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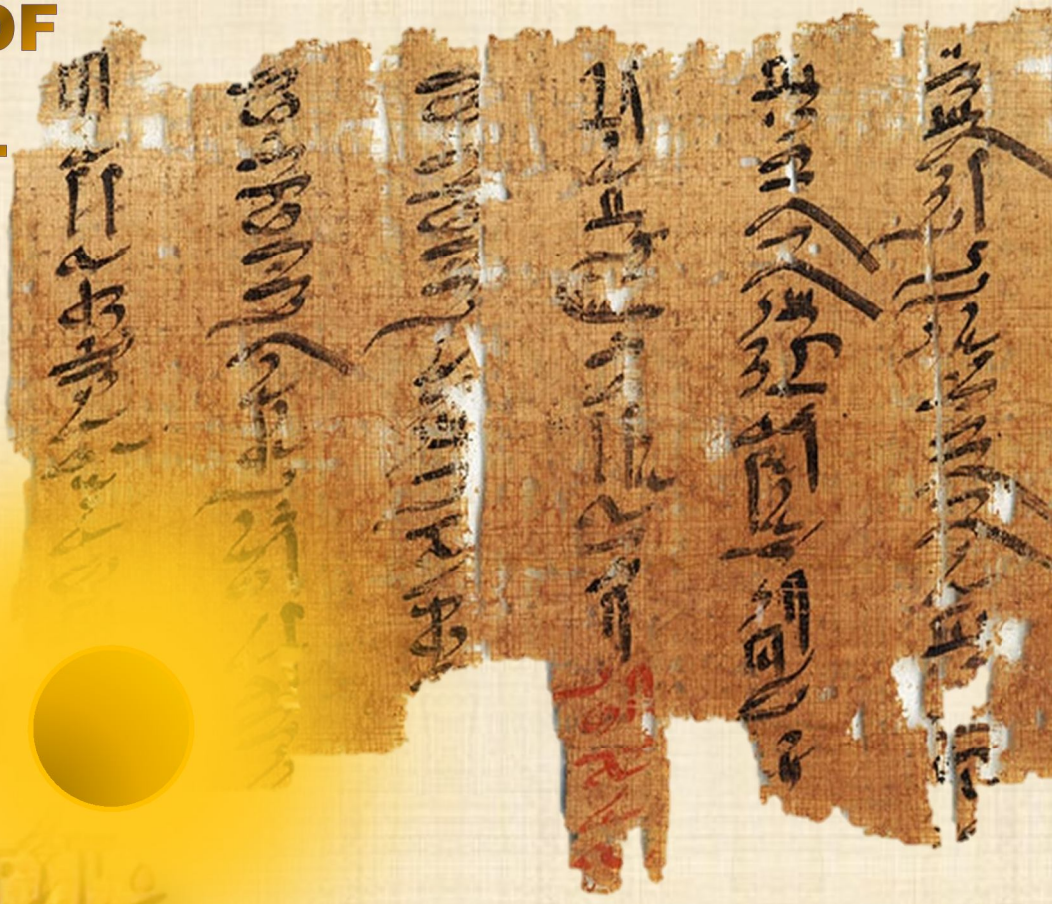

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Original article

Value of Middle Cerebral/Umbilical Artery Resistance Index Ratio in Neonatal Outcome in Patients with Intrauterine Growth Restriction (Prospective Study)

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ABSTRACT

Background: Disorders related to intra-uterine fetal growth usually had different perinatal morbidity and mortality. Accurate diagnosis of intrauterine fetal growth is a challenging difficult task, but recent technological advances are associated with significant improvements with positive impact on antenatal care.

Aim of the work: The aim of this study was to evaluate the accuracy of the umbilical and middle cerebral artery Doppler indices [e.g. resistance index] in prediction of fetal outcome in pregnancies with intra-uterine growth restriction (IUGR).

Patients and Methods: Forty-five pregnant females had been included in a prospective study. All had a confirmed diagnosis of IUGR. Doppler ultrasound used to record fetal middle cerebral artery [MCA] and umbilical and Doppler indices every one week (from 32 weeks onwards). Post-delivery birth weight, Apgar score at 0 and 5 minutes had been measured and correlated with Doppler indices.

Results: One-fifth of the mothers participating in the study (20%) had pre-term birth and 6.7% missed the follow-up. Umbilical artery resistance index (RI) at a cut off value of (0.79) had a diagnostic accuracy of 93%. MCA RI best cut off value was 0.63 with diagnostic accuracy of 73.9%. Also, for C/U ratio had diagnostic accuracy of 92.9%. Finally, there was significant, proportional correlation between MCA RA and C/U ratio from one side and APGAR score at 0 and 5 minutes from the other side. However, the correlation between UARI and Apgar score was inverse and statistically significant.

Conclusion: Doppler velocimetry of fetal circulation can provide important information regarding fetal well-being, with subsequent impact on fetal outcome.

Keywords: Intrauterine growth restriction; Doppler; Neonatal outcome; Resistance index; Mean cerebral artery.

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* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Intrauterine growth restriction (IUGR) is defined as a fetus whose birth weight is markedly below the normal weight (less than 10th percentile) for that gestational age[1]. IUGR affect approximately 10-15% of pregnant women. IUGR is an antenatal diagnosis, however, some of these fetuses, especially in absence of screening during pregnancy, may be firstly detected only postnatal. It is crucial for obstetricians to diagnose growth restricted fetuses, as this condition is usually associated with significant morbidity and/or mortality[2]. IUGR is one of the most common pregnancy-related complications, which associated with an iatrogenic prematurity. The most frequent etiology for IUGR is abnormal placentation, which results are frequently associated with impaired placental blood flow[3]. It is essential to identify placental insufficiency early so that its hazards can be reduced[4]. Doppler ultrasound is used as an integral part of clinical protocol in screenng of high-risk pregnancies. It gives direct information of feto-placental circulation and identifies placental circulatory failure. The advantage of Doppler ultrasound is that the technique is fast, reproducible and can be done on a daily basis[5]**.** Umbilical and middle cerebral artery velocimetry is a good predictor of IUGR at risk of antenatal compromise. Umbilical arterial (UA) Doppler is used in screening of fetal well-being in the last trimester of pregnancy. Abnormal umbilical artery Doppler is a marker of uteroplacental insufficiency and consequent intrauterine growth restriction. Umbilical artery Doppler has been shown to decrease perinatal mortality and morbidity, especially in risky obstetric conditions. Umbilical artery Doppler is very useful to differentiate the constitutionally small fetus from the pathologically small fetus[6]. The middle cerebral artery (MCA) may also predict fetal outcomes from alterations in cerebral blood flow and its direction. It was confirmed that during the prenatal period, the resistance in the cerebral artery of the fetus is high. However, this parameter can change in threatening conditions, such as placental insufficiency and hypoxemia, due to stimulation of chemoreceptors and alteration in vasodilator or vasoconstrictor agents[7]. Growth-restricted fetuses with sever impairment of umbilical artery blood flow are at increased risk of adverse outcomes such as intrauterine fetal demise (IUFD) and neonatal death as well as increased neonatal morbidity, including hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing entero-colitis, seizures, sepsis and respiratory distress syndrome[8]**.** The optimal timing for delivery for IUGR affected pregnancies remains controversial. Sever fetal morbidities and deaths may be prevented by proper antenatal surveillance tests and timed delivery[9].

AIM OF THE WORK

The aim of this study is to assess the accuracy of the middle cerebral to umbilical artery resistance index ratio (C/U RI) in predicting fetal outcome (birth weight & Apgar score at 0 and 5 minutes) in pregnancies with IUGR.

PATIENTS AND METHODS

This is a prospective study, which included 45 pregnant women. All cases were selected from Obstetrics and Gynecology department Al-Azhar University Hospital (New Damietta).

We included fetuses with IUGR based on clinical and U/S diagnosis (estimated fetal weight <10th percentile for gestational age), of singleton pregnancy and gestational age between 32– 37 weeks of gestation. On the other side, any fetus with congenital anomalies had been excluded from the study. The sample size had been calculated according to the following formula: $N= Z^2PQ/D^2$**,** where N denoted number of required subjects, Z for the normal standard deviation (1.96), P equals the frequency of intrauterine growth restriction in developing countries (3%) according to **Radon et al.[10],** Q equals (1-P) (The frequency of non-occurrence of an event) and D for degree of precision (0.05%). Accordingly, 45 patients had been required. $\boldsymbol{N}= (\mathbf{1.96})^2\ \mathbf{0.03}\ (\mathbf{1-0.03})/(\mathbf{0.05})^2 = 45$

Explanation of the intervention [procedure] had been achieved for each female participating in the study with complete data about the risks and benefit of study. Then, an informed written consent had been taken from all females before the start of the study. All females had been subjected to full history taking, general clinical examination, abdominal examination, and laboratory investigations (complete blood count, urine analysis, international normalization ratio (INR), liver & kidney function tests) in accordance with the hospital policy. Then, an ultrasound had been performed to determine the

estimated fetal weight (EFW), umbilical and middle cerebral arteries resistance index by Doppler study. The EFW had been determined on the basis of fetal biparietal diameter, abdominal circumference and femoral length**.** The UA Doppler waveforms had been registered from a free-floating part of the umbilical cord during slight fetal activity and during absence of fetal breathing. All measurements had been recorded in the semi-recumbent positions with slight elevation of head and chest. For measurement of the MCA, we obtained an axial view of the fetal head at the cerebral peduncles level, then the color Doppler had been performed for circle of Willis visualization, and with 1 cm of the MCA origin, a doppler sample volume had been placed that had been easily recognized as a major branch running anterolateral from the circle of Willis toward to the lateral edge of the orbit. We always set the angle between the ultrasonographic beam and direction of blood flow to <30 degrees. We used a 3.5 mHz transducer with curved array to record the Doppler signals. Measurement of C/U resistance index ratio: waveform analysis had been measured in the frozen display by estimating the maximum and minimum values of the velocity waveforms with the electronic calipers of the instrument. The Pourcelot resistance index (Systole- Diastole/Systole) of at least six waveforms had been calculated by a built-in microcomputer. The resistance index is a reflection of the impedance to blood flow in the artery that is being assessed. The mean of six registration of the MCA resistance index had been divided by the mean of six measurements of the UA resistance index to obtain the C/U ratio. It had been done every week from the 32nd week of gestation till the end of pregnancy using Voluson P8 BT16 ultrasound device with a deep probe of 3/5-5 MHz. figures (1 and 2) represented doppler ultrasound of UA and MCA.

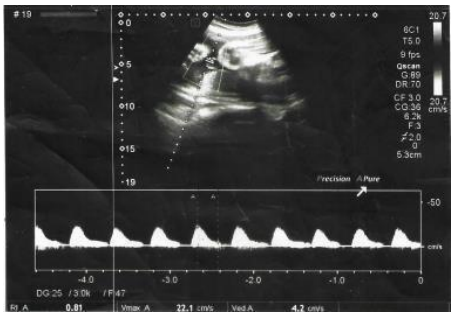

Figure (1): Umbilical artery Doppler showing decreased end diastolic flow (high resistance index).

Figure (2): Middle cerebral artery Doppler showing increased end diastolic flow (Reducing cerebral blood flow resistance)

Outcome: Stillbirth and neonatal death were the major adverse perinatal outcomes. Minor adverse perinatal outcomes were cesarean section for distressed fetus, admission to the neonatal intensive care unit. Post-delivery birth weight of the baby and Apgar score at 0 & 5 minutes had been noted.

Ethical Consideration: The study protocol had been submitted for approval by Institutional Research Board, Damietta Faculty of Medicine, Al-Azhar University (IRB number: ADIM-2203019). In addition, an informed written consent had been signed by each participant. Also, confidentiality and personal privacy had been respected through all stages of the study.

Statistical Analysis: Numerical data had been explored for normality by test of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). All data with normal (parametric) distribution except pulse had non-normal (non-parametric) distribution. Numerical data had been presented as mean, standard deviation (SD), 95% Confidence Interval (95% CI) median and range values. For parametric data, Student's t-test was used to compare two groups. For non-parametric variables, Mann-Whitney U test was used to compare two groups. Qualitative data had been presented as frequencies and percentages. Fisher's Exact test was used to compare between groups. ROC (Receiver Operating Characteristic) curve had been built to determine the cut-off values of middle cerebral artery resistance index (MCARI), uterine artery resistance index (UARI) and C/U Ratio for differentiation between mothers who had pre- and full-term births. Areas under the ROC curve (AUCs) were compared using *z*-statistic. ROC curve analysis had been performed with MedCalc Version 11.3 for Windows (MedCalc Software bvba). The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

RESULTS

Figure (3) represented the flow chart of the current study. Overall, 45 pregnant females had been included, 42 of them (93.3%) completed the follow up period. The other 3 patients (6.7%) missed the follow up. In addition, 13 out of 42 (30.95%) had good outcome, while 29 (69.05%) had poor outcome; 30 patients (71.4%) had been delivered by cesarean section (12 elective and 18 urgent CS), 12 patients (28.6%) delivered by normal vaginal delivery. Table (1) represented the descriptive statistics of study participants. Maternal age ranged between 20 and 35 years; the mean maternal age 26.2±4.3 years. body mass index ranged between 18.2 to 29.9kg/m^2, while gestational age ranged between 32 to 37 weeks, systolic blood pressure (BP) ranged between 100 to 160 mmHg, diastolic BP ranged between 60 and 100mmHg and estimated fetal weight (EFW) ranged between 1154 and 1399, with mean EFW of 1308.4 ± 64.2 g.

Table (2) depicts gravidity and parity of studied females, Gravida 1 represented the higher percentage (64.4%) followed by Gravida 2 (28.9%), while nulliparous women represented 53.3% followed by Para 1 (22.2%) and para 2(22.2%). Table (3) represented the doppler indices from the 32nd to 37th week of gestation. The overall mean UARR was 0.78±0.02, while the overall MCA RI was 0.65±0.03 and overall C/U ratio was 0.83±0.047.

Correlation between APGAR score and ultrasound indices revealed significant proportional correlation between MCA RI and C/U ratio and Apgar score at birth and after 5 minutes. On the other side, the correlation between UARI was inverse and statistically significant (table 4). Comparison between preterm and full-term groups revealed that, preterm delivery was significantly associated with high systolic blood pressure, significantly decreased MCA RI and C/U ratio and significant increase of UA RI (Table 5). Pair-wise comparison between areas under the ROC curve (AUC) of the three indices revealed that there was no statistically significant difference between areas under the curve of UA RI and C/U Ratio; both showed statistically significantly higher AUC than MCA RI (Table 6 and figure 4).

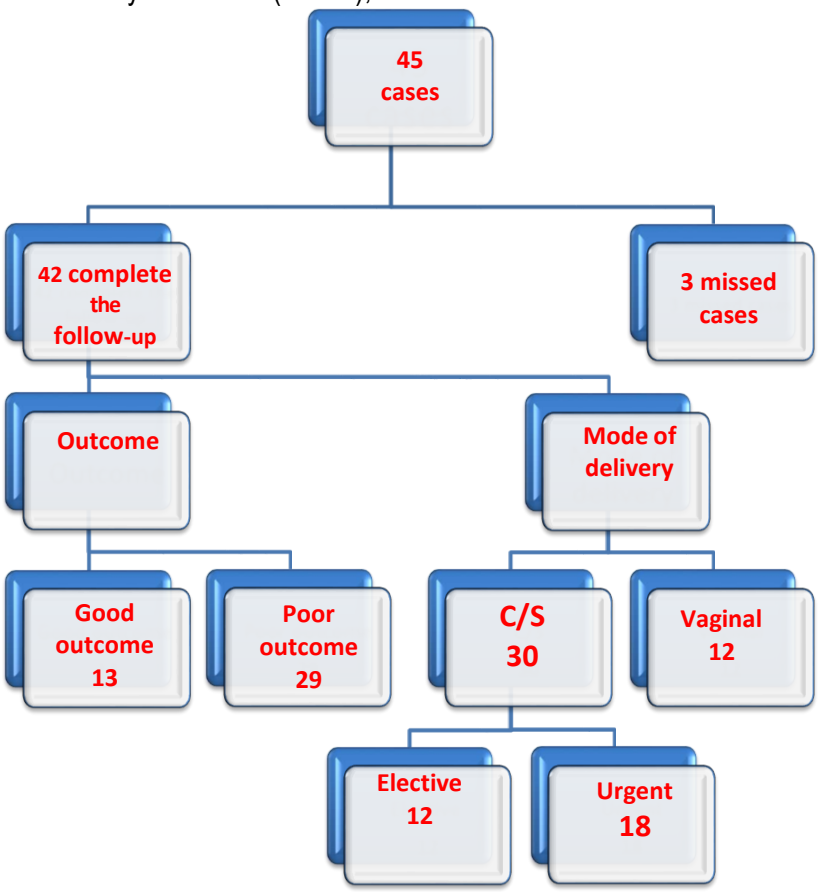

Figure (3): The flow chart of the current work

Table (1): Descriptive statistics of study participants

		Mean±SD	95% CI	Median (Range)
Maternal Age (years)		26.2±4.3	24.7 –27.4	26 (20 – 35)
BMI (kg/m^2)		25.1±3.5	24 – 26.1	25.7 (18.2 – 29.9)
Gestational age (weeks)		34.2±1.9	33.6 – 34.8	34 (32 – 37)
Blood pressure (mmHg)	**Systolic**	123.3±13.1	119.4 – 127.3	120 (100 – 160)
	Diastolic	78.4±10.6	75.2 – 81.6	80 (60 - 100)
Estimated fetal weight (g)		1308.4±64.2	1289.1 – 1327.7	1311 (1154 – 1399)

Table (2): Descriptive statistics for Gravidity and Parity

	Gravidity		**Parity**	
	No.	%	No.	%
None	-	-	24	53.3
Once	29	64.4	10	22.2
Twice	13	28.9	9	20
Three times	1	2.2	2	4.4
Four times	2	4.4	-	-

Table (3): Descriptive statistics for UA RI at different weeks

TIME	**UARI (MEAN±SD)**	**MCA RI (MEAN±SD)**	**C/U RATIO (MEAN±SD)**
32 weeks	0.82±0.008	0.67±0.007	0.85±0.011
33 weeks	0.81±0.007	0.66±0.007	0.81±0.014
34 weeks	0.81±0.007	0.65±0.007	0.8±0.013
35 weeks	0.8±0.007	0.63±0.009	0.79±0.016
36 weeks	0.78±0.005	0.66±0.006	0.79±0.009
37 weeks	0.74±0.006	0.67±0.007	0.86±.014
Overall	0.78±0.02	0.65±0.03	0.83±0.047

Table (4): Correlation between APGAR scores and ultrasound indices

APGAR score	MCA RI		UARI		C/U RATIO	
	r	P	r	P	r	P
At birth	0.377	0.014*	-0.792	<0.001*	0.783	<0.001*
5 minutes	0.386	0.012*	-0.607	<0.001*	0.628	<0.001*

Table (5): Comparison between pre-and full-term subgroup (births)

VARIABLES	PRETERM (9)		FULL-TERM (33)		STATISTICS MEASURES	
	Mean	SD	Mean	SD	P value	Effect size (d)
SBP (mmHg)	131.1	20.3	121.2	10.2	0.048*	0.769
DBP (mmHg)	83.3	14.1	77.3	9.4	0.135	0.571
Estimated fetal weight (EFW)	1303.9	62.4	1311.7	63.5	0.743	0.123
MCA RI	0.634	0.014	0.654	0.029	0.010*	0.750
UA RI	0.801	0.011	0.773	0.021	<0.001*	1.442
C/U Ratio	0.792	0.024	0.846	0.046	0.002*	1.270

Table (6): Cut-off values for ultrasound indices for prediction of preterm births

INDEX	CUT-OFF	SENSITIVITY	SPECIFICITY	+PV	- PV	ACCURACY	AUC	95% CI
MCARI	0.63	66.7	75.8	42.9	89.3	73.9	0.702	0.536–0.868
UARI	0.798	66.7	100	100	91.7	93	0.914	0.812–1.000
C/U Ratio	0.798	77.8	97	87.5	94.1	92.9	0.889	0.745–1.000

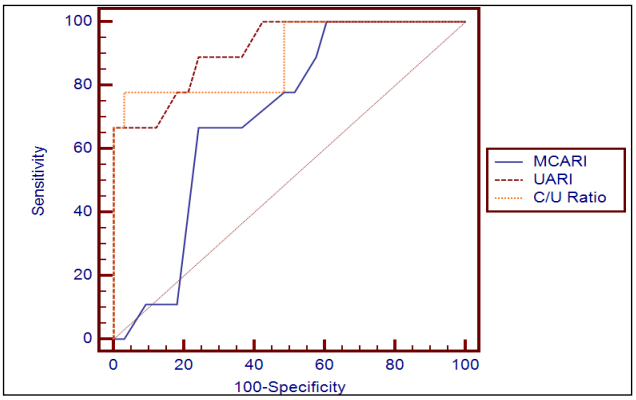

Figure (4): ROC Curves of MCARI, UARI and C/U ratio for differentiation between mothers who had pre- and full-term births

DISUCSSION

In the current work, about one-fifth (9/45; 20.0%) of the participating mothers had pre-term birth; the majority (33/45; 73.3%) had full-term birth while (3/45; 6.7%) of the cases missed the follow up. Mothers with pre-term birth had significant lower mean MCA RI than mothers with full-term birth (0.63, 0.65 respectively), significantly higher mean UA RI (0.80, 0.77 respectively), and significantly lower mean C/U Ratio (0.79, 0.84 respectively). UARI cut-off value was 0.79 with diagnostic accuracy 93%. MCARI cut off value was 0.63 with diagnostic accuracy 73.9%. C/U ratio cutoff value was 0.79 with diagnostic accuracy 92.9%. both MCA RI and C/U ratio proportionately correlated, while UA RI inversely correlated with APGAR scores. These data-collectively- reflected the good predictive power of doppler ultrasound to diagnose preterm birth or IUGR. **Khanduri et al.**[11] had been studied a total of 62 risky pregnancies submitted to measurement of color Doppler indices till delivery and reported an IUGR rate of 30.9%. On all visits [3 visits], the mean values of pulsatility index [PI] and resistance Index [RI] of UA, were significantly increased while MCA PI and RI recordings were significantly reduced in IUGR when compared to non-IUGR patients. They found UA indices to be the most sensitive and specific for the IUGR prediction at all three visits, with the maximum sensitivity and specificity at the third visit (82.1% sensitivity and 87% specificity). **Makhseed et al.** [12] in prospective case study, used color Doppler flow imaging for the estimation of the C/U ratio in 70 singleton IUGR pregnancies between 29 and 42 weeks of gestation. Then they had been categorized subjects into two groups, Group A of 35 small for gestational age (SGA) fetuses with a normal C/U ratio (1.05 or higher) and Group B of 35 SGA fetuses with an abnormal C/U ratio (below 1.05). They suggested that, the C/U ratio is a good predictor of neonatal outcome and could be used to identify fetuses at risk of morbidity and mortality. In addition, **Nikhar et al.** [13] carried a longitudinal study on 100 pregnancies of 30-40 weeks gestations. The majority (70%) had abnormal flow on Doppler scan. The umbilical artery indices were higher among the IUGR pregnancies whereas the MCA indices were reduced. They concluded that, MCA and the UA flow test i.e. color Doppler are very useful in identification of the IUGR and helps in management of it in an appropriate way.

Baschat et al. [14] in a retrospective cohort studied 236 IUGR fetuses, and observed three patterns of Doppler deterioration. The most common one started with a deteriorating UA Doppler (increased resistance) followed by brain sparing (decrease MCA resistance) and lastly, deterioration of venous indices [ductus venosus and inferior vena cava [IVC]]. In addition, **Turan et al.** [15] further reported the first time of appearance of Doppler abnormalities could be influenced by gestation age. The Doppler aberrations appeared later in pregnancy (median = 31.5 weeks) in cases with mild placental insufficiently and stopped at the brain sparing stage [i.e: there was no progression to venous abnormalities]. In severe placental insufficiency, the doppler abnormalities developed earlier (median = 27.1 weeks) with a more rapid deterioration pattern. Fetuses with severe insufficiently were delivered at a significantly earlier gestation age.

Al Qahtani [16] reviewed literature about the role of doppler ultrasound in suspected IUGR and concluded that, the available evidence mandates doppler ultrasound examination of fetal circulation,

as an integral part of fetal screening in IUGR.

On the other side, **Arias**[17] in a prospective controlled non randomized study for 115 females with high risk pregnancy due to different pregnancy comorbidities. Results revealed that, MCA-to-UA ratio remains relatively constant (mean ± SD 1.33 ± 0.19) between 27 and 37 gestational weeks. A cutoff value of 1.0 (sensitivity 57.9%, specificity 75.6%, false-positive rate 24.4%) was selected from the ROC curve analysis. This cutoff value successfully recognized a population at significant risk of IUGR (RR 3.07, 95% CI 1.73 to 5.45, p = 0.0009) and severe neonatal morbidity (U = 463.5, p = 0.03) but the MCA-to-UA ratio was not a predictor of preterm birth.

The strength of our study comes from that it was a combination of two arteries Doppler indices and detects the ratio between them and detects the neonatal Outcome according to this ratio.

Financial and Non-Financial Relationships and Activities of Interest

Authors declare that, there was no competing interest

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