Evaluation of the Diagnostic Criteria of Ultrasonographic Parameters In The Prediction of Intrauterine Growth Restriction

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I. INTRODUCTION

Abstract- <u>Aim:</u> To evaluate the diagnostic criteria of Ultrasonographic parameters to predict intrauterine growth restriction.

<u>Methods:</u> Normal pregnant females at different gestational ages that come for normal ultrasonography for routine check were recruited for the study. The USG markers to identify IUGR were assessed.

Results: The umbilical artery indices such as S/D ratio decreased from 2.63 to 1.96. In addition, PI (Pulsatility Index) decreased from 1.24 to 0.60 & RI decreased from 0.62 to 0.48 from 32 weeks onwards respectively. Doppler indices of MCA decrease after 32 weeks. The middle cerebral artery indices such as PI decreased from 2.16 to 1.36 and RI decreased from 0.89 to 0.62 from 32 weeks onwards. In control group Cerebro Placental Ratio (CPR) was more than 1. Out of 50 cases of the study group, 25 cases shows PI of Umbilical artery more than 2 SD, 23 cases with SDR of umbilical artery > 3, 20 cases with SDR > 95th percentile whereas in middle cerebral artery 15 cases with SDR > 95th percentile and 27 cases with CPR < 1. The prevalence of IUGR among the study group was 51.5%. The best cut-off value of the TCD/AC ratio for predicting IUGR was 15.4%, giving the sensitivity, specificity, positive predictive value and negative predictive value of 73.26%, 80.25%, 79.75%, and 73.86%, respectively and overall diagnostic accuracy was 92.4%.

Conclusions We conclude that, no single non-Doppler sonographic parameter permits the confident diagnosis of IUGR. Multiple Doppler and conventional sonographic parameters shows increase sensitivity and predictivity than single parameter in the study group. Low Estimated Fetal Weight combined with Umbilical (Systolic Diastolic Ratio) SDR >2 SD and HC/AC ratio combined with SDR >2 SD parameters shows increased predictivity and sensitivity. Considering that C/U RI (Cerebral/Uterine Resistivity Index) reflects not only the circulatory insufficiency of the placenta by alteration in the umbilical resistance index, but also the adaptive changes resulting in modification of the middle cerebral resistance index, it seemed to be a potentially useful tool in predicting adverse perinatal outcome in high risk cases. Our results support the correlation between abnormal fetal C/U RI and adverse perinatal outcome in patients with IUGR.

Index Terms— IUGR, Ultrasonographic parameters, Trans cerebellar diameter, Abdominal circumference, Head Circumference

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Intrauterine growth restriction refers to a condition in which the fetus is smaller than it should be at that particular gestational stage because the rate of growth inside the womb is not normal. The fetus, in this condition, fails to achieve its growth potential, which increases their perinatal morbidity and mortality. Intrauterine growth restriction can be of two types-symmetrical and asymmetrical. The major cause of IUGR is represented by uteroplacental insufficiency. The risk factors for IUGR comprise a wide range of conditions and their assessment is essential during pregnancy. IUGR is observed in about 24% of newborns; approximately 30 million infants suffer from IUGR every year [1]. In India, the prevalence of LBW has been reported as 26% [2]. While the proportion of IUGR has found to be 54% [3,4]. IUGR is one of the most common and complex problems in modern obstetrics and thus it are a wide topic for research today.

The uteroplacental circulation can be assessed by means of Doppler ultrasonography [5]. This procedure has been reported in numerous studies to be promising technique for predicting the level of risk for pre-eclampsia and intrauterine growth restriction [6-8]. Doppler ultrasonography may be performed via the transvaginal or transabdominal route in the first or second trimester [9]. Waveforms on Doppler are reported to be readily obtainable in more than 95% of patients [10]. The uterine artery is identified with the use of color Doppler ultrasonography and various indices can be calculated and assessed [9]. In case of an incomplete trophoblastic invasion of the spiral arteries, the maternal compartment fails to transform from a high resistance to a low resistance flow district and this impairment is associated with the development of pre-eclampsia and IUGR. In these cases, Resistance Index (RI) or a Pulsatility Index (PI) above the 90th-95th percentile and/or the presence of unilateral or bilateral notching associated with a value of the RI >0.58 or a value of the PI >1.45 [11]. Onset of fetal growth restriction is associated with reduced placental perfusion due to a decrease in villous cross-sectional vascular area, which leads to elevated umbilical artery blood flow resistance once villous damage exceeds 30%. In early onset disease, elevated umbilical artery Doppler resistance is followed by middle cerebral artery brain sparing, escalating blood flow resistance in the umbilical artery with progressive reverse shunting in the aortic isthmus followed by deterioration of venous Doppler parameters and finally the biophysical profile score.

Although it is a public health problem with around 10% incidence in the pregnancy population, fetal growth retardation is still a matter of debate starting from the

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definition, the multifactoral origin, the low levels of prediction, the questionable references like customized or uncustomized growth charts, and the methods of diagnosis and management [12].

Intrauterine growth restriction is one of the most severe complications in modern obstetrics. In about 75% of the cases, IUGR remains unrecognized until birth and the diagnosis comes retrospectively. As of today, no single marker has been found, be it ultrasonographic, serum markers or clinical factors that can help in the early diagnosis of this challenging condition. Various researches have been carried out in the same line, to establish a definite predictive marker in the detection of IUGR and to help reduce infant mortality and morbidity. According to literature, Ultrasonographic assessment has been found to be a very promising means for the detection of IUGR. A thorough investigation of the various parameters on ultrasonography will help to establish accurate marker/markers for the detection of IUGR and help in its efficient management thereby. Identification of such a diagnostic marker will aid extensively in the reduction of infant mortality and morbidity due to this condition, and will prove to be a revolution in the field of obstetrics. This study aims at assessing various ultrasonographic parameters accurately and establishing the relative reliability of each in the diagnosis of intrauterine growth restriction.

II. METHODS

Study Location: Department of Radiology, MGM Hospital, Navi Mumbai.

Study design: Prospective cohort study – Observational study, conducted from June-2016 to March 2017.

Sample size: 100 pregnant women at different gestational ages were assessed after informed consent was taken. They were grouped into control and IUGR categories.

Inclusion criteria:

• Singleton pregnant women, after obtaining consent.

• All women screened for IUGR and those being treated for the same.

• Clinically suspected IUGR/asymptomatic cases.

Exclusion criteria:

• Females of age less than 18 and more than 35 years, or unknown last menstrual period.

- A known case of gestational diabetes and hypertension.
- A known case of gestational complications.

• A known case of neurodevelopmental disorders or genetic disorders.

Parameters assessed:

[•] Umbilical artery Doppler indices- Resistivity index (RI) and Pulsatility index (PI)

- Transcerebellar diameter
- Abdominal circumference
- · Head circumference

III. METHODOLOGY

Informed consent and PCPNDT Act: Informed consent was taken from the pregnant women in a language best understood by them.

Under the PCPNDT Act, the sex of the fetus was not revealed during the process of data collection for this study.

Normal pregnant females at different gestational ages that



come for normal ultrasonography for routine checkup were recruited for the study. The following parameters were assessed to categorize the female to either control or IUGR group based on fetal weight less than 10th Percentile of normal weight. 1. The Middle cerebral artery and the 2. Umbilical artery was assessed on Doppler sonography.

The Doppler sample volume was placed within 1 cm of the origin of the middle cerebral artery that was easily identified as a major branch running in anterolateral direction from the circle of Willis towards the lateral edge of the orbit. While angle of correction is not necessary when measuring the middle cerebral artery Pulsatility index (PI), peak systolic velocity measurement should use angle correction and the angle of incidence should be <30 degrees; optimally as close to 0 degrees as possible. For the waveform analysis, maximum and minimum values of the velocity waveforms on the frozen image were measured by use of electronic calipers of the machine.

3. Transcerebellar diameter- This parameter was assessed with the fetus in the direct occiput anterior position. In this position, the posterior fossa appears closer to the transducer and thus the cerebellum was seen and the diameter was accurately measured [Figures-1, 2 and 3].

4. Head circumference- This was calculated using the shortest and the longest axes of fetal head measured outer to outer margins [Figure-4].

5. Abdominal circumference- The cephalocaudal plane is the position where the right and the left portal veins are continuous with one another. Secondly, the symmetric lower ribs were visualized, followed by visualization of the stomach bubble [Figure-5].

The TCD/AC and HC/AC ratios were correlated with advancing gestational age to know if these morphometric ratios were related to gestational age. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy for TCD/AC and HC/AC ratios in evaluating IUGR fetuses were calculated.



"Fig:1 Grade I cerebellum. The cerebellum is seen between the calipers"



"Fig:2 Grade II cerebellum. The cerebellum is seen between the calipers"



Fig:3 Grade III cerebellum. The cerebellum is seen between the calipers"



"Fig:4 Head circumference (HC) measurement"



"Fig:5 Abdominal circumference measurement"

OBSERVATIONS AND RESULTS:

In the present study, 50 pregnant women between 18-35 years of age showing asymmetrical foetal IUGR were examined with majority of them (28%) being in the age group 27-29 years [Table-I]. In majority of these pregnancies, the gestational age was between 34 to 36 weeks, accounting for 30% of population [Table-II]. Seventy percent of patients were primigravida [Table-III].

Table: I Age distribution of patients studied in IUGR and normal pregnancies:

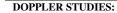
Age group	N (number of patients-IU	Percent	N (number of patients-	Percent
year	GR)	age (%)	Control)	age (%)
18-20	11	22	9	18
21-23	12	24	15	30
24-26	10	20	12	24
27-29	14	28	7	14
30-32	2	4	5	10
33-35	1	2	2	4
Total	50	100	50	100

Table:II- Period of gestation among IUGR and normal pregnancies

Gestational period	N (number of IUGR cases)		, i	Percenta ge (%)
20-21wk 6d	2	4	5	10
22-23w 6d	2	4	12	24
24-25w 6d	3	6	6	12
26-27w 6d	1	2	4	8
28-29w 6d	3	6	1	2
30-31w 6d	4	8	6	12
32-33w 6d	8	16	9	18
34-35w 6d	11	22	5	10
36-37w 6d	10	20	1	2
38-39w 6d	6	12	1	2
Total	50	100	50	100

Table:III- Gravidity distribution in IUGR pregnancies

Gravidity	N (number of patients)	Percentage		
Primi	72	72		
Multi	28	28		
Total	100	100		





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In middle cerebral artery, RI of IUGR fetuses was significantly lower than that of normal fetuses $(0.0.598 \pm 0.12)$ vs 0.0.742±0.129; p<0.01). Cerebroplacental ratio (MCA RI/UA RI) of IUGR fetuses was significantly lower than that of normal fetuses (0.814±0.20 vs 1.59±0.361; p<0.01. Umblical artery shows 73% sensitivity, 85% specificity, 35% positive predictive value with 96% negative predictive value when S/D ratio was more than 3. Sonography parameter such as HC/AC ratio shows 93% sensitivity, 95% specificity, 67% positive predictive value and 99% negative predictive value for IUGR. Low EFW shows 83% sensitivity and 85% specificity, 38% positive predictive value and 97% negative predictive value for estimation of IUGR. Out of sonographic parameters HC/AC ratio has better predictive value(67%). Combined sonographic and Doppler parameters such as Low EFW and SDR> 2 SD as well as CPR<1 and low EFW have better sensitive and predictive value.

IV. SONOGRAPHICAL PARAMETERS

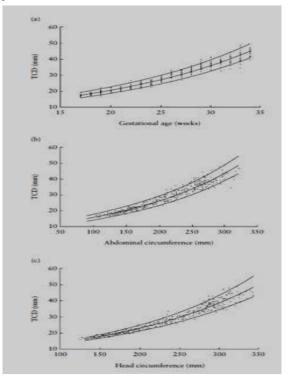
The prevalence of IUGR among the study group was 51.5%. The best cut-off value of the TCD/AC ratio for predicting IUGR was 15.4%, giving the sensitivity, specificity, positive predictive value and negative predictive value of 73.26%, 80.25%, 79.75%, and 73.86%, respectively and overall diagnostic accuracy was 92.4%.

The study showed that there is poor correlation (r2=0.13, p>0.05) between TCD/AC and gestational age after 20 weeks. Therefore, even though there was slight increase in the TCD/AC ratio with gestational age, this increase is insignificant suggesting that this ratio will be constant at any gestational age. The mean TCD/AC was 13.63±1.2% (2SD).



The ratio between TCD and AC was calculated and found to be 0.1436 +/- 0.0106 (SD) which remained fairly constant throughout pregnancy in control subjects.

Analysis of 50 normal singleton pregnancies showed a statistically significant log-linear relationship between TCD and gestational age (R2= 0.96; P<0.0001; Figure 6a). A statistically significant log-linear relationship was also demonstrated between TCD and AC (R2= 0.95; P<0.0001; Figure 6b), and between TCD and HC (R2= 0.96; P<0.0001; Figure 6c). In the latter two relationships the proportional distance of the 5th and 95th centile from the median increases with circumference. In the subset of 50 IUGR fetuses, TCD was below the lower limit of the normal range in 13 (26%) cases, vs. 33 (66%) cases which were below the lower limit of the normal range for HC. This difference was statistically significant (P< 0.0001). The TCD was above the upper normal limit of the TCD/AC chart in 41 (82%) out of 50 cases, and above the upper normal limit of the TCD/HC chart in 24 (48%) out of 50 cases. This difference was also statistically significant. The head circumference increased gradually with menstrual age from 9 cm per week to 33.51 cm per week at term in control group [Table-IV]. The phenotype of IUGR in this cohort was predominantly asymmetric, with 58% of fetuses (62/107) exhibiting an asymmetric pattern. This proportion is significantly greater than the expected proportion of fetuses with HC/AC ratio over the 95th percentile (5%) (Fisher exact test; P < 0.001)[13]. The proportion of IUGR fetuses with an elevated HC/AC ratio did not differ either by quartiles across the range of gestational age of ultrasound.



"Figure:6: Log-linear relationship demonstrated between (a)TCD and Gestational age, (b)TCD and AC and (c) TCD and Head Circumference."

Table-IV: Head Circumference (in cm) and standard deviations (SD) from 20th week to 35 weeks in normal control group.

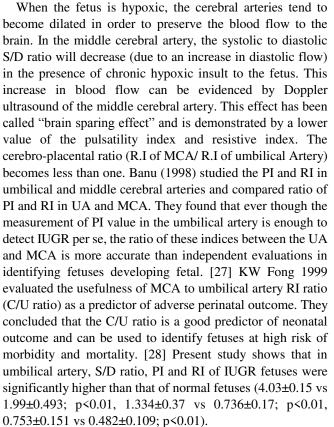
significant different mean in IUGR and normal pregnancy. [26]

Gestation age in weeks	Head circumference (HC) in cm	SD± in cm
20	17.63	0.17
21	18.65	0.19
22	19.94	0.36
23	21.15	0.16
24	22.13	0.21
25	23.6	0.5
26	24.6	0.23
27	25.6	0.3
28	26.5	0.42
29	27.48	0.25
30	28.7	0.1
31	29.6	0.11
32	30.5	0.06
33	31.28	0.08
34	31.67	0.17
35	32.15	0.25

V. DISCUSSION

Human foetuses normally direct one-third of their cardiac output to the placenta during the second half of pregnancy and one-fifth during the last couple of months.[21] In contrast, IUGR foetuses with early umbilical artery abnormalities direct a reduced volume of blood toward the placenta, both in absolute and relative terms, while maintaining relatively normal cardiac output .[22] Low cardiac output to the placenta may already be present at a stage of the disease that precedes the appearance of clinical evidence of a reduction in fetal growth and changes in impedance to flow in the fetal arterial and venous circulation [23]. This condition may suggest that, at an early stage of placental compromise, the volume of fetal blood flow toward the placenta is reduced, and more extensive recirculation of umbilical blood in the fetal body develops in an attempt to achieve more efficient extraction of oxygen and nutrients.[22-24] In control group 90% cases had BW> 2.5 kg and the mean birth weight is 2749 gm., which is normal according to Indian standards. In study group the mean birth weight is 1806 gm and 96% shows birth weight < 2500 gm. In the study by Mallikarjunappa cases of PIH with IUGR had an average birth weight of 1708 g. which correlates with this study. [25] Sonographic parameters (HC/AC Ratio, AFI and EFW) have been found to have a statistically significantly different mean value or frequency of occurrence, in growth retarded as compared with normal fetuses (1.2007±0.07 vs 1.0745±0.07; P<0.0001, 4.9967±2.1573 vs 11.10±1.99; P<0.0001, 1783.83±479.43 vs 2731±306.7; P<0.0001) in the present study. Crane JP, Kopta MM.

Prediction of intrauterine growth retardation via ultrasonically measured head/abdominal circumference ratios. Obstet Gynecol, 54, 1979, 597-601 has similar statistical



In middle cerebral artery, RI of IUGR fetuses was significantly lower than that of normal fetuses $(0.0.598 \pm 0.12)$ vs 0.0.742±0.129; p<0.01). Cerebroplacental ratio (MCA RI/UA RI) of IUGR fetuses was significantly lower than that of normal fetuses (0.814±0.20 vs 1.59±0.361; p<0.01 (Table 6). Similar study in the year 2000 by Yoon Ha Kim/Seok Mo Kim/Tae Bok Song/ Ji Soo Byun revealed that in umbilical artery, S/D ratio, PI and RI of IUGR fetuses were significantly higher than that of normal fetuses (3.34±0.69 vs 2.29±0.29; p<0.01, 1.27±0.27 vs 0.81±0.14; p<0.01, 0.70±0.07 vs 0.55±0.06; p<0.01). In middle cerebral artery, RI of IUGR fetuses was significantly lower than that of (0.72±0.09 vs 0.82±0.07; p<0.01). normal fetuses Cerebroplacental ratio (MCA RI/UA RI) of IUGR fetuses was significantly lower than that of normal fetuses (0.93±0.25 vs 1.35±0.16; p<0.01). They concluded that umbilical blood flow was affected but middle cerebral blood flow was maintained in IUGR fetuses. Hence fetal blood flow redistribution in favor of the brain at development of IUGR may be present and detectable by Doppler ultrasonography using Cerebroplacental ratio. [29]

In 2005, Alaa Ebrashy, Osama Azmy, Magdy Ibrahim, Mohamed Waly, Amira Edris, Obstetrics and Gynecology Department, Kasr El Aini Hospital, Cairo University; Reproductive Medicine Unit, National Research Center; and Neonatology Department, Kasr El Aini Hospital, Cairo University, Cairo, Egypt (Croat Med J, 46(5), 2005, 821- 825) performed prospective case-control study of 50 pregnant women with preeclampsia with or without intrauterine growth restriction (IUGR) middle cerebral/umbilical artery



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resistance index (C/U RI) ratio < 1 is considered abnormal. In the preeclampsia group, C/U RI was abnormal in 32 out of 38 fetuses with IUGR, and in only 5 out of 12 of fetuses without IUGR. [30] In the present study, although sensitivity was lower for the systolic to diastolic ratio (73%) of the umbilical artery than for the sonographic estimation of fetal weight (93%), the umbilical artery studies had a higher specificity (90 versus 85 %) (Table- 8 & 9).These findings indicate that sonographic biometry is a more sensitive technique for identifying IUGR but that the umbilical artery waveforms are a valuable adjunct for improving the diagnostic accuracy for the prenatal detection of IUGR.

Berkowitz GS, Mehalek KE also reported the same finding in Sonographic estimation of fetal weight and Doppler analysis of umbilical artery velocimetry in the prediction of intrauterine growth retardation: a prospective study. [31] The most common determination of fetal growth restriction is based on the estimated fetal weight, EFW, determined from a combination of BPD and AC (Campbell, 1975). Cerebroplacental ratio (CPR) less than one is seen in 90% of IUGR cases with positive predictive value 66% in the present study. Article by Tatjana Reihs and Matthias Hofer in chapter (6) of teaching manual of color duplex sonography by Matthias Hofer mentioned that this index (CPR) is very sensitive predictor (80%) of fetal growth retardation.[33] The middle-cerebral-to-umbilical-artery ratio remains relatively constant (mean \pm SD 1.33 \pm 0.19) between 27 and 37 weeks. A cutoff value of 1.0 (sensitivity 57.9%, specificity 75.6%, false-positive rate 24.4%) was selected from the receiver-operator characteristic curve analysis. This cutoff value successfully identified a population at significant risk of fetal growth retardation (relative risk 3.07, 95% confidence interval 1.73 to 5.45, exact two tailed p = 0.0009.[33]

A middle-cerebral-to-umbilical-artery ratio of ≤ 1.0 identifies a subgroup of patients at high risk for fetal growth retardation and severe neonatal morbidity. Alaa Ebrashy, Osama Azmy1, Magdy Ibrahim, Mohamed Waly, Amira Edris et al found C/U RI was abnormal (<1) in 32 out of 38 fetuses with IUGR in 50 preeclampsia pregnancy group. [34] In the present study sensitivity, specificity, positive and negative predictive values are evaluated for umbilical as well as middle cerebral artery. Umbilical artery shows 73% sensitivity, 85% pecificity, 35% positive predictive value and 96% negative predictive value when S/D ratio is more than 3. Overall, however, positive predictive values of Doppler criteria for IUGR were found to be poor. Benson CB, Doubilet PM have observed similar finding in their study. [35,36]

Sonographic parameters such as HC/AC Ratio shows 93% sensitivity, 95% specificity, 67% positive predictive value and 99% negative predictive value. Low EFW shows 93% sensitivity, 90% specificity, 50% positive predictive value and 99% negative predictive values. Ninety percent of fetuses are not growth-retarded, so any reasonable test will have a negative predictive value of at least 90%. Out of sonographic parameter HC/AC Ratio has better positive predictive value 67%. Overall, no single non- Doppler sonographic parameter permits the confident diagnosis of IUGR. Benson CB, Doubilet PM, Saltzman DH observed the similar findings in



their study of intrauterine growth retardation: predictive value of ultrasound criteria for antenatal diagnosis. (Radiology, 160, 1986, 415-417). [37] Multiple Doppler and conventional Sonographic parameters shows increase sensitivity and predictivity than single parameter in the study group. Low EFW combined with Umbilical SDR >2 SD, HC/AC ratio combined with SDR >2 SD and CPR<1 with low EFW parameters shows increased predictivity and sensitivity. Berkowitz GS, Chitkara U, Rosenberg J, Cogswell C, Walker B, Lahman EA, Mehalek KE, Berkowitz RL concluded that sonographic biometry is a more sensitive technique for identifying IUGR but that the umbilical artery waveforms are a valuable adjunct for improving the diagnostic accuracy for the prenatal detection of IUGR. [38] Ott WJ concluded that when used in combination, 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 will provide accurate evaluation of suspected IUGR. Above two studies support the findings. [39] Our study 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.

CONCLUSIONS

We conclude that, no single non-Doppler sonographic parameter permits the confident diagnosis of IUGR. Multiple Doppler and conventional sonographic parameters shows increase sensitivity and predictivity than single parameter in the study group. Low Estimated Fetal Weight combined with Umbilical (Systolic Diastolic Ratio) SDR >2 SD and HC/AC ratio combined with SDR >2 SD parameters shows increased predictivity and sensitivity. Considering that C/U RI (Cerebral/Uterine Resistivity Index) reflects not only the circulatory insufficiency of the placenta by alteration in the umbilical resistance index, but also the adaptive changes resulting in modification of the middle cerebral resistance index, it seemed to be a potentially useful tool in predicting adverse perinatal outcome in high risk cases. Our results support the correlation between abnormal fetal C/U RI and adverse perinatal outcome in patients with IUGR.

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