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STUDY OF FETAL DOPPLER INDICES AND AMNIOTIC FLUID INDEX IN GROWTHLY-RESTRICTED FETUSES

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ABSTRACT

Aim of the study: To evaluate the association between the renal artery (RA) and middle cerebral artery (MCA) resistance indices (RI) and amniotic fluid index as predictors of growthly restricted fetuses and their impact on fetal outcome. **Type of the study:** Prospective descriptive analytical study. **Setting:** Department of Obstetrics and Gynecology Menof General Hospital-Egyptian Ministry of Health and Menoufia University Hospital-Menoufia University, Egypt. **Methods**: Over almost 1.5 years, examination of a total 40 pregnant women between 34- 38 weeks of gestation. Women were divided into 2 groups; women with normal pregnancy (group I, n=20) and women with IUGR pregnancy (group II, n=20) were recruited and underwent ultrasonography (U/S) for amniotic fluid index (AFI) which was measured using four quadrants technique, and Doppler resistance indices of fetal renal artery (FRA) and middle cerebral artery (MCA), All data collected and correlated to see their impact on fetal outcome. **Results**: The Doppler index and the artery with highest coefficient were the fetal renal artery and its resistance index. The coefficient for this Doppler index was **-0.78**. In other word the resistance index of fetal renal artery has the maximum predictive as well as diagnostic value for intrauterine growth restriction. Accordingly the FRA RI had Cut off point 0.96, MCA RI had Cut off point 0.72, In the present study, Both FRA RI and MCA RI were equally sensitive (sensitivity 90%), and AFI had comparably low sensitivity (sensitivity 80%) in predicting adverse outcomes (5 minutes Apgar score < 7, death, meconium aspiration, admission to ICU). FRA RI was more specific (specificity 100%) (PPV 100%) than either MCA RI (specificity 95%) (PPV 94.7%) or AFI (specificity 85%) (PPV 84.2%) alone in predicting any adverse out come. While negative predictive value of FRA RI was 90.9% when compared to 90.5% for MCA RI and 80.6% for AFI. Diagnostic accuracy of FRA RI (accuracy 95%) was better than MCA RI (accuracy 92.5%) and AFI (accuracy 82.5%) in predicting adverse outcomes. **Conclusion**: This study has shown that abnormal AFI, MCA RI and FRA RI in particular are a strong predictor of adverse perinatal outcome in IUGR. MCA RI is more useful than AFI in prediction IUGR outcome when considered individually. FRA RI was more specific than either MCA RI or AFI alone in predicting any adverse outcomes. Combined sonographic and Doppler parameters such as Low EFW and low AFI as well as low MCA RI and High FRA RI have better sensitive and predictive value for estimation the adverse outcome. Further studies and randomized controlled trials are needed.

KEYWORDS: (MCA: Middle cerebral artery, **FRA:** Fetal renal artery, **RI:** Resistance index, **IUGR:** Intrauterine growth restriction, **U/S:** Ultrasonography).

INTRODUCTION

According to the American College of Obstetricians and Gynecologists, IUGR is "one the most common and complex problems in modern obstetrics.[1] Severe early onset fetal intrauterine growth restriction (IUGR) complicates approximately 0.4% 0f pregnancy.[2] It is associated with a perinatal mortality rate that is 6 to 10 times higher than that for normally grown fetuses. The cause of IUGR is multifactorial and complex, including intrinsic fetal conditions as well as maternal and environmental factors.[3]

Only recently, researchers have focused on the long term morbidity that is associated with this condition. Epidemiological studies have demonstrated low birth weight and fetal growth restriction to be risk factors contributing to renal disease and hypertension in adult life.[4]

Amniotic fluid is known to represent fetal wellbeing.[5] An adverse fetal environment as shown by raised placental resistance often results in decreased amniotic fluid indices as well. An amniotic fluid index of less than

5cm increases the risk of IUGR.[6]

Doppler has been used to test the hypothesis that infants exhibiting catch up growth as an indicator of IUGR have a higher incidence of pre-delivery abnormal Doppler results.[7] In IUGR, the Fetal middle cerebral artery velocimetry has been suggested as a predictor of fetal hypoxemia when a characteristic increase in diastolic blood velocities was present as a sign of fetal brain-sparing.[1] This condition occurs because blood flow from peripheral organs (kidneys) is diverted to the brain.[8]

During chronic fetal hypoxia there is continuous reduction of cerebral vascular resistance resulting in decrease Middle cerebral artery resistance index values gradually.[9] extensive changes occur in the circulation of the growth restricted fetus with increasing deterioration of its condition. These changes, often referred to as 'redistribution' or 'brain sparing effect', result in a reduction of the vascular resistance in those organs that are essential to fetal survival, such as the brain, the coronary arteries and the adrenals. The decrease in the amniotic fluid volume in relation to severe intrauterine growth restriction is usually deemed the result of changes in the fetal circulation, resulting in impaired renal perfusion.[10]

Circulatory redistribution in response to hypoxemia has been demonstrated in animal models by embolization studies.[11,12,13,14] More recently the phenomenon of circulatory redistribution has been confirmed by Doppler ultrasound studies in the growth-restricted human fetus by the demonstration of reduced impedance to flow in fetal cerebral vessels5 and increased impedance in the thoracic descending aorta.[15,16]

Doppler ultrasound studies on smaller arteries such as the fetal renal artery became easier to perform with the advent of color flow mapping. ***Vyas et al., 1989***[17], produced a reference range for the pulsatility index (PI) of the fetal renal artery in normal pregnancies between 18 and 42 weeks' gestation. In their study a number of growth-restricted fetuses were also examined and it was observed that the PI of the fetal renal artery was higher in the growth-restricted fetus than in the normally grown fetus, and an inverse relationship was found between PI-values in the fetal renal artery and the fetal arterial pO2 obtained by cordocentesis. Arduini and Rizzo[18] also provided reference values and confirmed that PI-values in the fetal renal artery were significantly higher in growth-restricted fetuses, particularly in the presence of reduced amniotic fluid, with an inverse correlation between PI-values in the fetal renal artery and the quantity of amniotic fluid in growth restricted fetuses.[18]

The aim of this study was to evaluate the association between the renal artery (RA) and middle cerebral artery (MCA) resistance indices (RI) and amniotic fluid index as predictors of growthly restricted fetuses and their impact on fetal outcome.

PATIENTS AND METHODS

In a prospective sectional and descriptive analytical study, 40 pregnant ladies participated randomly. This study was performed at the Menoufia university and Menof General Hospitals (Menoufia, Egypt) from Marsh 2016 to September 2017. The patients were suspected to have IUGR. This study was approved by Research Ethics committee of Faculty of Medicine, Menoufia University of Medical Sciences. A signed written consent was obtained from each patient.

Study Design

This prospective study was conducted on 40 patients, with their due consents, between Marsh 2016 to September 2017, which were scanned for various grey scale and Doppler parameters and then followed till delivery.

Eighteen patients were lost during follow-up, and hence 40 patients were studied to note the birth weight and mode of delivery. All guidelines prescribed by the Pre Natal Diagnostic Test (PNDT) act, 1994 were strictly followed.

The study was undertaken with the following parameters

Inclusion Criteria were

1. Age: Childbearing 22-36 years
2. The gestational age of patient was between 34 and 38 weeks (derived from LMP).
3. First trimester ultrasound,
4. The pregnancy was single.
5. The patient was a clinically diagnosed case of IUGR (based on findings such as Insufficient weight gain, decrease or no increase in abdominal girth and decrease or no increase in fundal height).

OR One of the following risk factors was present in the patient:

-Known case of preeclampsia.

-Gestational hypertension.

OR

-Maternal essential hypertension: This was diagnosed if a BP of 140/90 % mm Hg or more existed before 20 weeks of pregnancy without the evidence of previous chronic renal disease.

OR

Previous IUGR: a mother known to have produced a previous growth-retarded infant.

Exclusion criteria were

1. Multiple pregnancies; and
3. Unsure of LMP

Target population (subjects)

This is a prospective descriptive analytical study that comprised of 20 females for each group attending the

obstetric outpatient clinic in Menoufia University Hospital and Menof General Hospital (Menoufia, Egypt) in which patients will be divided into 2 groups:
Group I: Including patients with normal pregnancy (20 females)
Group II: Including patients with IUGR pregnancy (20 females)

Methodology
An SGA fetus was defined as one having and EFW[19] less than the 10^{th} centile for gestational age.

Ultrasonography
2DUS were performed with patients with empty bladder, in the supine position performed with PREMIUM LOGIQ P5 (General electric).
All 2DUS were performed with a 3.5-5MHZ abdominal probe.
By 2DUS:

Scanning for Bi-parietal Diameter and Head Circumference
The BPD was recorded as the maximum diameter of a transverse section of the fetal skull at the parietal eminences with the following features:

- A short midline
- The cavume septum pellucidum
- The thalami

Head circumference was measured in the same plane used for BPD measurement.

Scanning of femur length
The measurement of the FL was made from the center of the "U" -shape at each end of the bone. This represents the length of the metaphysic. The measurements were obtained from three separated images of the same femur. These should be within 1mm of each other.

Scanning for Abdominal circumference
The section on which the AC was measured included the following features:

- The outline is circular.
- A short length of umbilical vein centrally placed between the lateral abdominal walls to the fetal spine.
- The stomach usually visualized as a transonic area in the left side of the abdomen.

Scanning for Amniotic Fluid
Amniotic fluid volume was estimated by measuring the deepest vertical pocket of liquor amnii in each quadrant of the abdomen and summated to obtain AFI which was free of any fetal part or umbilical cord. Normal amniotic fluid index 5-10 cm.

The fetal weight was obtained by measuring the three ultrasound parameter (BPD, A.C, FL) using different equation.

Doppler examination
Prenatal Doppler ultrasound examination were performed by experienced operator using PREMIUM LOGIQ P5 (General electric).

Doppler recordings were performed in the absence of fetal movements and with voluntary suspended maternal breathing. Spectral Doppler parameters were measured automatically from three or more consecutive waveforms, with the angle of insonation as close to 0 as possible. A high-pass wall filter of 70 Hz was used to record low flow velocities and avoid artifacts.

Middle cerebral artery Doppler
The middle cerebral artery can be imaged with color Doppler ultrasound in a transverse plane of the fetal head obtained at the base of the skull. In this transverse plane, the proximal and distal middle cerebral arteries are seen in their longitudinal view, with their course almost parallel to the ultrasound beam.

Middle cerebral artery Doppler waveforms, obtained from the proximal portion of the vessel immediately near the circle of Willis, have shown the best reproducibility.[20]

Fetal Renal artery Doppler
The best way to assess the renal arteries is to find the abdominal aorta and the renal hilum the coronal axis view. The renal arteries are usually seen arising from the lateral aspect of of the abdominal aorta.[21]

Data management
Data were collected, tabulated, statistically analyzed using an IBM personal computer with Statistical Package of Social Science (SPSS) version 20 and Epi Info 2000 programs, where the following statistics were applied.

- **Descriptive statistics**: in which quantitative data were presented in the form of mean **()**, standard deviation **(SD)**, range, and qualitative data were presented in the form numbers and percentages **(%)**.

- **Analytical statistics**
- **Chi- squared test (χ^2)** was used to study association between two qualitative variables **Fisher's exact test** for 2 x 2 tables when expected cell count of more than 25% of cases was less than 5
- **Student's t- test** is a test used for comparison between two groups having quantitative parametric variables while **Mann-Whitney test** is a test of significance used for comparison between two groups not normally distributed having quantitative variables.
- **Receiver-operating characteristic (ROC)** curve was used to determine cutoff points, sensitivity and specificity for quantitative variables of interest and 2 x 2 tables used for calculation of PPV, NPV and diagnostic accuracy.
- P-value of (>0.05) was considered not statistically

significant.

- P-value of (≤0.05) was considered statistically significant.
- P-value of (≤0.001) was considered statistically highly significant

Ethical Consideration

It is unlikely that this study had any major ethical problem through consideration of the following points.

- The study is supposed to have great benefit in early detection of IUGR.
- Patients will be informed about the objectives of the study, expected benefits and possible inconvenience that might occur to them.
- The patients will be informed about their right to withdraw from the study at any time and their acceptance will be obtained from them before being included in the study.
- All patients who where diagnosed to have IUGR were referred to the high risk pregnancy unit for further follow up and management.

RESULTS

The goal of study was to determine the role of Amniotic fluid index and color Doppler of MCA and FRA in pregnant women with normal pregnancy and IUGR pregnancy and its role in management. This is a prospective analytical descriptive study included about 40 pregnant women divided into two groups (Fig 1),
(I) Normal pregnancy group included 20 pregnant women, and
(II) IUGR pregnancy group included 20 pregnant women.

The study was conducted in Menoufia university hospital–Faculty of Medicine and Menof general hospital–Egyptian Ministry of Health facility for a time of One and half year. The examination for the most part included pregnant ladies with age 22-36 years (Mean ± SD=28.4±3.1) included in this study.

Maximum number of cases was those of multiparas, i.e. 29 (72.5%), primipara, i.e. 11 (27.5%) of the total. Majority of high-risk cases were of Hypertension (HTN) that constituted 45% of IUGR cases; this was followed by 30% cases with diabetes mellitus (DM) and 25% of cases with preeclampsia (PIH), 30% of cases with previous history of having given birth to growth-retarded babies. Mean birth weight at conveyance was 3121.0±268.8 kg and 1676.9±589.1kg (2SD) of both groups respectively.

All neonates of IUGR group (n=14) had birth weight less than 2.5 kg. There were 7 intra uterine deaths and 33 live births. Of the 33 live births, (7+17=24) Neonates were admitted to NICU, (7+19=26) neonates had 5 min Apgar score of under 7 and 30 babies [11 (55%) in normal pregnancy group and 19 (95%) in IUGR pregnancy group] were born by emergency caesarian section in both groups respectively.

The present study has 6 primi (30%) and 14 multigravidas (70%) in normal pregnancy group, 5 primigravidas (25%) and 15 multiparas (75%) in IUGR group. Of them 9 (2 primigravidas and 7 multigravidas) had pregnancy induced hypertension (HTN) (45%), 6 (2 primigravidas and 4 multigravidas) had diabetes mellitus (DM) (30%) and 5 (1 primigravidas and 4 multigravidas) had preeclampsia (25%) in IUGR pregnancy group, There was highly statistically significantly higher in IUGR pregnancy group than normal pregnancy group as regarding risk factors (Diabetes Mellitus, Hypertension and Pre-eclampsia), there is no cases with risk factors in normal pregnancy group. But in both groups (8+20) had adverse outcome.

As regard Socio-demographic data of the participants there was no statistically significant difference between normal pregnancy group and IUGR pregnancy group as regards the maternal age (Mean ± SD= 28.4±3.1).

As regard gravidity, parity and previous delivery there was no statistically significant difference between the normal pregnancy group and IUGR pregnancy group ($p>0.05$) for all.

As regard risk factors (Diabetes Mellitus, Hypertension and Pre-eclampsia) there was highly statistically significant higher in IUGR pregnancy group than normal pregnancy group, ($P<0.001$).

In the present study, as regard fetal biometry (head circumference, abdominal circumference, head abdominal circumferences ratio, femur length, fetal weight and age by LMP and US) there was highly statistically significant higher in IUGR pregnancy group than normal pregnancy group ($P<0.001$).

In the present study, as regard 5 minutes Apgar score, gestational age at delivery and gestational weight at birth there was highly statistically significant higher in normal pregnancy group than IUGR pregnancy group as regarding ($P<0.001$).

While regarding Mode of delivery and Admission to ICU there was statistically significantly difference in IUGR pregnancy group than normal pregnancy group as ($P<0.05$).

However, There was no statistically significant difference between the normal pregnancy group and IUGR pregnancy group as regarding Death and Meconium aspiration ($P>0.05$).

In the present study, AFI, FRA RI and MCA RI characteristics, there were highly statistically significant higher in normal pregnancy group than IUGR pregnancy group ($P<0.001$).

pulsatility index in the renal artery among IUGR infants is inversely correlated to the amniotic fluid index.

Pulsatility index is a measure of acceleration rather than resistance.

In the present study, there was highly statistically significant difference between the two groups as regard Middle Cerebral Artery resistive index (MCA RI), and Fetal Renal Artery resistive index (FRA RI). Both FRA RI and MCA RI were equally sensitive (sensitivity 90%), and AFI had comparably low sensitivity (sensitivity 80%) in predicting adverse outcomes (5 minutes Apgar score < 7, death, meconium aspiration, admission to ICU). FRA RI was more specific (specificity 100%) (PPV 100%) than either MCA RI (specificity 95%) (PPV 94.7%) or AFI (specificity 85%) (PPV 84.2%) alone in predicting any adverse out come. While negative predictive value of FRA RI was 90.9% when compared to 90.5% for MCA RI and 80.6% for AFI. Diagnostic accuracy of FRA RI (accuracy 95%) was better than MCA RI (accuracy 92.5%) and AFI (accuracy 82.5%) in predicting adverse outcomes.

In the present study, Table (3) and Fig (1) show that, There was highly significant positive correlation between AFI and MCA RI, head circumference, abdominal circumference and estimated fetal weight. However, there was highly significant inverse correlation between AFI and FRA RI.

Table (4) and Fig (2) show that, There was significant negative correlation between AFI and FRA RI, Also There was significant positive correlation between AFI and head circumference, abdominal circumference, femur length and estimated fetal weight. While there were no significant correlation between AFI and MCA RI. However, there was highly significant inverse correlation between AFI and FRA RI.

Table (1): Comparison between normal pregnancy group and IUGR pregnancy group as regarding Fetal Biometry.

Items	Normal pregnancy (NO=20)	IUGR (NO=20)	Test of sig. p-value
Head circumference Mean ± SD (in mm)	323.5±11.3	278.8±27.9	**P (<0.001)**
Abdominal circumference Mean ± SD (in mm)	316.3±12.9	251.9±34.5	**P (<0.001)**
Head/abdominal circumferences ratio Mean ± SD	1.02±0.014	1.11±0.06	**P (<0.001)**
Femur length Mean ± SD (in mm)	69.6±3.4	61.7±6.7	**P (<0.001)**
Fetal weight Mean ± SD (in gram)	2797.7±333.8	1680.9±585.4	**P (<0.001)**
Difference in age by LMP and US Mean ± SD (in weeks)	0.0±0.0	4.2±1.9	**P (<0.001)**

Table (1): Shows that as regard fetal biometry (head circumference, abdominal circumference, head abdominal circumferences ratio, femur length, fetal weight and age by LMP and US) there were highly statistically significant difference in IUGR pregnancy group than normal pregnancy group (P<0.001).

Table (2): Comparison between normal pregnancy group and IUGR pregnancy group as regarding Fetal Outcome.

Items	Normal pregnancy (NO=20)		IUGR (NO=20)		Test of sig. p-value
Mode of delivery					
- **Vaginal**	9	45%	1	5%	**X^2= 8.5**
- **Cesarean**	11	55%	19	95%	**P (<0.05)**
Death					
- **Yes**	1	5%	6	30%	**Fisher's Exact = 4.3**
- **No**	19	95%	14	70%	**P (>0.05)**
Meconium aspiration					
- **Yes**	3	15%	3	15%	**Fisher's Exact = ---**
- **No**	17	85%	17	85%	**P -----**
Admission to ICU					
- **Yes**	7	35%	10	50%	**X^2= 0.9**
- **No**	13	65%	10	50%	**P (>0.05)**
5 minutes Apgar score					
- **≥7**					**X^2= 19.3**

- <7	13 7	65% 35%	0 20	0% 100%	**P (<0.001)**
Gestational age at last U/S Mean ± SD (in weeks)	38.4±0.99		33.4±1.5		**P (<0.001)**
Fetal weight at birth Mean ± SD (in grams)	3121.0±268.8		1676.9±589.1		**P (<0.001)**

Table (2): Show that as regard 5 minutes Apgar score, gestational age at delivery and fetal weight at birth there was highly statistically significant difference in normal pregnancy group than IUGR pregnancy group as regarding (P<0.001).

While regarding Mode of delivery and Admission to ICU there was statistically significant difference in IUGR pregnancy group than normal pregnancy group as (P<0.05).

However, There was no statistically significant difference between the normal pregnancy group and IUGR pregnancy group as regarding Death and Meconium aspiration (P>0.05).

Table (3): Predictive value of Sonographic and Doppler Indices for adverse outcomes.

Sonographic and Doppler Indices	No. of findings				Sensitivity	Specificity	Diagnostic Accuracy	Predictive values	
	TP	FP	TN	FN				+ve	-ve
Amniotic Fluid Index (AFI)	85	15	80	20	80	85	82.5	84.2	80.6
Fetal Renal Artery Resistance (FRA RI)	100	0	90	10	90	100	95	100	90.9
Middle Cerebral Artery Resistance (MCA RI)	95	5	90	10	90	95	92.5	94.7	90.5

TP: true positive, TN: true negative, FP: false positive, FN: false negative, +ve: positive, -ve: Negative

Table (3): Shows that: Both FRA RI and MCA RI were equally sensitive (sensitivity 90%), and AFI had comparably low sensitivity (sensitivity 80%) in predicting adverse outcomes (5 minutes Apgar score < 7, death, meconium aspiration, admission to ICU). FRA RI was more specific (specificity 100%) (PPV 100%) than either MCA RI (specificity 95%) (PPV 94.7%) or AFI (specificity 85%) (PPV 84.2%) alone in predicting any adverse out come. While negative predictive value of FRA RI was 90.9% when compared to 90.5% for MCA RI and 80.6% for AFI. Diagnostic accuracy of FRA RI (accuracy 95%) was better than MCA RI (accuracy 92.5%) and AFI (accuracy 82.5%) in predicting adverse outcomes.

Table (3): The correlation between AFI, U/S and Doppler parameters in all patient groups.

parameter	Amniotic fluid index	
	r	P value
Middle cerebral artery resistive index	**0.83**	**0.00****
Renal artery resistive index	**-0.84**	**0.00**
Head circumference	**0.68**	**0.00****
Abdominal circumference	**0.73****	**0.00****
Feumer length	**0.48**	**0.002***
Estimated fetal weight	**0.48**	**0.00****

***: Significant, **: Highly significant**

Table (3) and figure (1): Show the following results: There was highly significant positive correlation between AFI and MCA RI, head circumference, abdominal circumference and estimated fetal weight. However, there was highly significant inverse correlation between AFI and FRA RI.

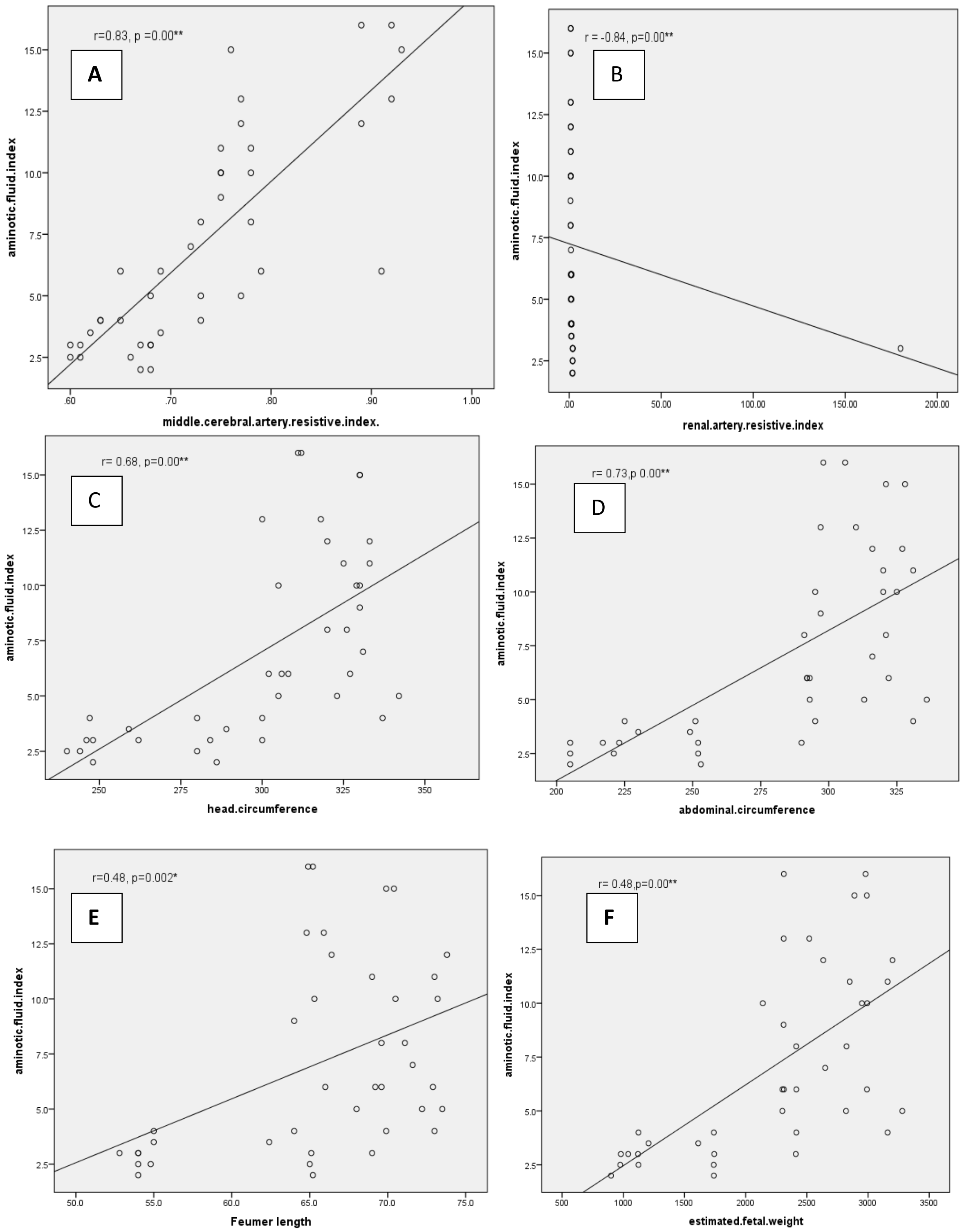

Figure (1): The correlation between AFI, U/S and Doppler parameters in all patient groups.

Table (4): The correlation between AFI, U/S and Doppler parameters in IUGR group.

Parameter	Amniotic fluid index	
	r	P value
Middle cerebral artery resistive index	0.41	0.08
Renal artery resistive index	-0.78	0.00**
Head circumference	0.69	0.001*
Abdominal circumference	0.67	0.001*
Feumer length	0.53	0.0016*
Estimated fetal weight	0.66	0.002*

Table (4) and Figure (2): Show the following results: There was significant negative correlation between AFI and FRA RI, Also There was significant positive correlation between AFI and head circumference, abdominal circumference, femur length and estimated fetal weight. While there were no significant correlation between AFI and MCA RI. However, there was highly significant inverse correlation between AFI and FRA RI.

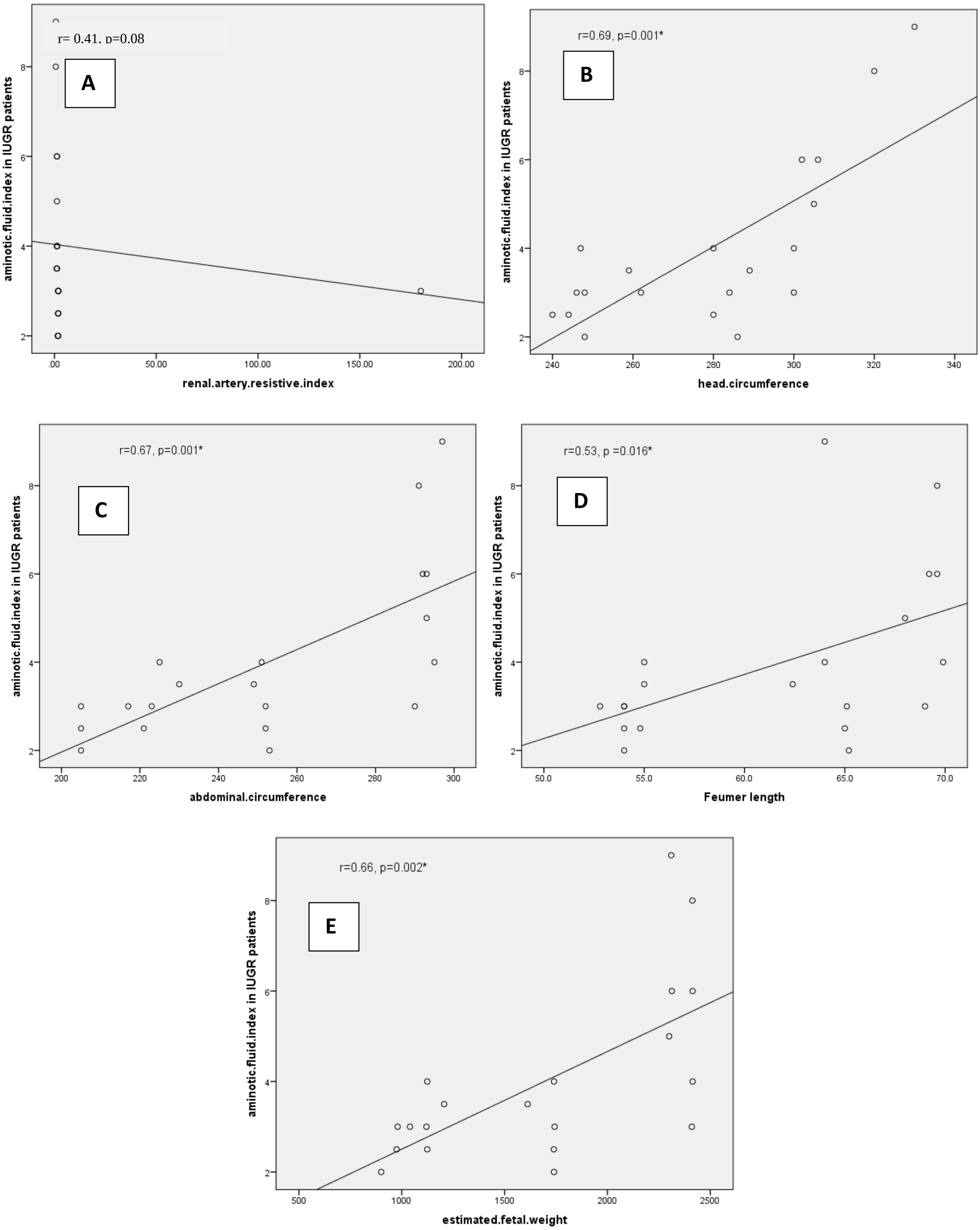

Figure (2): The correlation between AFI, U/S and Doppler parameters in IUGR patient group.

DISCUSSION

Intrauterine growth restriction (IUGR) is a major and silent cause of various morbidity and mortality for the fetal and neonatal population. It is defined as a rate of fetal growth that is less than normal for the growth potential of that specific infant.[22]

Amniotic fluid index (AFI) is one of the important components of fetal biophysical profile and its values correlate well with adequacy of fetal renal perfusion.[23] Amniotic fluid assessment by ultrasound is one of the essential tools in assessing the fetal health in all risk categories especially beyond the period of viability.[24]

Technological advances in Doppler velocimetry allowed the study of multiple fetal vessels such as middle cerebral artery (MCA) and renal arteries, improving detection of disturbances in fetus wellbeing. By monitoring the Doppler changes, it is possible to track the fetal-placental cell changes, which define the clinical picture of etiology for several fetal co morbidities.[25]

The present study aimed to determine the role of Amniotic fluid index and color Doppler of MCA and FRA in pregnant women with and without clinical suspicion of IUGR and its role in management. This prospective study was carried out on two groups each one included 20 patients; one group included normal pregnancy and other group of IUGR pregnancy attending Menof General Hospital–Egyptian Ministry of Health.

Results of the present study showed no statistically significant difference between normal pregnancy group and IUGR pregnancy group as regards the maternal age. This is agree with the study by ***Strobino et al. (1995)***[26] who did not find an association between maternal age and low birth weight and reported an independent effect of social factors on birth weight in adolescent mothers. In contrast ***Lee et al., (1988)***[27], ***Anju Suhag, (2013)***[28] revealed that several maternal demographic factors were associated with IUGR. Women at extremes of reproductive age, especially young maternal age were at high risk for IUGR, Also ***Aldous, (1993)***[29] stated that advanced maternal age was associated with low birth weight.

Abdel Sattar and Abdul Wahed, (2011)[30] revealed no statically significance difference between control pregnancy group and IUGR pregnancy group in relation to age but the control group has statically significant higher rate of vaginal deliveries in comparison to the patient group which is significantly higher in caesarean section rate than control group also higher body weight than control group.

The current study showed no statistically significant difference between the normal pregnancy group and IUGR pregnancy group regarding gravidity, parity and previous delivery. There was highly statistically significantly difference between the two groups regarding diabetes Mellitus, hypertension and pre-eclampsia.

This is agree with ***Divon et al., (2012)***[31] who concluded that maternal systemic conditions, such as chronic hypertension, preeclampsia, pregestational diabetes (class C, D, R, F), chronic renal insufficiency, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), could affect the fetal microcirculation thus decrease fetal perfusion, leading to hypoxia and IUGR.

Parity and maternal age had been shown to increase the risk of adverse neonatal outcomes, such as IUGR, prematurity, and mortality.[32]

Also our result agree with ***Burton et al. (2009)***[33] who found that hypertension was associated with two to three-time greater risk of growth restriction which is not improved by antihypertensive treatment. Also, ***Walfisch et al. (2006)***[34] concluded that the uteroplacental insufficiency associated with preeclampsia can be caused by failure of trophoblast invasion of the myometrial segment of spiral arteries causing failure of dilatation of these vessels, atherosis, occlusion, and infarction.

Koukkou et al. (1997)[35] showed that there was a significant although small reduction in fetal BPD in the presence of poor glycemic control during first half of pregnancy in diabetic mothers. ***Ang et al., (2006)***[36] stated that diabetes can cause hyperglycemia-related damage to the endothelial lining of micro- and macrovascular system and structural changes in placental decidual arteries, therefore causing hypoperfusion and growth restriction in fetuses of diabetic women.

A variety of sonographic parameters were used to diagnose IUGR. Most studies recorded reduced abdominal circumference (AC) is the most sensitive single morphometric indicator of fetal growth restriction (FGR).[37] Measurement of AC was more predictive of FGR than measurement of either head circumference (HC) or biparietal diameter (BPD) or the combination of AC with either one of these two variables. In 1975, Campbell and Wilkin first published a regression equation for estimating fetal weight based upon sonographic measurement of the AC and HC.[38] Other equations were published subsequently using two or more morphometric body measurements (e.g., BPD, AC, HC, occipital frontal diameter, abdominal diameter, transthoracic circumference, and femur length (FL)) to improve sonographic accuracy.[39]

Fetal abdominal circumference (AC) is the earliest affected parameter in the process of impaired fetal growth. Head circumference is another parameter which remains minimally affected by external pressure effects causing deformation of fetal head and by growth alterations. HC/AC ratio is another gestational age independent parameter which may be used in predicting IUGR.[40]

Our results showed highly statistically significantly difference between IUGR group and normal pregnancy group regarding head circumference (HC), abdominal circumference (AC), head / abdominal circumferences ratio (HC/AC ratio), femur length, age by LMP and US but lower regarding fetal weight (FW).

In agreement with our results ***Ott, (2000)***[41] found that using combination of abdominal circumference and Doppler, or estimated fetal weight and Doppler resulted in the best predictive values. Either estimated fetal weight or abdominal circumference (alone) is accurate predictors of IUGR. Combined with Doppler studies of the umbilical artery either method provides accurate evaluation of suspected IUGR. Also ***Anju Suhag, (2013)***[28]***, Handlock, (1983)***[41] ***and Crane, (1979)***[43] studied the role of other ultrasound parameters, such as AC alone, HC/AC ratio, FL/AC ratio, and ponderal index (PI), which can be used in identifying IUGR fetuses.

Sharma et al., (2014)[44] conducted a prospective study on 100 normal and 52 IUGR cases. In normal pregnancies; GA predicted by all parameters was within normal range. In IUGR pregnancies all parameters including BPD, HC & FL were showing disparity of > 3 weeks except TCD which in both groups were nearer to GA. ***Prasad and Likhitha (2014)***[45] conducted a study on 100 pregnant women (80 normal and 20 IUGR pregnancies) between 15 to 40 weeks of gestation and showed that BPD and FL was less than 5th percentile in 18/20 patients whereas AC, HC measurements were less than 5th percentile in all the 20 patients.

Niknafs and Sibbald, (2001)[46] results indicated that reduced AC was the best single parameter in discriminating between IUGR and non-IUGR fetuses with the highest sensitivity among the proposed parameters (BPD, FL, HC, AFI, and Doppler from umbilical arteries (S/D ratio) in the both Iranian and Australian sample. However, the PPV of this parameter is low.

In ***Haragan et al., (2015)***[47] study, EFW was considered a diagnostic test to which the investigated screening modalities (fundal height (FH), handheld ultrasound–measured fetal abdominal circumference (HHAC), and the abdominal circumference obtained from the formal ultrasound (USAC)) were compared. Although EFW is the current gold standard in the diagnosis of fetal growth abnormalities, other screening tests need to be considered to increase sensitivity in the detection of these fetuses.

The current study shows highly statistically significant difference between the two groups regarding gestational age at delivery and gestational fetal weight at birth, Sonographic parameters (HC/AC Ratio, AFI and FW) have a statistically significantly different mean value or frequency of occurrence, in growth retarded as compared with normal fetuses. This agrees with ***Ranjan et al., (2015)***[1] ***and Crane et al., (1979)***[43] who found similar statistical significant different mean in normal pregnancy and IUGR.

In our study, the control group 90% of cases had BW> 2.5 kg and the mean birth weight is 3121.0 gm., which is normal according to standards. In the study group the mean birth weight is 1676.9 gm and 98% shows birth weight < 2500 gm. In the study by ***Yelikar et al., (2013)***[48]***,*** cases of PIH with IUGR had an average birth weight of 1708 g. which correlated with this study.

The Present study shows a reduced birth weight in oligohydramnios cases, and increased fetal renal artery RI, indicates a similarity in the pathophysiology to intrauterine growth restriction. Reduced fetal growth is a well-recognized complication in oligohydramnios.

In agreement with our results, ***Roeder et al., (2014)***[49] and ***Rightmire et al., (1988)***[50] stated that Doppler studies had the best statistical performance.

The current study shows highly statistically significant difference between the two groups in fetal Outcome, mode of delivery, Admission to ICU, 5 minutes Apgar score. No statistically significant difference in Death and Meconium aspiration.

The present study shows highly statistically significant difference between the two groups, oligohydramnios (AFI</=5 cm) was seen in (85%) cases in IUGR pregnancy group, this agree with ***Sonia Madaan et al., (2015).***[51] In a study conducted by ***Marks and Divon et al.,(1992)***[52]***,*** on post-term pregnancy, oligohydramnios was demonstrated in (11.5%) of patients.

A study by ***Driggers et al. (2004)***[53] reported a 5-min Apgar score <7 in 3.8% patients in an oligohydramnios group versus 4.6% in a normal AFI group, and concluded that there was no significant difference. A study by ***Grubb and Paul, (1992)***[54] found the 1-min Apgar score <7 in 84% patients with AFI ≤ 5 as compared to 14% in the normal AFI group, which was highly significant ($p = 0.01$). In the same study, the 5-min score <7 was seen in 13% patients with AFI ≤ 5 versus 5% in the normal AFI group.

A review of 18 studies indicated that an AFI < 5 cm was associated with an increased risk of Cesarean section for fetal distress (relative risk [RR] 2.2; 95% confidence interval [CI] 1.5-3.4) and Apgar score of < 7 at 5 min (RR 5.2; 95% CI 2.4-11.3), but not with neonatal acidosis.[55]

Gumus et al.(2007)[56] reported an increased incidence of NICU admission, IUGR, meconium-stained amniotic fluid, and intrapartum fetal distress in pregnancies with a borderline AFI.

If diabetes is associated with macrosomia and neural tube defects, polyhydramnios may develop. In our study, it was observed that mean AFI of two patients with diabetes was more (12.3 cm) than non-diabetic patients (11.5 cm) though it was not statistically significant (P. value >/= 0.1). Also, pulsatility index in the renal artery among IUGR infants is inversely correlated to the amniotic fluid index. Pulsatility index is a measure of acceleration rather than resistance.

In IUGR fetuses reduced amniotic fluid volume and renal vascular resistance changes identified by Doppler ultrasonography appear to be correlated.

Magann, (2011)[57]***, Munn, (2011)***[58]***, Vyas et al., (1989)***[17] ***and Mari, (1993)***[59] and ***Akin et al., (2013)***[60] cleared that although studies showing a negative correlation between renal artery Doppler and oligohydramnios, some author report no link. ***Oz et al., (2014)***[61] evaluated 147 patients in a study on post-term pregnancies and found that renal artery Doppler was the only doppler parameter useful for predicting oligohydramnios.[62]

In a different study, where normal amniotic index pregnancies, oligohydramniotic, polyhydramniotic and twins where one fetus was oligohydramniotic and the other polyhydramniotic, pregnancies were compared, while there was no relationship between polyhydramnios and renal artery PI, the renal artery PI was higher in the oligohydramnios cases.[63]

In our study, patient population was similar to that in the above mentioned paper and, likewise, we found that while polyhydramnios group had no relation to the renal artery PI index, there was an increase in the PI values, as well as RI values, in the oligohydramnios group.

In a 1991 study, IUGR fetuses showed an increased renal artery PI and a negative correlation of this increase with AFI, however there was no such relationship in post-term pregnancies.[62]

Yoshimura et al., (1997)[63] showed a negative correlation between oligohydramnios and renal artery PI in IUGR fetuses, as well as those measuring according to dates

Selam et al. (2000)[64] found that patients with oligohydramnios had increased rates of renal artery resistance, which were significantly higher than the umbilical artery and MCA resistance rates. In our study the whole population was in the 3rd trimester and there were no post-term pregnancies included. All oligo-polyhydramnios pregnancies in the study were idiopathic. In all pregnancies indicators of fetal distress (UA, MCA, and NST) were all within the normal ranges. Regardless, the oligohydramnios group had increased renal artery RI and PI values when compared to the other groups. However, the source of the fetal renal artery, i.e. the fetal descendant aorta, had normal Doppler values.

In the present study, there was highly statistically significant difference between the two groups as regard Middle Cerebral Artery resistive index (MCA RI), and Fetal Renal Artery resistive index (FRA RI). Both (FRA RI) and (MCA RI) were equally sensitive (sensitivity 90%), and AFI had comparably low sensitivity (sensitivity 80%) in predicting any adverse out come.

FRA RI was most specific (Specificity=100%). It was more specific than either MCA RI (Specificity=95%) or AFI (Specificity=85%) alone in predicting any adverse out come.

FRA RI had highest Positive Predictive Value (PPV=100%) followed by MCA RI (PPV=94.7%) and AFI (PPV=84.2%), Negative Predictive Value of FRA RI was 90.9% when compared to 90.5% for MCA RI and 80.6% for AFI. Diagnostic accuracy of FRA RI (Accuracy=95%) was better than MCA RI (Accuracy=92.5%) and AFI (Accuracy=82.5%) in predicting adverse outcomes.

El-Behery et al. (2012)[65] evaluated 110 patients with color Doppler US, and 43 of them had IUGRs between gestational weeks 26–34. The renal artery PI was 0.79 and 1.75, respectively, in normally growing fetuses and growth restricted fetuses; and there was a statically significant correlation between these two groups. They also detected a negative correlation between the fetal arterial pO2 and AFI. A reduction in the fetal arterial pO2 or AFI caused increased resistance in the renal arterial PI.

In ***Khanduri et al., (2013)***[66] study, the sensitivity of the MCA PI ranged from 33.3 to 39.1%, while specificity and positive predictive values ranged from 88.9 to 94.4% and 88.9 and 93.8%, respectively. The negative predictive value of the criteria ranged from 37.8 to 38.1%. Overall, the sensitivity, specificity, PPV, and NPV of the criteria were 35.7, 92.6, 91.8, and 38.2%, respectively, with a diagnostic accuracy of 36.1%. ***Bano et al. (2010)***[67] observed the sensitivity, specificity, PPV, and NPV of the MCA PI was 8.9, 100, 100, and 52.3%, respectively, with a diagnostic accuracy of 54.4%. The sensitivity of Middle cerebral artery waveform in identifying IUGR in high-risk group was 7.7% with a specificity of 90%, a positive predictive value of 87.5 and a negative predictive value of 9.78.[68]

The present study shows that in fetal renal artery resistive index (MCA RI) of IUGR fetuses was significantly higher than that of normal fetuses. Findings of the present study simulate those of ***Arduini and Rizzo. (1991)***[62] ***and Fong et al., (1999)***[69] in Sonographic estimation of FRA RI in the prediction of intrauterine growth retardation.

Our results show that (MCA RI) of IUGR fetuses was significantly lower than that of normal fetuses. This result agrees with ***Mimica et al., (1995)***[9], who found continuous reduction of cerebral vascular resistance resulting in decrease Middle cerebral artery resistance index values gradually during chronic fetal hypoxia, also, ***Ranjan Sahoo et al., (2015)***[1]***, Arduini and Rizzo. (1991)***[62] reported the same finding in Sonographic estimation of MCA RI in the prediction of intrauterine growth retardation.

Ranjan Sahoo et al., (2015)[1] also showed that C/U RI had a better specificity than either middle cerebral or umbilical artery resistance indices as measured by Doppler in predicting poor neonatal outcome.

Wisam Akram et al., (2017)[70] concluded in the result section of this study the renal artery of the fetus is the first artery which starts to increase relative to both umbilical and middle cerebral artery. In fact the first hint which came across our mind stimulating us to make this complicated protocol and study was the frequent and recurrent papers issued over last 20 years which stress that Doppler indices of the renal artery among women with post term complicated pregnancy is much more accurate and surpass the umbilical artery in predicting fetuses at high risk of hypoxia.

Selam et al., (2000)[64] in the beginning of new millennium have shown that resistance index in the renal artery is more sensitive and more useful in clinical practice in predicting fetuses at risk of hypoxia in post term complicated pregnancy. While ***Barros et al., (2008)***[71] have suggested that oligohydramnios seen among women with post term pregnancy is associated with redistribution of blood so brain have extra perfusion which is diverted from normal perfusion to other organs like kidney, On the other hand papers which refer to low Doppler indices in the middle cerebral artery in IUGR were also quite diverse in the medical literature.

Severi et al., (2002)[72] has stressed on the fact that infants with IUGR irrespective of the cause have low middle cerebral artery Doppler indices while elevated umbilical artery indices. ***Simanaviciute et al., (2006)***[73] have shown the ratio of (middle cerebral artery PI/ uterine artery PI) ratio bellow 5th centile is associated with adverse pregnancy outcome like preeclampsia and IUGR suggesting middle cerebral artery has low resistance throughout normal pregnancy. As a matter of fact and to clarify this vague situation the solution comes from basic facts of medicine.

El-Behery et al., (2012)[65] found that pulsatility index in the renal artery among IUGR infants is inversely correlated to the amniotic fluid index.

Azpurua et al., (2009)[74] used the fetal renal artery Doppler in preterm labor and premature rupture of membrane or PROM and found that Doppler indices were not changed by those conditions.

All efforts should be done to predict correctly the prompt time of delivery for infants complicated with IUGR as fetal hypoxia is essential pathophysiology icon in IUGR.[75,76]

Doppler velocimetry is a noninvasive technique that evaluates the abnormal fetal hemodynamics that take place in response to changes in placental resistance. A Doppler index that reflects these changes can be useful in identifying the fetuses with increased renal and decreased cerebral resistance. We chose incidences of perinatal death, emergency section for fetal distress, NICU admission for complication of low birth weight and low Apgar score as outcome variables in concurrence with previous studies done.

Amniotic fluid index and Doppler ultrasound have a high sensitivity, specificity and diagnostic accuracy in predicting adverse perinatal outcome.

Regarding evaluating the usefulness of amniotic fluid index, renal and middle cerebral arteries Doppler in predicting the adverse perinatal outcome in IUGR, the present study indicated that both abnormal MCA and RA Doppler indices and Amniotic fluid index are strong predictors of adverse outcome in IUGR. FRA RI and MCA RI than Amniotic fluid index are reliable indicators when used alone. The combination of fetal renal and middle cerebral Doppler indices may increase the utility of Doppler ultrasound in clinically suspected IUGR.

Our results coincide with ***Dhand et al. (2011)***[77] who concluded that MCA Doppler indices were a better predictor for fetal outcome in IUGR in terms of sensitivity and predictive value.

While ***Fong et al., (1999)***[69] found that in suspected IUGR, while an abnormal UA PI is a better predictor of adverse perinatal outcome than an abnormal MCA or RA PI, a normal MCA PI may help to identify fetuses without major adverse perinatal outcome, especially before 32 weeks gestational age.

Regarding correlations between parameters in all patient groups, our results show highly significant positive correlation between AFI, MCA RI and FRA RI; highly significant positive correlation between AFI and head circumference, abdominal circumference and estimated fetal weight. Also, there was significant positive correlation between AFI and feumer length.

Regarding correlations between parameters in IUGR group, the current study revealed negative significant correlation between AFI and MCA RI or FRA RI. Our result agree with ***Stigter et al. (2001)***[10] who found that a reduction in renal artery peak systolic velocities with time and also a significant correlation between renal artery Vmax and both pH values in venous cord blood and Δ/SDAFI. These findings suggest that there is a reduction in cardiac output or a reduction in the percentage of cardiac output directed towards the kidneys resulting in the reduction of renal perfusion, urine production and amniotic fluid volume in the growth-restricted fetus.

Our results revealed significant positive correlation between AFI and head circumference, abdominal circumference, femur length and estimated fetal weight in IUGR group.

Kofinas and Kofinas (2006)[78] found a significant association between AFI and EFW. There are few reports that assess the possible association between AFI and the estimated weight.[79,80,81]

Chauhan et al., (2006)[82] found that between patients suspected for IUGR, the peripartum outcome was poorest for those with AC and EFW < or = 10% for GA, than for those with AC < or = 10% but EFW>10%. The detection of SGA was poor regardless of whether just AC or AC plus EFW are < or = 10%.

Benson et al., (1985)[83] studied 285 normal and 37 IUGR fetuses and concluded that the FL/AC ratio, though an age-independent measure whose mean value differs in normal and IUGR fetuses, was not clinically useful as a predictor of IUGR. The relationship of fetal mean abdominal diameter to fetal femur length (FL) in clinically normal pregnancies and 37 cases of intrauterine growth retardation (IUGR) was studied by ***Seeds et al., (1986)***[84]**,** in the growth retarded infants, 59% of the abdominal measurements fell below the lower 75% confidence limit. Of the abdominal measurements derived from infants with birth weight greater than 2 SD below the mean for gestational age, 86% fell below the lower 75% confidence limit. Fetal mean abdominal diameter was selectively depressed in many, but not all cases of IUGR and particularly in the more severely affected infant.

CONCLUSION

Fetal Doppler study should be an integral part in evaluation of a suspected IUGR pregnancy, diagnosing and predicting the adverse outcome.

1. Abnormal Amniotic fluid index, Middle cerebral and fetal renal arteries resistive indices, in particular is a strong predictor of adverse perinatal outcome in IUGR.
2. Middle cerebral artery is more useful than Amniotic fluid index in prediction of outcome in IUGR when considered individually.
3. Fetal renal artery RI was more specific than either MCA RI or AFI alone in predicting any adverse out come.
4. Combined sonographic and Doppler parameters such as Low EFW and low AFI as well as low MCA RI and High FRA RI have better sensitive and predictive value for estimation the adverse outcome.

Recommendations

- Further studies and randomized controlled trials are needed.
- Obstetricians should identify fetuses at risk of developing growth restriction, design a comprehensive surveillance plan, and carefully chose the time and mode of delivery.
- Antenatal surveillance should be instituted with an emphasis on Doppler analysis as the most important tool to grade the severity of the fetal disease.

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