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Role of Placental Volume Measurement in First Trimester and Uterine Artery Doppler in Second Trimester In The Prediction Of Intra Uterine Growth Retardation And Pregnancy Induced Hypertension

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Abstract:

Background: preeclampsia (pe) and intrauterine growth restriction (iugr) are causes of considerable maternal and fetal morbidity and mortality with partly understood etiology. Evaluation of utero- placental vascular modification during pregnancy using non-invasive methods such as ultrasound recently became possible. Uterine artery doppler measurements showed that impedance to flow in the urine arteries decreases with gestational age in normal pregnancies, that impedance to flow is increased in established iugr and that this increased impedance predates the onset of the clinical syndrome of iugr.

Objectives: to evaluate 3d placental volume in the first trimester and uterine artery doppler velocimetry in the second trimester in the prediction of pregnancies that subsequently develop pre-eclampsia and intrauterine fetal growth restriction.

Methods: 500 pregnant women attending the antenatal care clinic of benha university hospital were subjected to first trimester (between 11-13 weeks) 3d ultrasound for measurement of placental volume then second trimester (at 22-24 weeks) color flow mapping was used to identify the uterine arteries at the level of the uterine isthmus and pulsed wave doppler was used to obtain the waveforms by the abdominal transducer.participating women were then followed up for development of adverse pregnancy outcomes (preeclampsia or frtal growth restriction).

Results: this study included 465 pregnant ladies. The placental volume of the 465 patient was 62.1 cm3 ±10.9, uterine artery pulsatility index was 1.85±0.24. From those 38 patients, 28 patients had iugr alone and 10 patient had iugr with pet. Uterine artery p.i. Was significantly higher in iugr with pet and iugr complicated pregnancies versus normal pregnancies. In this study, 4 cases out of 10 (40%) of iugr with pet group were diagnosed at 32week which is significantly higher than iugr only pregnancies in which 2 cases only out of 28 cases had early onset iugr before 34 week . Placental volume and uterine artery pulsitility index showed significant correlation with estimated intrauterine fetal weight at 32, 34, and 36 weeks but all other studies comparing our results with focused only on the birth weight. There was significant decrease in gestational age between both iugr (mean 261 d ± 6.57) and iugr with pet complicated pregnancies (mean 248.4 d ±10.44), in comparison to normal pregnancies in which gestational age of labour ranged (mean 270.9 d ±4.52); furthermore, iugr with pet cases showed significantly decreased gestational age in comparison to iugr only cases.

Conclusions: the quantitative assessment of first trimester placental vasculature and placental volume in association with second trimester uterine artery doppler can be considered a promising modality for early prediction of adverse pregnancy outcomes (preeclampsia and fgr).

Keywords: preeclampsia, uterina artery doppler, placental volume, intra uterine growth retardation, fetal growth restriction.

1. Introduction

Preeclampsia (PE) and intrauterine growth restriction (IUGR) are causes of considerable maternal and fetal morbidity and mortality with partly understood etiology. [1]. It is widely believed that during the first half of pregnancy, trophoblasticvinvasion is responsible for remodeling of the spiral arteries into dilated, inelastic vessels capable of supplying large amounts of blood to the placenta and the developing fetus. This physiological process is responsible for the development of a functional uteroplacental circulation. [2]. Histological studies show that in uncomplicated pregnancies the invasion of the trophoblastic cells extends to the decidual and myometrial segments, changing the spiral arteries to low-resistance vessels capable of supplying high amounts of blood to the placenta. [3]. Impaired remodeling due to shallow trophoblastic invasion is associated with maintenance of high resistance and low flow spiral arteries as comparable to the non-pregnant uterus and related to possible subsequent development of pre-eclampsia with or without FGR and isolated IUGR. [4]. Various authors have reported that when trophoblastic invasion is impaired, the invasion is usually restricted to the decidual segments leaving the myometrial segment of the spiral arteries unchanged and retaining their musculo-elastic wall. [5]. Early monitoring of trophoblastic invasion may increase our knowledge about placental development. It enables us to identify women with high risk for developing obstetric complications, such as pre-eclampsia and/or FGR secondary to uteroplacental dysfunction, who require more intensive surveillance during pregnancy. In addition, early identification of high risk women might help to discriminate between FGR fetuses from constitutional small-for-gestational-age (SGA) fetuses. [5].

Doppler ultrasound is a non-invasive technique, which can easily be used for evaluation of maternal and fetal hemodynamics. Doppler ultrasound studies of the

uteroplacental circulation in the second trimester have demonstrated that increased impedance to flow in these vessels is associated with an increased risk for subsequent development of pre-eclampsia (PET) and fetal growth restriction (FGR). [6]. The introduction of three-dimensional (3D) ultrasound has made it possible to measure placental volume and 3D studies have reported that reduced placental volume in the second and first trimesters, is associated with the subsequent development of FGR [7].

The diagnosis of fetal growth restriction (FGR) has for long mainly be based on birth weight below a reference cut-off, most commonly the 10th percentile [8]. Birth weight (BW) or estimated fetal weight (EFW) below p10 indicates that the BW or EFW is within the lowest 10% of BW compared to the reference population. This is in essence not FGR but small for gestational age (SGA). There are some important diagnostic issues with this misnomer. First, about 75% of fetuses who are SGA (and therefore many who are FGR) remain unrecognized until they are born and the diagnosis is made on the baby scale, postnatally [9], meaning some are severely compromised, exposed to potential long term sequelae, or even stillborn. Second, fetuses who are too small according to the intra uterine reference chart may be physiologically small and appropriate grown according to their individual growth potential (based upon their genetic and epigenetic inheritance at conception), and therefore not at risk from diseases related to FGR, but are exposed to unnecessary investigations for FGR. Third, many cases of growth restriction remain unacknowledged, when a baby or fetus is too small according to its individual growth potential, but not necessarily too small in the population based reference chart. Thus fetal growth restriction overlaps with, but is not synonymous to, small for gestational age [10].

2. Objectives

To evaluate 3D placental volume in the first trimester and uterine artery Doppler velocimetry in the second trimester in the prediction of pregnancies that subsequently develop pre-eclampsia and intrauterine fetal growth restriction.

3. Methods

This is a Prospective, comparative, observational clinical study approved by the Human Research Ethics Committee of Banha faculty of medicine. Written consents were obtained from the individual patients. Total of 500 pregnant women attending the Antenatal Care Clinic of Benha University Hospital, of them 25 patients were dropped during the follow up, 6 patients had abortion and 4 patients were excluded due to ultrasound evidence of congenital anomalies at 20 week. The remaining 465 patients were observed all through the pregnancy with or without admission and followed till delivery to correlate the diagnosis and assessment of fetal wellbeing with the actual status of the outcome. All subjects fitting the selection criteria were enrolled. The sample size calculated is 400 (But the study was done on 500 patients to compensate any drop that might occur during the time of the study and cancellation rate.) Inclusion criteria: Egyptian, primigravida, singelton pregnancy, age (18-29) years, with no medical disorders like Diabetes, hypertension and autoimmune disordes, no aneuploidies detected, no pregnancies with fetal malformations, nonsmokers and no family history of preeclampsia in first degree relative.All participating women were subjected to the following: Full history : Personal, any complaint, present history, past history and detailed obstetric history.Examination: General and obstetric examination as a part of antenatal care. Routine Investigations: CBC, ABO, coagulation profile, urine analysis, kidney and liver functions. 3D-ultrasound examination: In first trimester between 11-13 weeks: 3D ultrasound for measurement of placental volume was done using (abdominal transducer, Voluson 730,General Electric). This machine is equipped with special 3D probes that can ascertain volumes by automatic movements of the transducer around adjustable angles using VOCAL software. Scanned volume datasets were stored on hard disk for later analysis. The placenta was systematically sliced from one end to the other and in each parallel image the placental circumferences was marked manually around the boundary between the placenta and surrounding tissues. On average, approximately 2 min were needed to mark the placental volume which was then automatically calculated by the equipment's software. The 10th centile of the placental volume for CRL (placental quotient) was Calculated. In second trimester at 22-24 weeks: Color flow mapping was used to identify the uterine arteries at the level of the uterine isthmus and pulsed wave Doppler was used to obtain the waveforms by the abdominal transducer(Voluson 730, General Electric). Presence of a diastolic notch was noted and the pulsitility index and resistance index and S/D ratio were measured. The pulsatility index (PI) was calculated after manual tracing of the waveforms. The 90th centile of the uterine artery mean PI (the average PI of the left and right uterine arteries) was calculated. Follow up of the patient during pregnancy to detect development of Preeclampsia or fetal growth restriction. Preeclampsia was defined as follow: Elevated blood pressure with proteinuria. Systolic blood pressure 140 mmHg or more or diastolic blood pressure 90 mmHg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a women with a preiously normal blood pressure. Systolic blood pressure 160 mmHGg or more or diastolic blood pressure 110 or more (Severe hypertension could be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy). Proteinuria: 300 mg or more per 24 hour urine collection or Dipstick reading of ++ (ACOG , Practice bulletin 2019). Intrauterine growth restriction (defined as EFW at or below 10th percentile for growth). At the end of pregnancy: Determination of maternal and fetal outcomes (if developed pre-eclampsia or fetal growth restriction, and correlate them with placental volume and uterine

artery Doppler results.The Data were collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 17) software. The statistical test used was as follow: The results of placental volume and uterine artery Doppler were compared to each other with the final outcome after delivery regarding IUGR and PET. The results were estimated through the test performance parameters. The study was started in April 2020 and finished in April 2022.

4. Results

The main clinical features of study group are shown in the following tables and figures.

Table (1) Basic characters of the studied sample.

Variable (n=465)		Mean ±SD	Range
Age (years)		24.1±4.8	18.1-28.7
BMI (kg/m2)		26.6±3.6	18.7-35.5
		No. (n=465)	%
Mode of delivery	**C.S**	160	34.4%
	VD	305	65.59%

Table (2) Fetal weight over the period of the study.

Variable	Mean ±SD(gm)	Range(gm)
Fetal weight at 32th w (n=465)	1924.1±108	1620-2125
Fetal weight at 34th w (n=463)	2308.7±132.8	2020-2577
Fetal weight at 36th w (n=457)	2709±166.2	2354-3082

Table (3) Incidence of IUGR.

Variable		No. (n=465)	%
Incidence of IUGR	**IUGR**	28	6 %
	IUGR and PE	10	2.15 %
	Normal	427	91.8 %

Table (4) Comparing according to placental volume and uterine artery Doppler.

Variable	IUGR (n=28)			IUGR and PET (n=10)			Normal (n=427)			ANOVA	P
	Mean	± SD	Range	Mean	± SD	Range	Mean	± SD	Range		
Placental volume (cm3)	52.7*	9.41	37.2-68.5	41.1*†	6.73	33.5-50.7	64.9	8.99	46.3-83.5	51.06	<0.001 (HS)
Uterine artery P.I.	1.98*	0.26	1.52-2.41	2.05*	0.15	1.82-2.23	1.81	0.23	1.32-2.31	9.9	<0.001 (HS)
Uterine artery R.I.	0.99	0.23	0.81-1.25	1.15	0.18	0.84-1.25	0.75	0.22	0.69-0.95	6.8	<0.001 (HS)
Uterine artery SD ratio	2.85	0.49	2.35-2.96	2.74	0.75	2.44-2.97	2.25	0.77	2.16-2.71	22.3	<0.001 (HS)

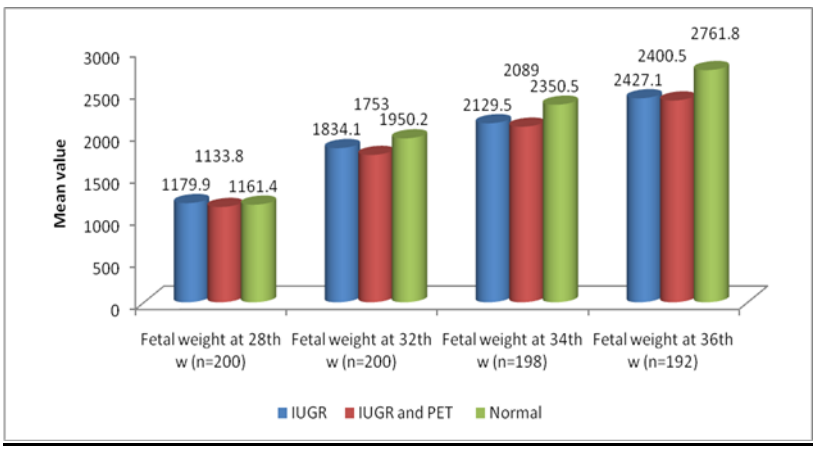

Fig. (1) Comparing the studied groups according to fetal weight

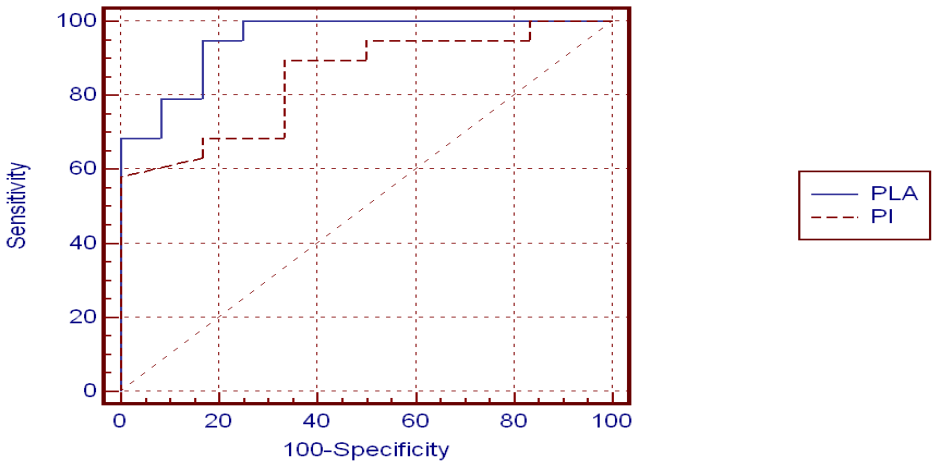

Figure (2) Comparison between placental volume and pulsatility index in prediction of preeclampsia

5. Discussion

This study included 465 pregnant ladies. The placental volume of the 465 patient was 62.1 cm3 ±10.9, this agrees with Guyomard et al. (2013) study which aimed to determine the feasibility, reproducibility, and distribution of placental volume measurements according to the crown-rump length between 11 weeks and 13 weeks 6 days in which placental volume was with a mean ± SD of 62.3± 14.8 cm^3.

Uterine artery pulsatility index was 1.85±0.24. This agrees with Augusto et al. (2013) which assessed uterine artery pulsatility index reference ranges parameter between 11wk : 14 wk and the mean value was 1.5 $\pm$ 0.5.

From those 38 patients, 28 patients had IUGR alone and 10 patient had IUGR with PET. This agrees with González-González et al. (2017) who showed increased incidence of PET with IUGR but with incidence 30 case of IUGR with PET out of 193 case of IUGR (15.5%).

Our study also agrees with Schwartz et al. (2014) who observed a significant alteration of all morphological parameters of the placenta obtained by 3D ultrasound in pregnancies with SGA newborns, including placental volume. This disagrees with Odeh et al. (2011) who concluded that placental volume in the first trimester was not a useful predictor of SGA births with no significant difference between normal pregnancies and those affected by IUGR. IUGR with PET complicated pregnancies also showed significantly low placental volume in comparison to both IUGR alone pregnancies and normal pregnancies. This result agrees with Gonzalez et al. (2014) who found that measurement of placental volume, vascular indices and PAPP-A levels, which were significantly decreased, while uterine artery PI was elevated in pregnancies complicated by preeclampsia with or without IUGR. This also agrees with Arakaki et al. (2015). The placental volume measurement was signicantly smaller in the early and late onset PIH groups than in the unaffected cases .

Stampalija et al. (2019) also agreed with our result who found that hypertensive disorders with pregnancy associated with SGA is characterized by impaired placental growth and perfusion as soon as in the first trimester of pregnancy. González-González et al. (2017) found significant reduction in placental volume , V.I , F.I and V.F.I between cases had IUGR associated with PET and IUGR alone cases . placental volume was which agree with this study results. But, this result also disagrees with Effendi et al. (2014) study which found that first-trimester placental volume is strongly associated with fetal growth and placental growth but did not observe a correlation between placental volume and the risk of preeclampsia. Hafner et al. (2013) and González-González et al. (2017), both studies showed significantly reduced placental vascular indices in pregnancies complicated with SGA supporting results of this study. These results also agree with Dar et al. (2010) and Costa et al. (2010) studies which found a significant decrease in placental volume and placental indices which was observed in preeclamptic patients with or without IUGR during the first trimester as well as the second and third trimesters. The decrease in 3D placental indices appeared before anomalies in uterine artery PI were seen. By contrast, Fariña (2015) concluded that first trimester placental volume was not useful as predictors of theses complications. Uterine artery P.I. was significantly higher in IUGR with PET and IUGR complicated pregnancies versus normal pregnancies. This result is supported by Stampalija et al. (2019) who found that The mean uterine artery pulsatility index was the highest in women with hypertensive disorders with pregnancy and SGA compared to all other groups (uncomplicated pregnancies).

This result also agree with Scandiuzzi et al. (2016) who concluded thatthe mean UAPI, values greater than 2.15 is considered abnormal during 2nd trimester (>95th percentile). PI >95th percentile in the first trimester of pregnancy increased the risk of hypertensive disorders by 23 fold. In this study, 4 cases out of 10 (40%) of IUGR with PET group were diagnosed at 32week which is significantly higher than IUGR only pregnancies in which 2 cases only out of 28 cases had early onset IUGR before 34 week . This results is supported by Scazzocchio et al. (2013) who demonstrated a detection rate of 69.2% for early-onset pre-eclampsia with a 5% false-positive rate by a 1st-trimester screening procedure combining maternal factors with the maternal blood pressure, uterine artery Doppler. Arakaki et al. (2015) studied the detection rate for PIH using the placental volume and uterine artery Doppler at 11 to 13 weeks' gestation. The placental volume measurement was signicantly smaller in the early onset and late onset PIH groups than in the unaffected cases (43 vs 62 cm^3), but these parameters were not signicantly different between the late-onset PIH and unaffected cases. In this study placental volume and uterine artery pulsitility index showed significant correlation with estimated intrauterine fetal weight at 32, 34, and 36 weeks but all other studies comparing our results with focused only on the birth weight. In this study, significant decrease in gestational age between both IUGR (mean 261 d ± 6.57) and IUGR with PET complicated pregnancies (mean 248.4 d ±10.44), in comparison to normal pregnancies in which gestational age of labour ranged (mean 270.9 d ±4.52); furthermore, IUGR with PET cases showed significantly decreased gestational age in comparison to IUGR only cases. This agrees with González-González et al. (2017) and Pomorski et al.(2012) who found gestational age was significantly lower in cases with IUGR with PET , IUGR only and normal pregnancies. In this study the results showed significant increase of the C.S labour rate in both IUGR complicated pregnancies and IUGR with PET ones in comparison to normal pregnancies. This agrees with Perrotin F(2013) study results which showed that Although elective caesarean section is the commonest method of labour in pregnancies complicated with IUGR however there is no current evidence supporting its systemic use. Sylvia (2019) also showed that Emergency CS rates were significantly higher among low-weight newborns (<2500 g) and macrosome newborns (>4000 g) than among normal-weight newborns. The high incidence of caesarian section rate in this study reflect the elevated caesarian section rate of our study group (34.4 %). Schwartz et al. (2010) demonstrated that a placental quotient (= placenta volume/crown-rump length) less than 1.00 predicted a small for gestational age (SGA) fetus with 56.5% sensitivity and 75% specificity. This supports our results in which 1st trimester placental volume ≤54.6 cm3 predict IUGR with 73.7 sensitivity and 86% specificity. Schwartz et al. (2014) studied 1st trimester placental volume and serum markers as predictors for SGA and analysed her results using Receiver operator characteristic (ROC) curves used for each significant variable and the area under the curve (AUC) served as a reflection of the overall ability of the variable to discriminate between pregnancies with an adverse outcome and those without in the same way as this study. In this study placental volume ≤ 54.6 cm3 has sensitivity 73.4% , positive predicting value 56%, specificity 86.4% and negative predicting value 93.3%. Regarding placental volume, Schwartz et al. (2014) found that placental volume ≤51.0 cm3 has specificity 75.4% to 82.4% and negative predicting value 96.7 % this agree with our study in which specificity and negative predicting value were 86.4% and 93.3% respectively. However sensitivity of placental volume in Schwartz et al. (2014) study was 46.4% (28.0:65.8) while in this study it was 73.4%. Schwartz et al. (2014) also assessed 1st trimester uterine artery P.I and study results found that P.I ≥ 1.92 has sensitivity 28.6%, a good specificity 80% and negative predictive value 95.7% . This disagrees with results of this study which found uterine artery P.I ≥1.92 has 63.2% sensitivity, 66.7% specificity and 88.5% negative predictive value.

6. Conclusions

The quantitative assessment of first trimester placental vasculature and placental volume in association with second trimester uterine artery Doppler can be considered a promising modality for early prediction of adverse pregnancy outcomes (Preeclampsia and FGR).

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