Original Article

US Doppler and Power Doppler Prediction of Recurrent Fetal Growth Restriction. Prospective Cohort Study

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ABSTRACT

Background: Intrauterine growth restriction(IUGR) has been defined as the rate of fetal growth that is below normal in light of the growth potential of a specific infant as per the race and gender of the fetus. A woman with a prior pregnancy complicated by IUGR has nearly a 20% risk of recurrence. Defects in placental vascular development can cause embryonic death, can negatively affect fetal growth and can confer a higher risk of disease in the postnatal life.

Objective: study aimed to assess the role of first trimester uterine artery Doppler pulsatility index, placental volume and placental vascularization assessed in prediction of recurrence of third trimester intrauterine growth restriction.

Methods: In this Prospective longitudinal observational study,two hundred pregnant women with singleton pregnancy from 11 up to 13 weeks with history of intrauterine growth restriction in a previous pregnancy underwent ultrasound assessment of gestational age, ultrasound assessment of uterine artery pulsatility index, placental volume by 3D ultrasound and placental vascularization by 3D power Doppler (3DPD).

Results: Placental volume, vascularization index, flow index(F.I), vascularization flow index, and Uterine artery pulsatility index were significantly lower in IUGR with PET(pre eclampatic toxemia) group and IUGRgroup versus normal group, (*p-value*<0.001).Further, placental volume and F.I were significantly lower in IUGR and PET group compared to IUGR only group.

Conclusions: The 1st trimester placental volume, uterine artery Doppler, and, placental vascular indices are useful parameters for prediction of recurrence of IUGR.

Key Words: Doppler, growth restriction, power doppler.

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INTRODUCTION

Intrauterine growth restriction (IUGR) has been defined as the rate of fetal growth that is below normal in light of the growth potential of a specific infant as per the race and gender of the fetus. It has also been described as a deviation from or a reduction in an expected fetal growth pattern and is usually the result of innate reduced growth potential or because of multiple adverse effects on the fetus[1].

A woman with a prior gestation complicated by FGR has nearly a 20% risk of recurrence[2]. The Doppler effect, first reported by Christian Doppler in 1842, describes the apparent variation in frequency of a light or a sound wave as the source of the wave approaches or moves away relative to an observer[3].

Reddy *et al*. assessed uterine artery velocimetry at 22 to 24 weeks. The risk of fetal death before 32 weeks when associated with fetal growth restriction was significantly linked to high resistance flow. They suggested that uterine artery Doppler velocimetry has a role as a screening tool to detect pregnancies at risk forstillbirth[4].

Placental volume is only routinely investigated and described at pathological examination, after delivery. Examination of placental volume can possibly disclose information for the detection of fetal growthrestriction. Evaluationof the placenta duringpregnancy isusually only performed to assess the location of the placenta or to diagnose placental adhesion disorders[5].

Looney *et al*. assessed placental volume of 2,393 pregnancies by three operators on the one hand, and this semi- automated tool on the other hand. The clinical utility of placental volume was tested by looking at prediction of SGA at term. Results showed good similarity between the operators and the tool, and almost identical clinical results for the prediction of SGA[6].

The placental vasculature also plays a critical role in normal development, as studies clearly indicate that growth-restricted fetuses with absent or reversed end-diastolic umbilical artery velocities (AEDV/REDV) experience even worse outcomes than fetuses with FGR and preserved end-diastolic velocities[7]. The aim of the

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study was to assess the role of first trimester uterine artery Doppler pulsatility index, placental volume and placental vascularization in the prediction of recurrence of third trimester intrauterine growth restriction

PATIENTS AND METHODS

This Prospective longitudinal observational study was conducted at Benha University hospital starting from December 2016 to May 2019 after approval of faculty Research Ethics Board. Two hundred pregnant women with history of IUGR in previous pregnancy were recruited for the study after full explanation of the method, aim of work and obtaining consent. Inclusion criteria:singleton pregnancy from 11 up to 13 weeks. History of intrauterine growth restriction in previous pregnancy Exclusion criteria:Multiple pregnancies,Smoking women,and pre-existing medical disorders which may affect fetal growth e.g. hypertension, diabetes mellitus, thyroid dysfunction or renal impairment.Ultrasound evidence of congenital anomalies.

All women underwent ultrasound study which was performed by a member of ultra-sound unit (Volsun 730 pro V; G.E medical system), for assessment of: Gestational age confirmed by crown-rump length assessment, Uterine artery pulsatility index (angle of insonation is<50°, the sampling gate set at 2mm), 3D ultrasound assessment of Placental volume, 3DPD for assessment of placental vascularization. The examination was done with the patient in lithotomy position with slight left lateral tilting to avoid supine hypotension.

After visualization of the placental vasculature, 3D static power Doppler scanning was performed.After scanning the region of interest, placental volume was measured using the VOCAL rotational technique and VOCAL software (3D SonoView, GE Medical Systems, Milwaukee, WI, USA). After completing a full rotation, another analysis was performed using VOCAL Software (3D SonoView, GE Medical Systems, Milwaukee, WI, USA), which automatically calculates placental volume, vascularization index (VI), flow index (FI) and vascularization flow index (VFI). Low dose aspirin 75mg was described for all cases with the beginning of 2nd trimester.

All cases were having a second trimester (between 20 to 24 weeks) and a third trimester ultrasound assessment for exclusion of congenital malformation and assessment of fetal growth parameter and identification of IUGR cases (according to fetal growth curves)[8]. In order to avoid including healthy, yet constitutionallysmall for gestational age fetuses to the IUGR group,patients' data were included in the study only in cases of IUGR diagnosis confirmed after delivery.

Primary outcome

- Assessment of placental volume, vascularization index (VI), flow index (FI) and vascularization flow index (VFI).
- Assessment for exclusion of congenital malformation and assessment of fetal growth parameter
- Identification of IUGR cases.

Statistical analysis

The collected data were tabulated and analyzed using SPSS version 16 soft ware (SpssInc, Chicago, ILL Company and MedCalc Software, Mariakerke, Belgium).

Categorical data were presented as number and percentages using Fisher's exact test (FET) and Z test of proportions for their analysis. Quantitative data were tested for normality using Kolomogrov Smirnove test, assuming normality at $P > 0.05$ as proved be normal, they were expressed as mean ± standard deviation and range. Difference among 3 independent means was analyzed using ANOVA. Significant ANOVA were followed by post hoc multiple comparisons using Bonferroni tests to detect the significant pairs. Correlations between variables were assessed by Person's correlation coefficient (r). ROC curves were constructed to detect cutoff values of the studied markers with optimum sensitivity and specificity in early diagnosis of recurrent IUGR. Binary logistic regression analysis was run to detect the significant predictors of recurrent IUGR. The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant). *P value* >0.05 is non significant (NS). $P < 0.05$ is significant (S). $P \leq 0.001$ is highly significant (HS).

RESULTS

This prospective longitudinal observational study was carried out on 209 pregnant women attending the Antenatal Care Clinic of Benha University Hospital with history of IUGR in previous pregnancy. Six patients were dropped during the follow up, 2 patients had abortion and 1 patient was excluded due to ultrasound evidence of congenital anomalies at 20 week. The remaining 200 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 demographic, clinical and ultrasonographic characteristics of the women were included in (Table 1).

Table 1: Basic characters of the studied sample

Variable (n=200)		Mean ±SD	Range
Age (years)		27.2±4.8	18.1-39.5
BMI(kg/m^2)		26.6±3.6	18.7-35.5
		No. (n=200)	%
Parity	P_1	136	68.0
	P_2	58	29.0
	P_3	6	3.0
No ofprevious IUGR	Once	192	96.0
	Twice	8	4.0
Mode of delivery	C.S	164	82.0
	VD	36.0	18.0
Placental volume (cm3)		62.1±10.9	33.5-83.5
V.I.		9.4±1.7	6.08-13.8
F.I.		49.5±2.4	40.8-53.9
V.F.I.		4.99±1.14	1.21-7.19
Uterine artery Doppler PI		1.85±0.24	1.32-2.41
Fetal weight at 32thw (n=200)		1924.1±108	1620-2125
Fetal weight at 34th w(n=198)		2308.7±132.8	2020-2577
Fetal weight at 36th w(n=192)		2709±166.2	2354-3082
Incidence of IUGR	IUGR	28	14.0
	IUGR and PE	10	5.0
	Normal	162	81.0
Birth weight (gm)		3161.1±392.6	Range 1730-3719

From 200 women completed the study , 28women developed IUGR alone and 10 women developed IUGR and PET .On comparing the three groups (IUGR, IUGR & PET and normal) according to relevant factors ,it was found that the age and BMI of women were significantly increased in IUGR and PET group relative to normal and IUGR groups. From 192 women giving history of once IUGR, 17.7% developed recurrent IUGR while 50% developed recurrent IUGR from those with history of twice IUGR(8 women) and this difference was significant (Table 2).

The values of 3D PD were significantly lower in IUGR group than normal group and higher when compared to IUGR and PET group. On contrast, the u PI was significantly higher in IUGR group than normal group and lower when compared to IUGR and PET group (Table 2).

At 32 week, 2 women developed IUGR alone and 4 women developed IUGR and PET. Only 2 women terminated the pregnancy between 32-34 weeks. At 34 week, 12 women developed IUGR alone and 4 women developed IUGR and PET. Only 6 women terminated the pregnancy between 34-36 weeks. At 36 week, from the remaining 192 women, 14 women developed IUGR alone and 2 women developed IUGR and PET.

On comparing the estimated fetal weight at different gestational age groups (32 w, 34 w, 36 w and at birth), it was noted that the fetal and birth weights at the four age groups was significantly lower in IUGR and IUGR and PET groups when compared to normal group Table 2).

On assessment of the findings of the 3DPD of the placenta and colour Doppler of the uterine artery to detect predictability to recurrent IUGR, The ROC curves were used. It was found that the placental volume≤ 54.6 (cm^3) was the most specific factor to predict recurrent IUGR, while the FI ≤ 49.4 was the most sensitive. (Figure 1,Table 3).

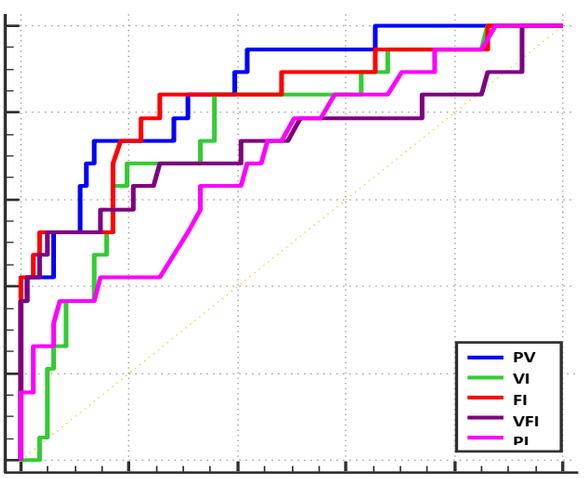

Fig. 1: ROC curves for the performance of placental volume,V.I.,F.I. and VFI and UAPI in prediction of recurrentIUGR

Table 2: Comparing the studied groups according to different factors

Variable	IUGR (n=28)		IUGR and PET (n=10)		Normal (n=162)		A ANOVA	*P*
	Mean± SD	Range	Mean± SD	Range	Mean± SD	Range		
Age (ys)	26.2±6.78	18.5-39	31.5*†±7.69	18.1-39.5	27.0±4.10	19-36	4.74	0.01 (S)
BMI (kg/m^2)	25.2±5.15	18.7-33.5	29.2*†±2.92	24.7-33.3	26.7±3.33	19-35.5	4.81	0.009 (S)
Placental volume (cm^3)	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)
V.I.	8.43*±1.43	6.3-11.3	7.63*±0.88	6.8-9.02	9.67±1.67	6.08-13.9	13.2	<0.001 (HS)
F.I.	47.5*±2.78	43.2-52	44.5*†±2.92	40.8-48.9	50.1±1.65	46.2-53.9	57.06	<0.001 (HS)
V.F.I.	4.13*±1.69	1.93-6.74	3.46*±1.55	1.21-5.45	5.23±0.81	3.13-7.19	25.9	<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)
			Groups			Total	FET	*P*
			IUGR	IUGR and PE	Normal			
No. of IUGR 1Count			34 (17.7%)					
% within Groups			26	8	158	192		
			13.54%	4.16%	82.3%	96.0%		
No. of IUGR 2 Count			4 (50%)				6.95	0.018 (S)
% within Groups			2	2	4	8		
			25%	25%	2.5%	4.0%		
Total Count			28	10	162	200		
% within Groups			100.0%	100.0%	100.0%	100.0%		
Fetal weight at 32th w (n=200)(gm)	1834.1*±77.6	1650-1940	1753.0*±94.8	1620-1876	1950.2±94.8	1761-2125	36.7	<0.001 (HS)
Fetal weight at 34th w (n=198) (gm)	2129.5*±83.1	2020-2260	2089.0*±65.5	2048-2195	2350.5±102.5	2139 - 2577	80.04	<0.001 (HS)
Fetal weight at 36th w (n=192)(gm)	2427.1*±26.4	2370-2456	2400.5*±53.6	2354-2447	2761.8±120.8	2497 - 3082	115.2	<0.001 (HS)
Birth weight (gm)	2550.2*±143.0	2150-2725	2236.0*±331.7	1730-2600	3323.8±190.4	2386-3719	310.7	<0.001 (HS)

Table 3: Validity and predictivity of placental volume, V.I., F.I. and VFI and UAPI in prediction of recurrentIUGR

Variable	Sens%	Spec%	PPV%	NPV%	AUC	95%CI	*P*
Placental volume ≤54.6(cm^3)	73.7%	86.4%	56%	93.3%	0.859	0.79-0.92	<0.001 (HS)
V.I. ≤ 8.46	68.4%	80.2%	44.8%	91.5%	0.757	0.67-0.84	<0.001 (HS)
F.I. ≤ 49.4	84.2%	74.1%	43.2%	95.2%	0.829	0.75-0.91	<0.001 (HS)
VFI ≤ 3.66	52.6%	95.1%	71.4%	89.5%	0.733	0.62-0.84	<0.001 (HS)
Uterine artery P.I. ≥ 1.92	63.2%	66.7%	30.8%	88.5%	0.695	0.60-0.79	<0.001 (HS)

Binary logistic regression analysis was used to detect the most significant predictors of recurrent IUGR .It was found that the placental volume ≤54.6 (cm3) was the most significant predictor for recurrent IUGR followed by F.I. ≤ 49.4. (Table 4)

Table 4: Multivariable binary logistic regression model for the predictors of recurrent IUGR

	B (coefficients)	Sig.	Odds ratio	95.0% C.I. for odds ratio	
				Lower	Upper
No of IUGR (2)	2.11	0.031 (S)	4.28	1.210	56.6
Placental volume ≤54.6 (cm3)	2.38	0.009 (S)	5.84	1.90	26.8
V.I. ≤ 8.46	0.122	0.865	1.13	0.28	4.58
F.I. ≤ 49.4	2.29	0.012 (S)	5.28	1.82	13.9
VFI ≤ 3.66	1.07	0.099	2.93	0.81	10.5
Uterine artery P.I. ≥1.92	0.64	0.185	1.91	0.73	4.93
Constant	3.44				

DISCUSSION

The majority of cases of both PE and IUGR are due to Defective placentation and an impaired placental circulation. This impairment was attributed to failure of trophoblastic invasion of spiral vessels causing outflow resistance in the maternal uterine arteries and fetal umbilical arteries .For many years, measurement of resistance to flow in the uterine arteries has been used to predict IUGR or PE. Also measurement of resistance to flow in the umbilical arteries is used to evaluate fetal well-being in IUGR[9]. Over 80% of villous circulation has to be obliterated before any impact on umbilical artery resistance is detected[10]. Imaging the placental circulation in *vivo* could be an important method of predicting IUGR or PE, for early preventative modalities to be used.

Several studies tried to evaluate the placental vasculature and volume. Yu *et al* assessed the vascular parameters for a small fixed placental volume. Another study introduced a technique called vascular placental biopsy through scanning apart of placenta with the highest vascular intensity[11,12,13]. Both studies found that the placental vascular parameters increased during the course of pregnancy while Guiot *et al*. used five constant region of the placenta and later on de Paula *et al* revealed the values of vascular parameters remain constant during pregnancy when measured from the entire placenta. All these studies were done in the second half of pregnancy in a trial to detect early IUGR cases. Our study was done for the entire placental volume in the first trimester to predict IUGR cases and revealed that the placental volume and vascular parameters were significantly lower in PET and IUGR group and IUGR alone group when compared to normal cases. Also the u PI was higher in the pregnancy complicated groups when compared to normal group[14,15].

Previous studies investigated the role of 3DPD for early detection of impaired placental vasculature and volume together with the u PI and others added some serum markers a PAPP A but conflicting results were found[16,17,18]. In line with our findings, some studies found that first-trimester placental volume is strongly associated with fetal growth and placental growth and observed a correlation between placental volume and the risk of preeclampsia and IUGR[19,20,21]. Other studies detected no significantly placental vascular indices in complicated pregnancy. Mohamed *et al*. compared pregestational diabetic cases with control cases at the first trimester of pregnancy especially with good glycemic control but changes may be present with poor glycaemic control. In addition they recommended evaluation of placental volume and vascular indices in pregestational diabetic at the last two trimester of pregnancy giving more time for the pathological effect of diabetes mellitus to appear[17]. Furthermore Odeh *et al*. 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 or PET. This disparate finding can be explained by that all PET cases were mild and developed at 34 weeks or more but in our study some severe cases developing before 32 weeks[22].

The receiver operating characteristic curve was used to detect which variable is more discriminative of adverse pregnancy outcome. Similar to our study Schwartz *et al*.[19] found that placental volume ≤51.0 cm^3 has the highest specificity and negative predicting value while the FI is the most sensitive vascular parameters to predict IUGR. It was found that using placental volume less than the 10^{th} percentile as cutoff level, the placental volume had high specificity and negative predicting valueSoongsatitanon *et al*.[21].

Odeh *et al*. stated that vascular indices without any factor of correction did not give any discriminate ability for IUGR[22]. However Rizzo *et al*.suggested that in selected populations with other risk factors for IUGR and PE, such as poor obstetric history, the vascular indices could predict the disease with better results[23]. In contrast to our results, the placental vascular parameters were too low to be used in clinical practice Gonzalez *et al*[16]. Similar to our results, previous studies have noted that the FI, which means blood flow intensity, is the most valuable vascular index due to lower intra placental variability and higher intra- and inter-observer correlations[24]. In addition Chen *et al*. also concluded no significant difference in the FI between the first and second trimesters in the FGR group, indicating that the FI is a reliable and stable index in FGR placentas[25].

In a previous sonographic study performed to examine the indices of spiral artery jets, the pulsatility and resistance indices were different in SGA pregnancies[26]. Also a morphometric analysis of stem villus arteries found a higher vessel wall thickness/lumen ratio in SGA/FGR placentas[27]. These results indicated that the intensity of placental blood flow may be lower in FGR pregnancies, supporting our findings of a significantly lower placental FI and VFI in the FGR group.

The higher sensitivity of our study can be accepted regarding to selection criteria of our study group as a high risk group with history of IUGR which also explains the high rate of incidence of IUGR with/ without PET. In this study we found that decrease in placental volume and vascularity was associated also with increased incidence of PET with IUGR which can be attributed to the same pathogenesis of defective deep placentation which occurs in both IUGR and preeclampsia.

Our study was limited by small number of cases. However, hundreds of cases were needed .for placental volume to reach significant power.

CONCLUSION

The 1st trimester placental volume, uterine artery Doppler, and, placental vascular indices are useful parameters for prediction of recurrence of IGUR .

ABBREVIATIONS

RI: resistance index, **ROC:** Curve receiver operator characteristic curve, **S:D:** systolic/diastolic, **SD:** standard deviation, **SGA:** Small gestational age, **VFI:** Vascularization Flow Index, **VI:** Vascularization Index, **VOCAL:** Virtual Organ Computer–Aided Analysis software, **WT:** weight, **B-hCGbeta:** human chorionic gonadotropin, **AEDV:** absent end diastolic velocity, **REDV:** reversed end diastolic velocity, **IUGR:** intra uterine growth restriction

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CONFLICT OF INTERESTS

There are no conflicts of interest.

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