested that 3D-power Doppler evaluation of the placenta in the first trimester for predicting adverse pregnancy outcomes including preeclampsia and fetal growth restriction [5]. Although, the results of these studies are promising, the methodologies used, and the definitions of abnormal indices have varied [7].

We aimed in this study to estimate the utility of first-trimester 3D-placental volume and vascular flow indices in the prediction of preeclampsia.

Patients and Methods

This is a prospective cohort study which was conducted at Tanta University hospital, Obstetrics and Gynecology Department, on 200 women at risk factor of preeclampsia as women with singleton pregnancy especially at the extremes of reproductive age. The study has been done during the period from August 2016 to December 2017. The study protocol was approved by the Ethical Committee of faculty of medicine, Tanta University.

All women included in this study were fulfilling the following criteria:

Inclusion criteria

1. Singleton pregnancy.
2. Familial history of preeclampsia as it has a genetic predisposition.
3. Regular menstrual cycles before pregnancy.
4. Females had preeclampsia in a previous pregnancy.
5. Gestational diabetes or essential hypertension or chronic nephritis with pregnancy" they will be seen between 11 - 14 weeks' of gestation.

Exclusion criteria

1. Cases with fetal anomalies.
2. Dead fetuses.

All females in the study were subjected to the following

1. Written informed consent concerning tests was obtained from each patient.
2. Full history taking in terms of (Age, Duration of marriage, Parity, Occupation, Residence, Mode of delivery and history of abortion).
3. General Examination including: (Pulse, Blood Pressure, Breathing, Anxiety, nervousness, Temperature and Chest and cardiac examination).
4. Abdominal and Local examination.
5. Investigations: Abdominal Ultrasonography and Laboratory investigation: (Complete blood picture,), Coagulation profile: (PT and PC), Liver function: (ALT, AST and Bilirubin), Renal function: (Urea, Creatinine and Urine output), and fasting and postprandial blood sugar.

Pregnancy related hypertensive diseases in this study were defined according to the guidelines of the International Society for the Study of hypertension in Pregnancy (ISSHIP). Gestational hypertension was defined as a blood pressure of at least 140/90 mmHg taken on two occasions more than 4 h. apart after the 20th week of pregnancy. Preeclampsia was defined as a blood pressure 140/90 mmHg and proteinuria of 300 mg in 24 hours, or two readings of at least 2+ on dipstick analysis of midstream urine specimens if no 24-hour urine collection was available in absence of urinary tract infection. Fetal growth restriction was defined as fetal weight < the 5th percentile for gestation.

Ultrasonography assessment: Woman underwent an abdominal ultrasonographic examination including color-Doppler techniques at the period of 11-14 weeks of gestations to assess the following data:

- Gestational age was determined from the onset of the last normal menstrual period; measurements of fetal crown-rump length (CRL) were done to confirm the fetal gestational age.
- The fetal viability and careful search for any fetal abnormalities present.
- The measurement of the pulsatility index (PI), the resistance index (RI) in the uterine arteries both on the left and right side, detection for the presence of notch and determine whether it is unilateral or bilateral.
- The time of examination was approximately 20 minutes.
- The ultrasound equipment used for both abdominal sonography and color Doppler technique was *GE* ultrasound machine (model??) equipped with pulsed and color Doppler options was used with the probe frequency of 7 MHz.

Trans-abdominal ultrasound examination was performed with the woman placed in a recumbent or semi recumbent position & carried out for measurement of fetal CRL and diagnosis of any major fetal defects and measurement of UtA-PI & UtA-RI. A sagittal section of the uterus was obtained For the Doppler studies, and the cervical canal and internal cervical os were identified. The transducer was gently tilted from side to side and color flow mapping was used to identify each UtA along the side of the cervix and uterus at the level of the internal os.

the sampling gate set at 2mm to cover the whole vessel and care was taken to ensure that the angle of insonation was less than $60°$. When three similar consecutive waveforms had been obtained the UtA-PI and UtA-RI were measured, and the mean UtA-PI and UtA-RI of the left and right arteries were calculated. Uterine artery Doppler was obtained with the patient in a semi recumbent position following a previously described technique [14]. A sagittal view of the uterus and of the cervical canal was obtained and color flow mapping was used to identify the uterine arteries coursing along the side of the cervix and uterus. The pulsed Doppler sample volume was placed on the ascending branch of the uterine artery closest to the internal os. The pulsatility index (PI = S _ D/M) was measured on three consecutive waveforms and the mean value between the left and right arteries was calculated. The presence of an early diastolic notch in the waveforms was recorded. An abnormal value was considered a mean PI greater than 2.36 corresponding to the 95th centile of a cross-sectional study on 3045 pregnancies 3D transabdominal ultrasound of the Placental volume: the transducer with a full bladder and the transducer placed perpendicular to the placenta to see the entire

placenta. The adjustments to 3D placental scan were an angle of 70° and a maximum region of interest that allowed the full placental surface. The external limits of the placenta were defined by the basal plate and the chorionic plate excluding the myometrium. Another acquisition was done, if the quality criteria were not attained.

After sonography, the placental volume was calculated with 4D View software (GE Healthcare) by a single operator. The calculation was done twice using the same image, and the time spent was recorded. The VOCAL mode with an angle of rotation of 30° was chosen; the axial plane was the reference; and the calipers were placed on either side of the placenta. With 6 planes, it was possible to reconstruct the volume measured in cubic centimeters.

Statistical analysis of the data was performed by using SPSS_22 software package. Categorical data parameters were presented in the form of frequency and percent. Quantitative data were expressed in the form of mean; SD. Comparison was performed by chi-square test for categorical data and T-test for quantitative data. Probability level (P-value) was assumed significant if less than 0.05 and highly significant if P-value was less than 0.001.

Results

In this study, a total of 200 women at risk factor of pre-eclampsia as women with singleton pregnancy especially at the extremes of reproductive age. the mean age of all studied cases was 27.8 year, the mean gestational age was 31.5 week, the mean maternal weight was 76.2 kg, 72 women (36.0%) were primigravida while, 128 patients (64.0%) were multigravida. Forty-eight cases (24.0%) had vaginal delivery and only four cases (2.0%) only had previous history of abortion. Mean systolic blood pressure was 151 and for diastolic blood pressure were 98. Forty one of the all cases were hypertensive and 122 cases, (61.0%) had previous history of pre-eclampsia. the mean hemoglobin (Hb) concentration was 10.4 (g/dL), mean of RBCs was 4.4 (million cells/mcL), PLT was 148 (10^8/L), mean TLC was 11420 and random blood sugar was 136 (mg/dL). For liver function, the present results

showed that total bilirubin was in the normal range 0.71 (U/L), ALT was 37.2 (U/L), AST was 47.3 (U/L), Prothrombin time was 11.9 and prothrombin concentration was 88.1. Regarding kidney function, blood urea was 26.4 (mg/dL), creatinine concentration was 0.79 (mg/dL). The results of urine analysis (24 hours) showed that normal cases had < 300 mg however, preeclampsia cases had 3000 mg. The number of cases who developed Preeclampsia of all studied cases were 22 cases (22.5%) from the total 98 cases. The results of table (1) showed that Placental volume (PV), Vascularization index (VI), Flow index (FI) and Vascularization flow index (VFI) decreased significantly (P≤ 0.05 and 0.01) in Preeclampsia group than the normal pregnancy group, for placental volume (83.7 vs. 75.2 cm³) for normal pregnancy group and preeclampsia group respectively), for Vascularization index (12.8 vs. 7.42 for the two groups respectively), flow index (43.7 vs. 38.2 for normal pregnancy group and preeclampsia group respectively), as regard Vascularization flow index (5.84 vs. 2.19 for the two groups respectively).

Results of table (2) indicated that pulsatility index (PI) and Resistance index (RI) were significantly (P≤ 0.01) higher in pre-eclamptic group of women than the normal pregnancy women. For pulsatility index it was (0.87 in the first group vs. 1.09 in preeclampsia group), however, Resistance index was 0.59 vs. 0.82 in the two groups respectively.

The screening characteristics for PET of uterine artery velocity waveforms and placental volume are compared in table (1 and 2) An abnormal PI in uterine arteries (sensitivity 61 and specificity 97.2) or a placental volume below the 5th centile (sensitivity 66.5 and specificity 98.1) showed nearly similar sensitivities and specificity in predicting PET but the sensitivities for both parameters were decreased (28) and the specificity increased (99.5) when both parameters are abnormal, while the higher sensitivity values (72.3) were reached when uterine arteries PI and placental volume were used in combination considering the result of the test positive when at least one of the parameters was abnormal.

Parameter	Groups		P. value (Sig.)
	Normal pregnancy group	Preeclampsia group	
Placental volume (PV), cm³	83.7 ± 12.4	75.2 ± 10.3	0.043*
Vascularization index (VI)	12.8 ± 3.21	7.42 ± 2.49	<0.001**
Flow index (FI).	43.7 ± 6.75	38.2 ± 7.61	0.024*
Vascularization flow index (VFI)	5.84 ± 1.27	2.19 ± 0.94	<0.001**

** Significant difference at p. value (P≤ 0.01). * Significant (P≤ 0.05).

Table 1: Placental volume measurements between Normal pregnancy group and Pre-eclampsia group.

Parameter	Groups		P. value (Sig.)
	Normal pregnancy group	**Preeclampsia group**	
Pulsatility index (PI)	0.87 ± 0.04	1.09 ± 0.05	<0.001**
Resistance index (RI).	0.59 ± 0.08	0.82 ± 0.07	<0.001**

** Significant difference at p. value (P≤ 0.01). * Significant (P≤ 0.05).

Table 2: 3D Doppler measurements.

Discussion

Pathogenesis of most pregnancy complications could be due to placental maldevelopment. So, the placental volume and vascular indices are crucial in helping to evaluate early fetal growth and development. Inadequate placental volume or vascularity might indicate poor fetal growth or gestational complications [8].

Primarily, preeclampsia is a vascular disorder which was characterized by new-onset hypertension and proteinuria at ≥20 weeks of gestation [9]. They added that the clinical pictures of preeclampsia result from the involvement of many organs including the liver, kidneys, heart, brain, lung and pancreas. It was reported that preeclampsia is can be considered as a leading cause of perinatal morbidity and mortality and it is responsible for about 50,000 maternal deaths annually [10].

As regarding the gravidity, the results of the present study indicated that 72 cases (36.0%) were primigravida while, 128 cases (64.0%) were multigravida. 48 cases (24.0%) had vaginal delivery. Four cases (2.0%) only had previous history of abortion. Regarding systolic blood pressure, its mean was 151 and for diastolic blood pressure were 98. Forty-one cases were hypertensive and 61 cases (61.0%) had previous history of pre-eclampsia. In a meta analysis of 26 studies by Luo et al.,]11], they reported that primiparous women had higher risk factor of preeclampsia (2.42 fold) than in multiparous patients and this may be attributed to some factors including angiogenic profile, differences in immune response or in insulin resistance reactivity pattern between primiparous and multiparous women.

As regarding the laboratory results the present results indicated that the preeclamptic women had 24 hours urine analysis of 3000 mg. However, in normal cases it was less than 300mg. Proteinuria (> 300mg/dL per 24 hrs.) is one of the major manifestations of preeclampsia and is likely due to a lesion known as glomerular endotheliosis and this same lesion also is responsible for the elevated creatinine seen in many preeclamptic patients (Obstetric Medicine Curriculum Bibliography, 2005). Henry et al., reported that the local vascular dysfunction becomes generalized in severe preeclampsia, leading to dysfunction of hepatic, renal, cerebral, and hematologic systems and they added that, clinical findings of severe preeclampsia are severe blood pressure elevation >160/110 mm Hg, proteinuria and oliguria. [12] reported that women who tend to develop preeclampsia may have subtle increase in systolic blood pressure and mean arterial pressure in first and second trimester well before the onset of clinical disease.

As regarding the sensitivity of the placental volume & indices Our results showed that the number of cases who developed Preeclampsia of all studied cases were 44 cases (22.0%). These results agreed with those of Schuchter et al., [13] who evaluated placental volume and uterine artery Doppler in the prediction of preeclampsia in the 1st trimester and found that preeclampsia occurred in around (20.0%) of all pregnancies. Yücesoy et al., [14] reported that the previous history of preeclampsia may affect the incidence of preeclampsia.

The present results indicated that preeclampsia cases had significantly (P≤ 0.05 and P≤ 0.01) lower placental volume (PV), Vascularization index (VI), Flow index (FI) and Vascularization flow index (VFI) than normal cases. These results agreed with Noguchi et al., [15] who studied the vascularization indices in 208 normal versus 13 growth-restricted fetuses. They found a significantly lower VI, FI and VFI in most of the small for gestational age (SGA) pregnancies. Similar results were observed by Rizzo et al., [5]. Also, Lai et al., [16] found that there were significant differences in the values of vascularization index, flow index, and vascularization-flow index between normal and preeclamptic women.

In agreement with our findings, Rizzo et al., [5] reported that the assessable measurement of the placental volume and structural changes in placenta may be useful for better understanding the pathophysiology and for the chance of early prediction of the preeclampsia. Additionally, these results are in line with those of Abdel Moety et al., Theam et al., and Hafner et al., [17,18,19].

As regarding the uterine artery indices, Steegers et al., and Visser et al., [20,21] reported that the pathogenesis of early onset preeclampsia is attributed to impaired trophoblastic invasion of spiral arteries resulting in placental ischemia and oxidative stress. Uterine artery Doppler ultrasonography can measure the high-resistance blood flow in uteroplacental circulation [12]. Using uterine artery Doppler as a screening tool for preeclampsia in 1st trimester resulted in a detection rate of only 40 % and has low positive predictive values for term disease in low-risk population [22]. However, when attention is focused on early-onset preeclampsia, uterine artery Doppler serves as an important predictor, and it is better to identify the "at risk" population in first trimester itself if the disease outcome must be modified by adding aspirin [23].

The present results revealed that preeclamptic cases had significantly (P≤ 0.01) higher pulsatility index (PI) and resistance index (RI) than the normal cases. These results are in consistent with Khalil et al., [24] who investigated the predictive value of first-trimester uterine artery Doppler pulsatility index (PI) and resistance index (RI) for assessing the risk of preeclampsia in high-risk women. They found that PI and RI increased significantly in the presence of preeclampsia and they concluded that PI and pulse-wave analysis is promising for the prediction of preeclampsia in women at increased a priori risk and may be useful in clinical practice.

Similarly, Schuchter et al., evaluated placental volume and uterine artery Doppler in the first trimester in the prediction of preeclampsia; they concluded that the combination of placental volume measurement and uterine artery Doppler in the 1st trimester may determine women at risk for subsequent development of pregnancy complications. Also, Zhong et al., [25] reported that the improvement in ultrasound technology provides potentially useful tools for evaluating placental structure and the use of 1st trimester uterine artery Doppler screening is promising as a potential screening tool.

In agreement with our findings, Costa et al., [26] found that FI, VI and VFI were lower in preeclampsia cases in comparison with normal pregnancy cases in all regions of the placenta. They concluded their results as 3D ultrasound to assess placental vascularity and flow intensity appears to be an interesting research tool.

Furthermore, Hashish et al., [27] studied that 3D assessment of placental volume and vascularization indices at 11-13 weeks of gestation and uterine artery Doppler scan (RI and PI) at 21-22 weeks. They found that the mean values of placental volume, vascularization index and vascularization flow index were significantly lower in the group of high risk. Meanwhile, uterine artery RI (0.011) and PI (<0.001) was significantly higher in the study group. They added that uterine artery PI is inversely correlated with placental volume and vascularization indices (-0.36). They suggested that 3D placental volume measurement and 3DPD assessment of placental vascular indices in the first trimester has the potential to detect women at risk for subsequent development of preeclampsia.

On the other hand, Öznur et al., analyzed the role of placental volume measured between 11 and 13 weeks of gestation on the subsequent development of preeclampsia. They found that mean placental volume was significantly higher in the late preeclampsia group and in the unaffected group compared to the early preeclampsia group. no significant difference between the late preeclampsia group and the unaffected group in terms of the placental volume values. They added that it is difficult to provide prediction of preeclampsia only by using these two parameters according to the literature data and it may be helpful to obtain successful results for preeclampsia prediction by adding other factors associated with patient Also, Hafner et al., *(28)* found that placental volume had a low sensitivity for prediction of preeclampsia.

As regarding the combination between uterine artery indices and the placental volume

Hafner et al [7] found that a low placental volume in the first trimester is strongly associated with abnormal uterine Doppler in second trimester and that placental volume at 12 weeks of gestation and uterine Doppler screening at 22 weeks have similar sensitivities for the prediction of PET. In agreement with our findings, Rizzo et al., [5] reported that the sensitivity of these combination increased when at least one parameter of them is abnormal.

Conclusion

In conclusion, there was a statistically significant difference between preeclampsia patients and normal pregnancy cases as regard uterine artery Doppler indices, placental volume and vascular indices in first trimester. 3D power Doppler ultrasound can be used as a specific screening to for early prediction of adverse pregnancy outcomes and complications of uteroplacental insufficiency. Much more studies with large number of patients must be developed to reach conclusive evidence of the significance Doppler in prediction of preeclampsia.

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