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Original Research Article

A study to evaluate a correlation between various Gray Scale parameters and period of gestation

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ABSTRACT

Background: Accurate prediction of the gestational age (GA) is very important in the management of obstetric patients for planning a timely and uneventful outcome. Fetuses with intrauterine growth restriction (IUGR) are at high risk for poor short- and long-term outcome. The present study was conducted with the aim to evaluate a correlation between various Gray Scale parameters and period of gestation.
Methods: A total of 100 clinically suspected FGR subjects were enrolled for the present study. Women with singleton pregnancies with fundal height being less than the period of gestation by 4 weeks or more and certainty of last menstrual period with previous 3 menstrual cycles were included in the present study. Ultrasound examination both by Gray Scale USG carried out serially every three weeks starting from 30 weeks till delivery. Chi-square test was used to compare the proportions while Independent Samples "t"-test was used to compare the parametric variables in two groups. Receiver-Operator curve analysis was performed to find out appropriate cut-off points for prediction of FGR.
Results: Diagnostic accuracy of TCD/AC ratio as a marker of FGR was found to be 77%, of HC/AC ratio was found to be 93% and FL/AC ratio was 59%.
Conclusions: Among three gray scale parameters being assessed, HC/AC ratio at 36 weeks was observed to be having 98.5% sensitivity and 82.9% specificity, thus showing the highest diagnostic accuracy (93%). However, from the point of view of early detection, TCD/AC ratio was found to be most efficient with 81.5% sensitivity and 68.6% specificity and overall diagnostic accuracy of 77%. Precision of Grayscale findings at later stage (36 weeks) are higher.

Keywords: FL/AC ratio, Gray scale USG, HC/AC ratio, TCD/AC ratio

INTRODUCTION

Accurate prediction of the gestational age (GA) is very important in the management of obstetric patients for planning a timely and uneventful outcome.[1] Fetuses with intrauterine growth restriction (IUGR) are at high risk for poor short- and long-term outcome.[2] Monitoring fetal growth and assessing its predictors have important place in antenatal care management.[3] Biparietal diameter, head circumference, abdominal circumference and femur length (FL) are considered reliable predictors and are used as routine parameters.

These parameters are helpful in the estimation of fetal age in patients whose fundal height on abdominal examination does not corresponding to the last menstrual period, in cases where the measurement is not reliable

femoral length and humeral length allow reliable estimation of fetal age. [1]

Accurate prediction of gestational age (GA) and birth weight (BW) is clinically important. Up to 10% of all liveborn babies and at least 30% of those of low birth weight suffer from fetal growth restriction; their perinatal mortality is four to 10 times higher than that of normally grown babies. Poor growth also exposes the fetus and the newborn to perinatal complications like neurodevelopmental disability.[3]

Although there are many underlying etiologies, IUGR resulting from placental insufficiency is most relevant clinically because outcome could be altered by appropriate diagnosis and timely delivery. A diagnostic approach that aims to separate IUGR resulting from placental disease from constitutionally small fetuses and those with other underlying etiologies (e.g., aneuploidy, viral infection, nonaneuploid syndromes) needs to integrate multiple imaging modalities. [2]

The present study was conducted with the aim to evaluate a correlation between various Gray Scale parameters and period of gestation.

METHODS

A total of 100 clinically suspected FGR subjects who reported to the Departments of Obstetrics and Gynecology, Radiology and Pediatrics, Era's Lucknow Medical College and Hospital, Lucknow were enrolled for the purpose of this study after informed consent in patient's language This study was approved by Institutional Review Board and Institutional Ethical Committee. The present study was carried over a period of eighteen months. Women with singleton pregnancies with fundal height being less than the period of gestation by 4 weeks or more4 and certainty of last menstrual period with previous 3 menstrual cycles (after withdrawal of oral contraceptive pills) were included in the present study. Patients with congenital malformations of the fetus were excluded from the study.

A detailed history and examination was done. Ultrasound examination by Gray Scale USG was carried out serially every three weeks starting from 30 weeks till delivery.

Procedure of Gray Scale Ultrasonography: The patient was advised to lie on her back. A film gel was applied to the abdomen to improve the conduction of sound. A transducer was then moved slowly over the abdomen, and the echoes of sound waves were recorded. The following parameters were recorded and measured by Hadlock's method incorporated in the USG software.

- TCD/AC ratio
- HC/AC ratio
- FL/AC ratio

After collection of data the clinical data was correlated with radiological findings using Statistical Package for Social Sciences Version 15.0. Chi-square test was used to compare the proportions while Independent Samples "t"-test was used to compare the parametric variables in two groups. Receiver-Operator curve analysis was performed to find out appropriate cut-off points for prediction of FGR.

RESULTS

A significant difference between FGR and TCD/AC ratio was seen (Table 1). It was seen that at all time intervals, the mean TCD/AC ratio in FGR group was significantly higher as compared to no FGR group.

Table 1: TCD/AC Ratio in two groups at different time intervals.

Time interval	Non-FGR Group (n=35)			FGR Group (n=65)			Statistical significance	
	Mean	SD	95% CI	Mean	SD	95%CI	"t"	"p"
30 week	12.87	2.82	11.90-13.84	15.46	2.15	14.92-15.99	5.127	<0.001
33 week	13.09	2.75	12.15-14.04	15.52	2.09	15.01-16.04	4.959	<0.001
36 week	13.17	2.67	12.26-14.09	15.56	1.95	15.07-16.04	5.105	<0.001
39 week	13.19	2.71	12.26-14.13	15.59	2.09	15.07-16.11	4.923	<0.001

In non-FGR group, the mean TCD/AC ratio was found to be 12.87±2.82 (95% CI 11.90-13.84), 13.09±2.75 (95% CI 12.15-14.04), 13.17±2.67 (95% CI 12.26-14.09) and 13.19±2.71 (95% CI 12.26-14.13) at 30 wk, 33 wk, 36 wk and 39 wk respectively. In contrast in FGR group, the mean TCD/AC ratio was found to be 15.46±2.15 (95% CI 14.92-15.99), 15.52±2.09 (95% CI 15.01-16.04), 15.56±1.95 (95% CI 15.07-16.04) and 15.59±2.09 (95% CI 15.07-16.11) at 30 wk, 33 wk, 36 wk and 39 wk respectively. Thus, we can clearly see that in the FGR group, the 95% confidence interval's lower limit was always higher than that of non-FGR group. The 30-wk TCD/AC ratio was regressed with the help of Receiver Operator Curve analysis to differentiate between non-FGR and FGR groups. A poor correlation (r=0.039;

p=0.437) was seen between gestational age and TCD/AC ratio.

Table 2: Receiver operator curve analysis to find out appropriate cut-off of TCD/AC ratio for FGR detection.

Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% confidence interval	
			Lower	Upper
0.762	0.055	<0.001	0.654	0.871

a. Under the nonparametric assumption; b. Null hypothesis: true area = 0.5

The analysis of diagnostic efficacy of TCD/AC ratio to detect FGR was checked in the present series and the results have been shown in Table 2. The area under curve was found to be 0.762. The cut-off value above 14.18 was regressed to be 81.5% sensitive and 68.6% specific (Table 2).

Table 3: Diagnostic efficacy of TCD/AC ratio as a marker of FGR (Cut-off 14.18).

TCD Ratio >14.18	Outcome		Total
	FGR (n=65)	No FGR (n=35)	
Positive	53	24	36
Negative	12	11	64
Total	65	35	100
Sensitivity	**Specificity**	**PPV**	**NPV**	**Diagnostic accuracy**
81.5	68.6	82.8	66.7	77.0

On evaluation, the cut-off value of 14.18 was found to be 81.5% sensitive and 68.6% specific with a positive predictive value of 82.8% and a negative predictive value of 37.5% (Table 3). The diagnostic accuracy was found to be 77%.

Table 4: HC/AC ratio in two groups at different time intervals.

Time interval	Non-FGR Group (n=35)			FGR Group (n=65)			Statistical significance	
	Mean	SD	95%CI	Mean	SD	95%CI	"t"	"p"
30 wk	1.08	0.07	1.05-1.10	1.10	0.07	1.08-1.12	1.580	0.117
33 wk	1.02	0.05	1.00-1.03	1.12	0.06	1.10-1.13	8.882	<0.001
36 wk	0.97	0.04	0.95-0.98	1.13	0.06	1.11-1.14	13.790	<0.001
39 wk	0.96	0.03	0.95-0.97	1.14	0.06	1.12-1.15	16.819	<0.001
Correlation with time	r=-0.669			r=0.219			Overall r= -0.081	

The mean HC/AC ratio was higher in FGR group as compared to non-FGR group at all the time intervals (Table 4). However, a significant difference between two groups was seen from 33 weeks onwards.

It was seen that in non-FGR group, the mean HC/AC ratio showed a regular decrease from 30 weeks (1.08±0.07; 95% CI 1.05-1.10) to 39 weeks (0.96±0.03; 95% CI 0.95-0.97), however, in FGR group a regular increase was seen from 30 weeks (1.10±0.07; 95% CI 1.08-1.12) to 39 weeks (1.14±0.06; 95% CI 1.12-1.15). In FGR group the mean HC/AC ratio was found to be above 1 at all the time intervals whereas in non-FGR group at 30 and 33 weeks it was found to be above 1 and from 36 weeks onwards its value was below 1. Overall an almost negligible negative correlation (r=-0.081) in HC/AC ratio and gestational age was seen.

However, in non-FGR group this correlation was moderately negative (r=-0.669) while in FGR group this was very mild and positive (r=0.219). The receiver operator curve analysis for detection of FGR was performed. As the mean values were different at different time intervals, four cut-off values were explored at different time intervals (Table 5).

Table 5: Receiver operator curve analysis to find out appropriate cut-off of HC/AC ratio for FGR detection.

Time	Area	Std. Error (a)	Asymptotic Sig. (b)	Asymptotic 95% confidence interval	
				Lower	Upper
30 wk	0.598	0.061	0.106	0.478	0.718
33 wk	0.919	0.029	<0.001	0.863	0.975
36 wk	0.991	0.008	<0.001	0.976	1.006
39 wk	0.999	0.001	<0.001	0.997	1.002

a. Under the nonparametric assumption; b. Null hypothesis: true area = 0.5

The area under curve was found to be ranging from 0.598 (30 weeks) to 0.999 (39 weeks). The maximum value was obtained at 39 weeks.

As the area under curve at 30 weeks provided only a limited diagnostic efficacy, it was not explored further. At 33 weeks, the cut-off value above 1.075 indicated 80% sensitivity and 85.7% specificity.

At 36 weeks, the cut-off value above 1.045 was 96.9% sensitive and 100% specific and at 39 weeks the cut-off value above 1.025 was found to be 98.5% sensitive and 100% specific.

As most of the studies have mentioned a cut-off value above 1 from 36 weeks onwards the diagnostic efficacy of HC/AC ratio was assessed for this value.

Table 6: Diagnostic efficacy of HC/AC ratio as a marker of FGR (Cut-off 1 at 36 week).

HC/AC Ratio >1	Outcome		Total
	FGR (n=65)	No FGR (n=35)	
Positive	64	6	70
Negative	1	29	30
Total	65	35	100

Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
98.5	82.9	91.4	96.7	93.0

HC/AC ratio >1 at 36 weeks showed to be 98.5% sensitive and 82.9% specific with a positive predictive value of 91.4% and negative predictive value of 96.7%. Overall diagnostic accuracy was found to be 93% (Table 6).

Table 7: FL/AC ratio in two groups at different time intervals.

Time interval	Non-FGR Group (n=35)			FGR Group (n=65)			Statistical significance	
	Mean	SD	95%CI	Mean	SD	95%CI	"t"	"p"
30 wk	22.89	2.20	22.13-23.64	23.94	2.40	23.35-24.54	2.158	0.033
33 wk	22.91	2.44	22.07-23.74	24.05	2.77	23.36-24.73	2.046	0.043
36 wk	23.01	2.66	22.09-23.92	24.07	2.66	23.37-24.77	1.828	0.071
39 wk	23.06	2.61	22.16-23.96	24.17	3.07	23.41-24.94	1.818	0.072
Correlation with time	r=0.029			r=0.029			r=0.028	

Statistically, a significant difference between two groups was seen for mean FL/AC ratio at 30 weeks and 33 weeks time intervals (Table 7). At 36 weeks and 39 weeks intervals there was no significant difference between the two groups. A very mild (almost negligible) positive correlation between gestational age and mean FL/AC was seen in both the groups. Calculation of cut-off point through receiver operator curve analysis has been shown in Table 8.

Table 8: Receiver operator curve analysis to find out appropriate cut-off of FL/AC ratio for FGR detection.

Time	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
				Lower	Upper
30 wk	0.632	0.057	0.030	0.520	0.744
33 wk	0.633	0.058	0.029	0.520	0.746
36 wk	0.628	0.058	0.035	0.513	0.742
39 wk	0.630	0.058	0.033	0.516	0.743

a. Under the nonparametric assumption; b. Null hypothesis: true area = 0.5

The area under curve ranged to be 0.628 (36 week) to 0.633 (33 week), thereby showing a very poor association. At 30 weeks the cut-off value >23.05 was regressed to be 58.5% sensitive and 57.1% specific. At 33 weeks same efficacy was seen at cut-off of 23.17 while at 36 weeks this value was found to be 23.47 and at 39 weeks it was 23.35. None of the choices showed a good diagnostic accuracy.

For the purpose of calculation of diagnostic efficacy, the cut-off value of 23.50 at 36 weeks was chosen.

The FL/AC ratio >23.5 was found to be 58.5% sensitive, 60% specific and had a PPV of 73.1% and a NPV of 43.8% (table 9 and graph 3). Overall diagnostic accuracy of the test was only 59%.

Table 8: Receiver operator curve analysis to find out appropriate cut-off of FL/AC ratio for FGR detection.

FL/AC Ratio >23.5	Outcome		Total
	FGR (n=65)	No FGR (n=35)	
Positive	38	14	52
Negative	27	21	48
Total	65	35	100

Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
58.5	60.0	73.1	43.8	59.0

DISCUSSION

Fetal growth restriction (FGR) is a condition in which fetus does not reach its growth potential.[5] The present study was conducted at a tertiary care centre in Lucknow which was attended by patients from both rural and urban segments. Gray scale ultrasound parameters studied were TCD/AC ratio, HC/AC ratio and FL/AC ratio.

On Gray scale analysis, a statistically significant difference between study and control group was observed for TCD/AC ratio in both the groups with FGR group showing significantly higher mean value as compared to non-FGR group. At 30 weeks TCD/AC ratio with cut-off >14.18 was found to be 81.5% sensitive and 68.6% specific.

In the study of Haller et al TCD/AC ratio showed a poor correlation with gestational age (r2 = 0.15788) and a slight increase was noted during gestation.[6] In present study too, a poor correlation (r=0.028) was seen between TCD/AC ratio and gestational age. In this study too, a slight increase in TCD/AC ratio was seen from 30 weeks to 39 weeks. Haller et al reported that a TCD/AC ratio greater than 15.5 was present in 80% of SGA infants when measurements were performed within 1 week of delivery. However, in present study a TCD/AC ratio above 14.18 was found to be having 77% accuracy in detection of FGR. Thus, present findings are in concurrence with the findings of Haller et al.[6]

In present study it was seen that at all time intervals there was a statistically significant difference in TCD/AC ratio between FGR and non-FGR groups, it was seen that the mean value of TCD/AC ratio in FGR group was always higher to the upper limit of 95% CI of non-FGR group. Campbell et al[7] have reported the mean TCD/AC ratio to be 13.7% (fifth and 95th percentiles of 11.9 and 15.9%, respectively. They have found that this ratio was gestational age-independent and have applications in assessment of fetal growth rate. In the present study TCD/AC ratio was found to be 81.5% sensitive in detection of FGR, however, in the study of Ott W,[8]

TCD/AC ratios were reported to be only 53% sensitive in predicting IUGR. Thus, present results are in consistence with the results of Tongsong et al who reported that 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.[9] Though the cut-off value obtained in the present study was 14.18%, yet it was able to provide a good diagnostic accuracy. Though the incidence of higher false positivity affected the specificity and negative predictive value to some extent in present study. The mean HC/AC ratio was higher in FGR group as compared to non-FGR group at all the time intervals. However, a significant difference between two groups was seen from 33 weeks onwards.

The mean HC/AC ratio was higher in FGR group as compared to non-FGR group at all the time intervals. However, a significant difference between two groups was seen from 33 weeks onwards. It was seen that in non-FGR group, the mean HC/AC ratio showed a regular decrease from 30 weeks (1.08±0.07; 95% CI 1.05-1.10) to 39 weeks (0.96±0.03; 95% CI 0.95-0.97), however, in FGR group a regular increase was seen from 30 weeks (1.10±0.07; 95% CI 1.08-1.12) to 39 weeks (1.14±0.06; 95% CI 1.12-1.15).

In FGR group the mean HC/AC ratio was found to be above 1 at all the time intervals whereas in non-FGR group at 30 and 33 weeks it was found to be above 1 and from 36 weeks onwards its value was below 1. With time a moderately negative correlation between RI and gestational age was observed (r=-0.669) in non-FGR group while in FGR group this was very mild and positive (r=0.219).

HC/AC ratio >1 at 36 weeks showed to be 98.5% sensitive and 82.9% specific with a positive predictive value of 91.4% and negative predictive value of 96.7%. Overall diagnostic accuracy was found to be 93%.

In a non-FGR normal pregnancy the HC/AC ratio is >1.0 prior to 36 weeks however, with increase in gestational age the ratio shows a decrease. In FGR pregnancy, this ratio either does not change or shows increment.[10] In present study, we found similar patterns. At 30 and 33 weeks, the mean HC/AC ratio in both FGR and non-FGR groups was above 1.

However, on 36 weeks and 39 weeks, the mean HC/AC ratio in non-FGR group was found to be less than 1 while in FGR group, it was seen to be above 1. According to Peleg et al between 20 and 36 weeks of gestation, the HC/AC ratio normally drops almost linearly from 1.2 to 1.0.[11] The ratio is normal in the fetus with symmetric growth restriction and elevated in the fetus with asymmetric growth restriction. In a study by Blackwell et al, the asymmetric-IUGR group had HC/AC ≥95% tile for GA, and the symmetric-IUGR group had HC/AC <95% tile.[12]

In present study too, at all time intervals the upper limit of 95% confidence interval in non-FGR group was either

equal (at 33 weeks) or below (at all the other time intervals) the mean value of HC/AC ratio in the FGR group. Thus HC/AC ratio in present study was found to be a significant predictor of FGR. In the study of Hebbar et al a statistically significant difference in HC/AC ratio of non-FGR and growth restricted group was seen with non-FGR group showing a significantly lower value as compared to HC/AC ratio.[13]

Present results are in accordance with their findings. In their study they had found a cut-off value of 1.02 to be 67% sensitive, 65% specific with a PPV of 54% and NPV of 76%. However, in our study the cut-off value of 1 was found to be 98.5% sensitive, 82.9% specific, with a PPV of 91.4% and an NPV of 96.7%. Thus, results in present study were found to be provide diagnostic more accurate information as compared to the other studies. The study of Jasovic-Siveska et al showing HC/AC ratio at different gestational ages showed it to be significantly higher in gross IUGR group as compared to that in low IUGR group at 26, 32, 36 and 38 weeks of gestational age.[14] In present study, except for 30 weeks, at all the time intervals the mean HC/AC ratio of FGR group was significantly higher as compared to non-FGR group.

Statistically, a significant difference between two groups was seen for mean FL/AC ratio at 30 weeks and 33 weeks time intervals. At 36 weeks and 39 weeks intervals there was no significant difference between the two groups. A very mild (almost negligible) positive correlation between gestational age and mean FL/AC was seen in both the groups which is not statistically significant. The FL/AC ratio >23.5 at 36 weeks was found to be 58.5% sensitive, 60% specific and had a PPV of 73.1% and an NPV of 43.8%. Overall diagnostic accuracy of the test was only 59%.

Benson et al have shown FL/AC ratio to be a poor prognostic indicator of IUGR.[15] They reported that with a cut-off of 23.5, the sensitivity was 56% and the specificity 74%. In present study, the cutoff of 23.5 showed to be 58.5% sensitive, 60% specific and had a PPV of 73.1% and a NPV of 43.8%, thus confirming the findings of Benson et al.[15] Ott WJ and Shalev E et al have used cut-off varying from 24% to 27% but showed a very low sensitivity.[8,16] However, in the study of Hebbar et al, FL/AC ratio above 24% was found to be 77% sensitive, 73% specific and having 64% PPV and 84% NPV.[13] The high variability in selection of a cut-off and its diagnostic efficacy act as a deterrent for broader use of FL/AC ratio as a diagnostic test for detection of FGR.

The findings in present study suggested that while Gray scale ultrasound provide maximum efficacy at 36 week gestational age (HC/AC and FL/AC ratio) though TCD/AC ratio showed a promising efficacy at 30 weeks gestational age itself. Thus, it was observed that both gray scale ultrasound for all parameters and resistive index of uterine artery and umbilical artery both showed a promising utility as a diagnostic marker for FGR.

CONCLUSION

Among three gray scale parameters being assessed, HC/AC ratio at 36 weeks was observed to be having 98.5% sensitivity and 82.9% specificity, thus showing the highest diagnostic accuracy (93%). However, from the point of view of early detection, TCD/AC ratio was found to be most efficient with 81.5% sensitivity and 68.6% specificity and overall diagnostic accuracy of 77%.

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