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" Fetal Cerebroplacental Artery Ratio versus Uterine Artery Doppler Ultrasonography For Prediction of Late Onset Intrauterine Fetal Growth Restriction among High Risk Pregnant Women "

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ABSTRACT:

Background: A higher risk of adverse perinatal outcomes has been significantly correlated with intrauterine growth restriction (IUGR) caused by placental insufficiency in both preterm and term fetuses.

Aim and objectives: to analyze the significance of uterine perfusion and fetal redistribution in predication of late onset IUGR in high-risk pregnant women.

Subjects and methods: This present study was a prospective randomized control trial which was conducted on 119 high risk pregnant ladies with singleton pregnancy from January 2021 to December 2022 firstly at ElShatby Maternity University Hospital after the approval of the ethical committee of Faculty of Medicine- Port-said University being allocated randomly into either group A which undergone cerebroplacental ratio (CPR) or group B which undergone uterine artery (UtA) evaluation.

Results: there was a significant variation among the examined groups regarding fetal weight, Comparison of fetal CPR Doppler ultrasonography and stepwise linear regression analysis for Doppler predictors of IUGR. Umbilical artery (UA) Pulsatility index (PI) and UtA PI have high sensitivity and specificity to predict IUGR.

Conclusion: CPR as well as UtA Doppler are of predictive value in predicting late onset IUGR in risky pregnancy.

Keywords: Cerebroplacental ratio, Uterine Artery, Doppler Ultrasonography, Intrauterine Fetal Growth

Introduction :

Fetal Growth Restriction (FGR) is diagnosed when the fetus does not develop or grow to its full potential while still inside the mother's uterus. FGR that manifests after 32 weeks of gestation is referred to as late-onset FGR. It is estimated that between five and ten of people will develop late-onset FGR, and it is one of the primary causes of perinatal mortality & morbidity. Close monitoring and prompt delivery are the two most important aspects of management for FGR because there is currently no treatment that is proven to be beneficial **(1)**.

Histological indicators of placental under perfusion are found in the placentas of fetuses with late-onset of FGR. These indicators include vascular blockage & villous hypoplasia. Doppler indications of increased placental vascular resistance are usually related with worse pregnancy outcomes that results in FGR. The amount of blood that flows via the umblical artery (UA) is a representation of the degree of perfusion to the fetal–placental unit **(2)**.

Unfortunately, the data has indicated that the UA Doppler does not reliably predict worse perinatal outcomes of late-onset IUGR. This is due to the fact that the UA Doppler will only become aberrant if a significant portion of the placenta is involved. It has been demonstrated that middle cerebral artery (MCA) Doppler can be used to predict bad outcomes in near-term IUGR fetuses with good specificity, but with low sensitivity for practical relevance **(3)**.

Uterine artery (UtA) that's not typical Doppler, which represents placentas that receive insufficient blood flow from the mother, is linked to poor trophoblast invasion. Due to the fact that the UtA has variable findings in terms of its prediction accuracy, it is debatable as to whether or not it should be utilized as a predictive indicator **(4)**.

It has been found that the cerebroplacental ratio (CPR) is very sensitive to hypoxia, which increases the sensitivity of the UA and MCA when used together. Its ability to foretell negative consequences in the third trimester is, however, still up for debate. Therefore, it is crucial to seriously evaluate the need for improved Doppler predictors of bad outcomes in pregnancies impacted by late-onset intrauterine growth restriction (IUGR) **(5)**.

The objective of this work was to assess the diagnostic performance of CPR and UtA Pulsatility index (PI) Doppler ultrasonography & compare between them in high-risk mothers in predication of late onset IUGR.

Patients and Methods:

This prospective randomized control trail was carried out from January 2021 to December 2022 firstly at ElShatby Maternity University Hospital after the approval of the ethical committee of Faculty of Medicine- Port-said University.

Study population:

I. All high risk pregnant ladies for IUGR were eligible for this study. Eligibility was determined according to the following **inclusion criteria:**

-a singleton pregnancy

-chronic hypertension (HTN), pregestational diabetes, systemic lupus erythromatosis (SLE), chronic kidney disease (CKD), vasculopathy and metabolic disorders

-history of IUGR.

II. **Exclusion criteria:** Those of low-risk pregnant ladies or those with Multiple gestations, documented major congenital abnormality, aneuploidy or genetic syndrome as well as congenital infection were excluded.

Sample size:

Based upon a previous study aimed to assess the diagnostic performance of fetal MCA and UA by Doppler ultrasonography in high-risk mothers and association with perinatal consequence the required minimal sample size was calculated. **Malik and Saxena (6)** concluded combined use of both UA and MCA Doppler study including the CPR increase the sensitivity of the Doppler studies for prediction adverse perinatal outcome.

Based on their findings, sample size of 119 pregnant women was the enough required sample to conduct this diagnostic test accuracy study, assuming a level of significance 95% (α=0.05), and statistical power (1 – β) of 90%, with assumption of discrimination power of Doppler PI in pregnant women is 70% area under the ROC curve **(7)**.

Randomization:

All high-risk patients eligible to this study willing to participate in this present study after giving a written informed consent regarding the nature and the aim of the study was randomly allocated into either of the two groups: group **A** (those who were undergone **CPR** evaluation) or group **B** (those who were undergone **UtA** Doppler evaluation) using computer-generated randomization

Each participant was allocated into either two groups using simple random sample, 1:1 randomization in which computerized random sample was taken from study population. Each one received a sealed envelope provided to the patient by the nurse in the outpatient clinic.

The current study was started on those eligible patients at **20 weeks** gestational age pregnancy when all risky patients were evaluated thoroughly about :

I. Age of the pregnant lady

II. Gestational age (GA) the most accurate technique for it is measuring the crown rump length (CRL) between 8-14 weeks gestation. In cases of not having first trimester scan ;head circumference(HC) with or without femur length(FL) can be used **(8, 9)** as well as using Negele's rule in case of normal 28 day cycle **(10)**.

III. Obstetric history: Gravidity & Parity (detailed history about length of pregnancies, method of deliveries, weight of babies & their gender ,complications before, during and after delivery)

IV. Past medical history (HTN, uncontrolled diabetes mellites (DM), SLE ,CKD , vasculopathy and metabolic disorders)

Each group was evaluated then (after being randomly allocated to either one):

Group **A**; was assessed through evaluating the **CPR (11)** which was calculated by dividing mean MCA PI (The PI **(12)** is calculated by dividing the peak systolic velocity (PSV) minus the end-diastolic velocity (EDV) by the time-averaged velocity(TAV)) by mean UA PI

- **PI = (PSV - EDV) / TAV**

UA Doppler **(13)** were obtained at **24-28** weeks of gestation for each patient in a free floating umbilical cord loop as well as **MCA** in the circle of Willis cross sectionally in the absence of fetal movement or uterine contractions keeping the angle of insinuation at less than 30 degrees **(14)** were recorded. Mean value of at least 3 consecutive waveforms of UA and MCA PI was recorded. CPR was calculated as the simple ratio among the MCA PI and the UA PI assuming that cutoff value of CPR 1 or more as normal while ≤ 1 as abnormal **(11)**.

Group **B:** was assessed through evaluating the **UtA** Doppler over the iliac fossa and tracking its course from its origin in the internal iliac artery (IIA) in the lateral pelvic wall. Pulsed Doppler was then administered 1 cm medially, at an angle of insinuation of less than 30 degrees, at the point of passing over the external iliac artery (EIA); The PI to be obtained both left and right by measuring mean value of three similar consecutive waveforms **(15)**, (taking into consideration the placental side). UtA Doppler measurement was said to be abnormal if any of the following is present: notching, PI >95th percentile or ≥2 standard deviation (SD) above the mean, resistance index (RI) > 0.50, or any abnormal waveform. Each patient was first evaluated at **20–24 weeks** of gestation.

Then all those eligible ladies (i.e .both groups) were followed and were assessed through Serial ultrasound every 2 weeks using Hadlock's formula to estimate the fetal weight **(16)** Those obtained values were converted into centiles **(17)**.

Taking those fetuses who are **less than 10th** percentile & diagnosed **after 32** weeks to be the **growthly restricted one of late onset** .

Ultrasound and Doppler studies were performed using Mindray DC 70 ultrasound systems and 3-7 MHz probes.

-In addition to further parameters which were evaluated postnatal as: mode of delivery (emergency cesarean section(cs) due to fetal distress), , fetal sex as well as its birth weight.

Statistical analysis: The acquired data was evaluated, and a manual coding process was applied. The Statistic Package for the Social Sciences, Version 22 (SPSS 22) for Windows, was employed to do statistical analysis on these numerical codes.

Descriptive statistics: Quantitative data and Qualitative data

Analytical statistics: Comparing groups was done via Chi square-test (X^2), Student's " t "- test, Mann Whitney test, ANOVA test, Pearson correlation, Stepwise linear logistic regression analysis and Receiver operating characteristic curves (ROC)

The coefficient interval was set to 95%. The following probability (P) values determined significance: $P<0.05$ was statistically significant, $P<0.001$ was highly significant and $P>0.05$ was non-significant.

Results:

Among current studied pregnant females; 69.7% were primigravida and 30.3% were multipara; their age ranged between 18-38 years. 68.1% were born via ceserean section (CS). 50.4% have HTN, 22.7% have DM, 11.8% have SLE, 5.9% have CKD, 5% have anti-phospholipid $, while 4.2% have vasculopathy. At the time of assessment GA ranged between 32-33 weeks and fetal weight ranged between 1123 – 1476 gm. **[Table 1], figure (1)** and **figure (2)**.

Fetal weight at the time of assessment was significant lower in IUGR than normal weight group. However, there is no significant variation between IUGR and normal weight neonates as regard the gestational age at the time of assessment.**[Table 2]**

UA PI and umbilical cerebral ratio (UCR) are significant higher in IUGR than normal weight group. While, CPR, MCA PI, & MCA PSV are statistically significant lower in IUGR than normal weight group. **[Table 3]**

Stepwise linear regression analysis revealed that UA PI, UtA PI and MCA PSV are significant predictors of IUGR. **[Table 4]**

At cutoff value ≥1.105 UAPI has 85.5% sensitivity and 84% specificity to predict IUGR. At cutoff value ≥0.755 UCR has 78.3% sensitivity and 84% specificity to predict IUGR. At cutoff value ≥1.395UtAPI has 58% sensitivity and 64% specificity to predict IUGR. At cutoff value ≥0.675 UtARI has 72.5% sensitivity and 60% specificity to predict IUGR. MCAPI, MCAPSV and CPR have low sensitivity and specificity to predict IUGR. **[Table 5]**

Discussion:

Analysis of the present findings revealed that as regard maternal data; 69.7% were primigravida and 30.3% were multipara; their age ranged between 18-38 years. 68.1% were born via CS. 22.7% have Pre_gestational DM, 50.4% have HTN, 11.8% have SLE, 5.9% have CKD, 5% have anti-phospholipid syndrome, while 5% have vasculopathy. At the time of assessment GA ranged between 32-33 weeks and fetal weight ranged between 1123 – 1476 gm.

In agreement with present findings, the study of **Prajapati et al., (18)** on 400 high risk women revealed that there were 375 people in the age bracket of 20–30 years, with the mean age ± standard deviation of research participants being 25 ± 3.3 years. Anemia accounted for 67 (16.75%) of the problems that occurred during the most recent pregnancy, whereas hypertension caused 15 (3.75%) of the cases & diabetes caused 11 (2.75%).

In the present study, we compared between women with IUGR and normal weight as regard obstetric data; IUGR was statistically significant more frequent in primipara & have statistically significant higher rate of cs than normal weight neonates. There is no statistically significant alteration amongst IUGR and normal weight one as regard maternal age or BMI.

In accordance with present findings, the research of **El-Kady et al., (19)** who aimed to assess role of CPR in prediction of perinatal outcome in high-risk pregnancies with IUGR and reported that there were no significant differences between the studied groups regarding demographic characteristics.

Furthermore, in the current study; IUGR neonates were statistically significant more frequent in mother with SLE and statistically significant less frequent in mother with DM, there was no statistically significant difference in the frequency of IUGR in mothers with CKD, HTN, anti-phospholipid $ and vasculopathy.

In consistent with present findings, the study of **Abdwani et al., (20)** When contrasted neonates born to healthy control moms, it was found that neonates born to women with SLE had a higher risk of being preterm (28.5% vs. 1.0%; p under 0.001), having a low birth weight (2,500 g) (32.1% vs. 1.0%; p= 0.001), & being related with stillbirth (7.1% vs. 0.0%; p = 0.010). In addition to above findings, the fetal weight at the time of assessment was significant lower in IUGR than normal weight group. However, there is no significant alteration amongst IUGR and normal weight neonates as regard the gestational age at the time of assessment.

Interestingly, in the current study, UA PI and umbilical cerebral ratio are statistically significant higher in IUGR than normal weight group. While, CPR, MCA PI, and MCA PSV are statistically significant lesser in IUGR than normal weight group.

In agreement with present findings, the study of **Coenen et al., (21)** It was observed that pregnancies impacted by FGR had a lower median CPR as well as conversely greater median UCR (1.17 vs. 1.62; p

under 0.001; 0.86 vs. 0.62; p less than 0.001, respectively). This disparity can be linked back to the fact that FGR is identified by abnormal Doppler measurements.

In the current study; at cutoff value ≥1.105 UAPI has 85.5% sensitivity and 84% specificity to predict IUGR. At cutoff value ≥0.755 UCR has 78.3% sensitivity and 84% specificity to predict IUGR. At cutoff value ≥1.395 UtA PI has 58% sensitivity and 64% specificity to predict IUGR. At cutoff value ≥0.675UtA resistance index (RI) has 72.5% sensitivity and 60% specificity to predict IUGR. MCA PI, MCA PSV and CPR have low sensitivity and specificity to predict IUGR.

Ouda et al., (22) it was found that the UtA PI attained significance for predicting IUGR at a cutoff point of 1.63 or above, having a sensitivity of 83.2% and a specificity of 91.6%, as well as having a positive predictive value (PPV) of 54% and a negative predictive value(NPV) of 88%. While UtA RI reached statistical significance for IUGR prediction at a cutoff point of at least 0.67, with a sensitivity of 71.8% and a specificity of 87.2%, PPV47%, & NPV 82%.

Present study disagreed with the outcomes of **Adefisan et al. (4)** who determined that the sensitivity of RI as well as PI in the prediction of IUGR was only 23.1% and 0%, respectively. Second trimester PI has been determined to not increase the risk of IUGR in a low-risk pregnancy.

Conclusion:

CPR is of predictive value in high risk pregnancy as well as UtA Doppler in predicting late onset IUGR in those risky cases.

Table (1): Descriptive maternal data of the studied population

		No.= 119
Maternal age (year)	Range	18 – 38
	Mean ± SD	26.49 ± 4.98
Parity	Primigravida	83 (69.7%)
	Multipara	36(30.3%)
BMI (kg/m^2)	Range	22 – 36
	Mean ± SD	25.89 ± 3.28
GA at assessment (weeks)	Range	32 – 33
	Mean ± SD	32.63 ± 0.48
Fetal weight at assessment (gm)	Mean ± SD	1290.81 ± 97.23
	Range	1123 – 1476

Table (2): Comparison of the GA and fetal weight at the time of assessment between the studied groups

		IUGR	**Normal weight**	**t/x²**	**P-value**	**Sig.**
		No.= 69	**No.=50**			
GA at assessment (weeks)	Range	32 – 33	32 - 33	0.195 •	0.846	NS
	Mean ± SD	32.64 ± 0.48	32.62 ± 0.49			
fetal weight at assessment (grams)	Range	923 - 1056	1124 - 1476	-5.052 •	**<0.0001**	**HS**
	Mean ± SD	984.89 ± 43.54	1339.62 ± 93.50			

Table (3): Comparison of fetal CPR Doppler ultrasonography of the studied groups

		IUGR	**Normal weight**	**t/x²**	**P-value**	**Sig.**
		No.= 69	**No.=50**			
UA PI	Range	1.03 – 1.70	0.89 – 1.45	9.320 •	**<0.0001**	HS
	Mean ± SD	1.30 ± 0.18	1.04 ± 0.13			
MCA PI	Range	1.27 – 1.80	1.56 – 1.98	-7.935 •	**<0.0001**	HS
	Mean ± SD	1.52 ± 0.16	1.71 ± 0.10			
UCR	Range	0.49 – 1.23	0.51 – 0.87	8.399 •	**<0.0001**	HS
	Mean ± SD	0.85 ± 0.13	0.69 ± 0.07			
CPR	Range	0.83 – 1.96	0.83 – 1.98	-2.843 •	**0.005**	HS
	Mean ± SD	1.42 ± 0.28	1.57 ± 0.28			
MCA PSV	Range	40.50 – 59.00	48.00 – 64.5	-7.504 •	**<0.0001**	HS
	Mean ± SD	48.54 ± 5.03	54.57 ± 3.72			

Table (4): stepwise linear regression analysis for Doppler predictors of IUGR

Coefficients[a] Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	2608.347	122.256		21.335	<0.0001	2366.225	2850.469
	UAPI	-830.097	101.379	-0.604	-8.188	<0.0001	-1030.872	-629.321
2	(Constant)	1000.307	91.112		10.979	<0.0001	819.849	1180.766
	UAPI	-2799.37	100.359	-2.035	-27.893	<0.0001	-2998.145	-2600.596
	UtAPI	2748.473	125.289	1.601	21.937	<0.0001	2500.321	2996.624
3	(Constant)	864.794	96.729		8.94	<0.0001	673.192	1056.395
	UAPI	-2494.027	133.888	-1.813	-18.628	<0.0001	-2759.234	-2228.82
	UtAPI	2299.886	181.987	1.339	12.638	<0.0001	1939.405	2660.368
	MCAPSV	8.166	2.485	0.156	3.285	0.001	3.242	13.089

a. Dependent Variable: birth weight

Table (5): Sensitivity, Specificity and cutoff value of ultrasonographic Doppler parameters to predict IUGR

	Cutoff value	Area Under Curve	Sensitivity %	Specificity %	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
UAPI	1.105	0.915	85.5%	84%	0.859	0.971
MCAPI	1.635	0.187	30.4%	20%	0.110	0.263
UCR	0.755	0.852	78.3%	84%	0.781	0.924
CPR	1.445	0.329	47.8%	28%	0.229	0.430
MCAPSV	50.75	0.184	27.5%	24%	0.109	0.259
UtAPI	1.395	0.605	58%	64%	0.503	0.708
UtARI	0.675	0.719	72.5%	60%	0.627	0.811

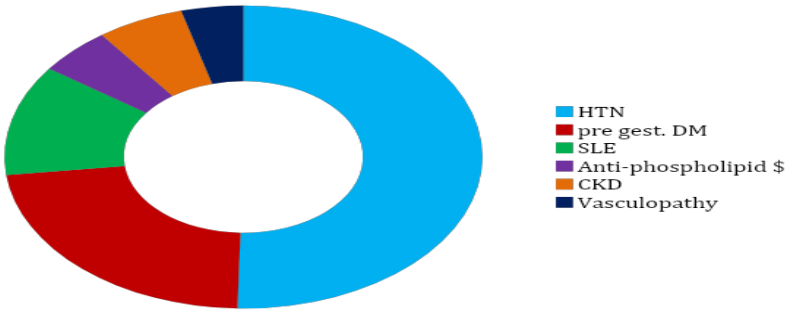

***Figure 1*:** maternal diseases among the studied groups

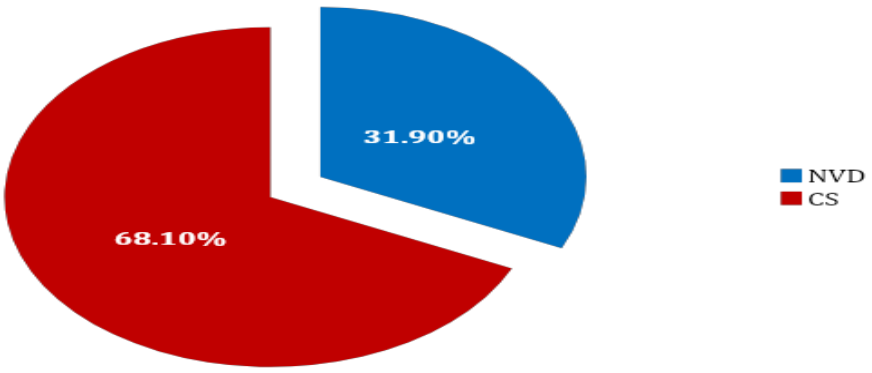

Figure 2: Mode of delivery of the studied population

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