VOLUME-6 | ISSUE-3 | MARCH - 2017 • ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

DIAGNOSTIC VALIDITY OF GESTATIONAL AGE INDEPENDENT MORPHOMETRIC INDICES IN ASYMMETRIC FOETAL GROWTH RESTRICTION – A STUDY AT A TEACHING HOSPITAL IN SOUTH INDIA.

Obstetrics

KEYWORDS: Foetal growth restriction, TCD/AC, HC/AC, BPD/AC, FL/AC.

Farheen Naaz — Department of Obstetrics & Gynaecology, ESIC Medical College, Sanathnagar, Hyderabad.

Mohammed Ismail Khan — Department of Obstetrics & Gynaecology, ESIC Medical College, Sanathnagar, Hyderabad. - Corresponding Author.

ABSTRACT

Background: Foetal Growth Restriction(FGR) is an undesirable obstetric diagnosis in view of the dire consequences that it poses to the foetus and neonate. Early diagnosis is essential to plan appropriate surveillance methods and implement obstetric protocols. This raises a need for an index which has high diagnostic validity and accuracy.

Materials and Methods: The study was conducted as a prospective observational study on 125 antenatal cases in the third trimester of pregnancy. Weekly foetal biometric scans were performed. After birth the diagnosis was made by calculating the ponderal index and birth weight centile. Diagnostic validity and accuracy were then calculated.

Results: TCD/AC appeared as the best index and FL/AC emerged as the index with least accuracy. The sensitivity, specificity, PPV and NPV of TCD/AD were 83.13%, 90.48 %, 94.52% and 73.08 % respectively, compared to 67.47%, 73.81 %, 83.58%, 53.45 % respectively for FL/AC. A difference of 4.82% in sensitivity, 7.14% in specificity, 4.35% in PPV and 6.81% in NPV was noted between HC/AC and BPD/AC, with a higher validity favoring HC/AC.

Conclusions: TCD/AC appears to be a gestational age independent index with relatively higher sensitivity and specificity. A higher accuracy in the diagnosis of FGR could help improve pregnancy outcomes.

INTRODUCTION

The Royal College of Obstetricians and Gynaecologists (RCOG) defines small for gestational age (SGA) foetus as foetal abdominal circumference (AC) or estimated foetal weight (EFW) less than 10th centile [1]. The RCOG further classifies SGA fetuses into constitutionally small and foetal growth restriction (FGR).

Constitutionally small refers to a foetus that fulfills the criteria of SGA but is found normal when it's growth characteristics are plotted on a maternal customized centile graph which implies that the fetus is normal for maternal ethnicity and size. On the other hand FGR refers to a pathological restriction of the genetic growth potential. This implies that the fetus is compromised hence FGR is associated with poor perinatal and infant outcomes [1].

FGR has conventionally been classified as symmetric and asymmetric depending on the gestational age (GA) of onset, as variable aetiologies operate at different GA.

FGR predisposes a fetus to adverse outcomes in fetal, neonatal and infantile periods whose sequelae continue well into childhood and adulthood. Perinatal mortality is increased in the FGR foetus and newborn [2]. If the baby survives, the chances of suffering with respiratory distress, necrotizing enterocolitis, perinatal asphyxia and hypoxic ischemic encephalopathy are high. Such infants are at higher risk of sepsis because of a compromised immune system. In long-term these babies are shorter and lighter, more likely to be diagnosed with cerebral palsy and have a lower IQ [3].

Intrauterine diagnosis of FGR is essential to plan and implement appropriate management protocols in fetal interest. Such diagnosis is dependent upon assessment of fetal growth by sonographic measurements. Abdominal circumference (AC), head circumference (HC), biparietal diameter (BPD) and femur length (FL) have specific GA matched centiles which predict fetal growth patterns but sometimes they are clinically not applicable due to uncertainties in menstrual dates. This has lead to the use of GA independent indices namely HC/AC, BPD/AC and FL/AC. AC is considered as the earliest parameter indicating growth impairment [4] due to its easy variability with changes in liver glycogen stores. HC, BPD and FL are not easily affected by late onset FGR. When these indices are compared to AC which varies rapidly due to growth aberrations we get GA independent ratios.

Though HC, BPD and FL are relatively unaffected in asymmetric FGR, they could be affected in early onset FGR. Hence transverse cerebellar diameter (TCD) emerges as a better indicator of gestational age. It is relatively resistant to hypoxia due to the brain sparing effect which ensures blood supply to the brain is maintained at the cost of systemic hypoperfusion[5]. Thus the morphometric relation of TCD/AC appears a better indicator of detecting FGR [6].

The study aims at assessing and evaluating various age independent indices used in the diagnosis of FGR. Four indices namely, HC/AC, FL/AC, BPD/AC and TCD/AC, which are commonly used in clinical practice, were evaluated for their diagnostic performance. All these ratios show insignificant correlation to GA when analysed by regression and hence are GA independent [7, 8, 9]

MATERIALS AND METHODS:

The study was conducted at ESIC Medical College Hospital, which is a tertiary care teaching hospital with referrals from 35 ESIC hospitals and dispensaries, in addition to its own patients. The study was conducted over a year from 2015 to 2016, on 125 consenting patients as a prospective observational study. The study was taken up after approval from Institutional Ethics Committee.

Expectant mothers in third trimester of pregnancy were included in the study with previous normal scan findings thus ruling out symmetric FGR. Those with EFW less than 10th centile, at eligibility were then included after obtaining consent for collecting, processing and publishing their data. A 3.5MHz transducer was used for all morphometric analysis.

GA was calculated from early first trimester scan, calculated by crown rump length (CRL). For calculating expected ratios, foetal biometric data for AC, HC, BPD and FL proposed by Sabbagha et al was used [10]. Biometric values for TCD proposed by Sniders et al were used [11]. Ratios were calculated considering 50th centile biometry values. These were considered for supporting or refuting the diagnosing of asymmetric FGR.

AC was measured in the transaxial view of the fetal abdomen at the level of the fetal liver, using the umbilical portion of the left portal vein and stomach bubble as landmarks. The measurement was taken from the outermost aspects of the fetal soft tissues by tracing the trackball.

HC was measured in the transaxial plane traversing the thalami and equidistant from the temporoparietal bones with cavum septum pellucidum appearing anteriorly. When both cerebral hemispheres and calvaria appeared symmetric an ellipse was drawn with the

calipers till the outer perimeter of the calavaria. At the same point the BPD was calculated from one outer end to the other inner end. Similarly in the same plane when the transducer was rotated by 30° the cerebellum and cistern magna became visible. The cerebellum appeared as a homogenously echogenic and triangular structure and TCD was measured by placing the calipers end to end.

The FL was measured along the long axis of the bone from one end to the other, disregarding the curvature and excluding the femoral neck and both epiphyseal cartilages and considering only the osseous part.

The pregnancy was monitored with antepartum surveillance and delivery was planned in accordance with Greentop Guideline – 31[1]. Weekly sonographic biometry was performed. After birth ponderal index (PI) was calculated by using the formula, $PI = \frac{weight}{height^3} \times 100$ (where weight is in kilograms and height is in meters). A value below 2 was considered confirmatory for FGR or foetal wasting [12]. Birth weight of neonate, less than 10th centile on a GA specific centile chart also confirmed or ruled out FGR. The previous scan biometric ratios were then considered and compared with post natal diagnosis of FGR and the diagnostic validity .....(of ratios calculated using medcalc online software).

Explanation: This text illustrates the most important part of method and if this becomes missing then paper may not be understood by the reader. This is there in manuscript but might have been missed in typesetting.

Inclusion Criteria:

1. Age 18 – 40 years.
2. USG criteria for FGR (EFW < 10th centile).
3. LMP known from first trimester (CRL).
4. Third Trimester of pregnancy.
5. Late onset FGR.

Exclusion Criteria:

1. Early onset FGR.
2. Unbooked / referred cases.
3. Twin gestation.
4. Foetal anomalies and / or chromosomal anomalies.
5. Absent or reduced end diastolic velocity (AREDV) at eligibility.
6. Maternal stature less than 145cm.
7. Preexisting or coexisting obstetric/placental pathology.

Research Involving Human Participants:

- All procedures performed on the patient were in accordance with the ethical standards of the institutional and national research committee and with the 1975 Helsinki declaration and its latest amendment in 2000 and other comparable ethical standards.
- All treatment protocols followed are in accordance with the latest accepted Evidence Based Medicine Norms of the RCOG
- Foetal sex was neither detected nor informed, in accordance with the PNDT Act 1994.

RESULTS:

We had 4163 deliveries in the past one year; out of these 732 were SGA babies, which bring the incidence to 17.58%. Of these, 125 consenting patients fulfilling our criteria were considered for study. Table-1, shows the demographic details of the study group, when evaluated by goodness of fit, they show a statistically significant distribution. Maximum number of cases were seen in 21 – 25 years age bracket, in primigravidas, 36 to 37 completed weeks of gestation and in mothers with BMI <18.kg/m^2.

TABLE – 1 DEMOGRAPHIC CHRACTERISTICS

Demographic Characteristics						P value†
Distribution of age						
Age	< 20 yrs	21– 25 yrs	26– 30 yrs	31 – 35 yrs	>35 yrs	< 0.001*
Frequency (N = 125)	12	56	36	15	6	
Distribution of order of birth						
Parity	Primi	Gravida 2	Gravida 3	Gravida 4	Grand Multi	< 0.001*
Frequency (N = 125)	55	36	18	11	5	
Distribution of gestational age at presentation						
Gestational age	30^{+0} wks to 31^{+6} wks	32^{+0} wks to 33^{+6} wks	34^{+0} wks to 35^{+6} wks	36^{+0} wks to 37^{+6} wks	38^{+0} wks to 39^{+6} wks	< 0.001*
Frequency (N = 125)	19	23	27	37	19	
Distribution of body mass index (BMI)						
BMI	< 18.5 kg/m^2	18.5 - 24.9 kg/m^2	25 – 29.9 kg/m^2	30 – 34.9 kg/m^2	>35 kg/m^2	<0.001*
Frequency (N = 125)	43	34	26	14	8	

† - Chi square calculated by goodness of fit | * - Statistically Significant

Table – 2 shows the biometric values and calculated ratios from GA at viability(Indian standards), the data is collected from Sabbagha et al [10] for AC, HC, BPD and FL. TCD are adopted from Snijders et al [11]. As these are age independent ratios, the mean of ratios is calculated and considered as the cutoff point for classifying foetuses as FGR.

TABLE – 2 GESTATIONAL AGE INDEPENDENT RATIOS

Gestational age	AC* [10] (mm)	TCD* [11] (mm)	**TCD/ AC (%)**	HC* [10] (mm)	**HC/ AC**	BPD* [10] (mm)	**BPD/ AC (%)**	FL* [10] (mm)	**FL/A C (%)**
28	253	32	**12.6**	270	**1.0**	72	**28.4**	52.5	**20.75**
29	269	33	**12.2**	280	**1.0**	75	**27.8**	54.5	**20.26**
30	274	35	**12.7**	285	**1.0**	78	**28.4**	57.5	**20.98**
31	280	36	**12.8**	290	**1.0**	80	**28.5**	59.5	**21.25**
32	287	37	**12.8**	290	**1.0**	83	**28.9**	62	**21.6**
33	290	39	**13.4**	295	**1.0**	85	**29.3**	63	**21.72**
34	301	40	**13.2**	305	**1.0**	87	**28.9**	65	**21.59**
35	322	41	**12.7**	315	**0.97**	88	**27.3**	67	**20.8**
36	333	42	**12.6**	320	**0.96**	90	**27.0**	68	**20.42**
37	344	43	**12.5**	325	**0.94**	92	**26.7**	70	**20.34**
38	357	44	**12.3**	325	**0.91**	93	**26**	71	**19.88**
39	359	45	**12.5**	330	**0.91**	94	**26.1**	73	**20.33**
Mean	-	-	**12.69 ±0.33**	-	**0.97± 0.03**	-	**27.7± 1.13**	-	**20.82 ±0.6**
ULN§	-	-	**13**	-	**1.0**	-	**29**	-	**21.5**

ULN – Upper limit of normal | *- 50th centile value | § - approximated to nearest value

[10] - Tamura, R, Sabbagha, R, et al, Glob. libr. women's med.2008. (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10207.

[11] - Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. Ultrasound Obstet Gynecol. 1994;4(1):34-48.

Table – 3 illustrates the false positive and false negative rates with different age independent ratios used. TCD/AC had the least false positive rate (9.5%) whereas FL/AC had highest false positive rate (26.19%). Maximum number of cases were missed using FL/AC (32.53%) compared to 16.8% missed using TCD/AC. A difference of 7.14% and 4.82% in false positive and false negative rates was observed between HC/AC and BPD/AC, with a better outcome associated with HC/AC.

TABLE – 3 FALSE POSITIVE AND FALSE NEGATIVE RATES WITH VARIOUS INDICES

Parameter	TCD/AC	HC/AC	BPD/AC	FL/AC
True Positive (n)	69	66	62	56
False Negative (n)	14	17	21	27
False Positive (n)	4	6	9	11
True Negative (n)	38	36	33	31

VOLUME-6 | ISSUE-3 | MARCH - 2017 • ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

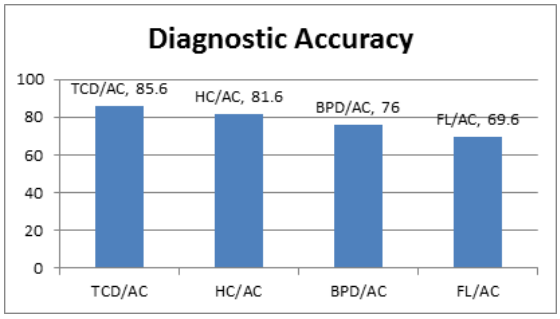
False Positive Rate	9.5%	14.28%	21.42%	26.19%
False Negative Rate	16.86%	20.48%	25.3%	32.53%

In Table – 4, various diagnostic validity indicators have been enlisted. Disease prevalence was found to be 66% after post natal confirmation with PI and centile marked age specific growth charts. Highest sensitivity (83%) and specificity (90%) was noted with TCD/AC, FL/AC showed the lowest sentistivity and specificity of 67.47% and 53.45% respectively. HC/AC showed a better diagnostic validity compared to BPD/AC (sensitivity 79% vs 74% and specificity 85% vs 78%). The diagnostic accuracies hence obtained are represented in Figure -1.

TABLE – 4 DIAGNOSTIC VALIDITY OF VARIOUS INDICES

Characteristics	TCD/AC	HC/AC	BPD/AC	FL/AC
Sensitivity (95% CI)	83.13% (73.32% - 90.46%)	79.52% (69.24% - 87.59%)	74.70% (63.96% - 83.61%)	67.47% (56.30% - 77.35%)
Specificity (95% CI)	90.48 % (77.38% - 97.34%)	85.71 % (71.46% - 94.57%)	78.57 % (63.19% - 89.70%)	73.81 % (57.96% - 86.14%)
PPV (95% CI)	94.52% (87.11% - 97.78%)	91.67% (83.88% - 95.88%)	87.32% (79.21% - 92.57%)	83.58% (74.99% - 89.63%)
NPV (95% CI)	73.08 % (62.50% - 81.55%)	67.92 % (57.66% - 76.71%)	61.11 % (51.25% - 70.14%)	53.45 % (44.52% - 62.16%)

FIGURE – 1DIAGNOSTIC ACCURACY WITH VARIOUS INDICES



DISCUSSION:

FGR is a challenging diagnosis with dire consequences in terms of foetal and perinatal outcomes. Late onset FGR could be an indicator of hypoxia in the growing foetus which could cause foetal distress or demise. A growth lag would also imply iatrogenic prematurity and organ immaturity which could potentially complicate neonatal period. Matters of grave concern are the long term effects of FGR on childhood development and adult well being. Added to this is the fact that FGR has high incidence (~10%) and low recognition (< 40%) in general obstetric population [4].

AC is the most easily modifiable parameter in late onset FGR whereas FL, HC, BPD and TCD are relatively non modifiable. These non modifiable parameters, which act as functions of GA are then compared to AC. This serves best to demonstrate foetal wasting of late onset in patients with unreliable dates. Campbell and Thoms first suggested the use of HC/AC for determination of FGR [7] . Blood supply to the head is maintained at the cost of systemic circulation due to the 'brain sparing effect' as a result very less changes in head biometry are seen in late onset FGR [5,9,13].

Further studies reported that cerebellum is present in posterior cranial fossa it is well from external compression. It has also been documented that cerebellar growth is more preserved compared to other cerebral structures [14]. The growth spurt of cerebellum is also unique in that it starts late and ends sooner than that in other parts of the brain [15].

Meyer et al reported a higher diagnostic sensitivity with TCD/AC compared to HC/AC and our study is in agreement with their findings [16]. Campbell et al reported a specificity of 77% with the use of TCD/AC and our findings are consistent with their original work [17]. We report a specificity of 85% with HC/AC which is again compliant with the findings of Meyer et al [16]. A difference has been observed between HC/AC and BPD/AC which could possibly be explained by the fact that BPD is more related to growth and is easily modified by disorders which alter the shape of the skull [18]. Original work by Hadlock et al reported a sensitivity of 60% with the use of FL/AC which tends to resemble the findings in our study.

A study done on Indian patients comparing TCD/AC to HC/AC also concluded a higher diagnostic validity with the use of TCD. Considering the evidence TCD/AC appears to be a reliable index for diagnosing and assessing asymmetrical FGR foetuses. This is reinforced by the fact that TCD/AC is a stable, GA independent index which doesn't appear to change after 20 weeks of gestation [6, 19]. There is availability of strong evidence that TCD is also an accurate measure of calculating the GA [20,21] but this was not considered as it was not included in our operational definition.

CONCLUSION:

Though FGR remains a frustrating obstetric diagnosis due to lack of specific evidence based interventions, to prevent or revert the effects of FGR on the foetus. Still the diagnosis remains an important step to plan surveillance and determine the time and mode of delivery. An antenatal diagnosis of FGR would thus help us plan appropriate measures to prevent further irreversible hypoxic damage to the foetus.

DECLARATIONS:

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of ESIC Medical College.

ACKNOWLEDGEMENT:

The authors sincerely thank the Dr.M. Srinivas (Dean, ESIC Medical College, Hyd), Dr. T. Madhuri (Academic Registrar, ESIC MC) and Dr. M. Ashwin Kumar (Incharge, Medical Education Unit, ESICMC), for their continued efforts in our academic growth and enlightenment. The authors also thank the Department of Radiology, ESICMC for their co-operation and support.

REFERENCES:

[1] Royal College of Obstetricians and Gynaecologists. (2014), "The Investigation and Management of the Small–for–Gestational–Age Fetus." Green top Guideline No. 31. 2nd edition.
[2] Ann Quinton, Colleen Cook, Michael Peek. (2015), "The prediction of the small for gestational age fetus with the head circumference to abdominal circumference (HC/AC) ratio: a new look at an old measurement." Sonography, 2, 27–31.
[3] Pallotto EK, Kilbride HW. (2006) "Perinatal outcome and later implications of intrauterine growth restriction." Clin Obstet Gynecol, 49, 257–69.
[4] Bhimarao, Rashmi M. Nagaraju, Venkataramana Bhat, Puttanna VN Gowda. (2015) "Efficacy of Transcerebellar Diameter/Abdominal Circumference Versus Head Circumference/Abdominal Circumference in Predicting Asymmetric Intrauterine Growth Retardation." Journal of Clinical and Diagnostic Research, 9(10), 1-5.
[5] Vinkensteijn AS, Mulder PG, Wladimiroff JW. (2000) "Fetal transverse cerebellar diameter measurements in normal and reduced fetal growth." Ultrasound Obstet Gynecol, 15(1), 47-51.
[6] Saifon Chawanpaiboon, M.D., Sujin Kanokpongsakdi, M.D., Chanchai Vantanasiri, M.D. (2008) "Predicting Fetal Intrauterine Growth Retardation by Using Reference Centile Charts for the Ratio of Fetal Transverse Cerebellar Diameter to Abdominal Circumference in a Thai Population." Siriraj Med J, 60(6), 316 – 319.
[7] Campbell S, Thoms A. (1977) "Ultrasound measurement of the fetal head to abdomen circumference ratio in the assessment of growth retardation." Br J Obstet Gynaecol, 84, 165–74.
[8] Frank P. Hadlock, Russell L. Deter, Ronald B. Harrist, Ellen Roecker, Seung K. Park. (1983) "A Date-Independent Predictor of Intrauterine Growth Retardation: Femur Length/Abdominal Circumference Ratio". AJR, 141, 979-984.
[9] Campbell WA, Nardi D, Vintzileos AM, Rodis JF, Turner GW, Egan JF. (1991) "Transverse cerebellar diameter/abdominal circumference ratio throughout pregnancy: a gestational age-independent method to assess fetal growth." Obstet Gynecol, 77(6), 893-896.
[10] Tamura, R, Sabbagha, R, et al, Glob. libr. women's med.,(ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10207.
[11] Snijders RJ, Nicolaides KH. (1994) "Fetal biometry at 14-40 weeks' gestation." Ultrasound Obstet Gynecol, 4(1), 34-48.
[12] A. Indrayani, L. Satyanarayana. (2000) "Reference values in medicine and validity of diagnostic tests." Indian Pediatrics, 37, 285-291.

[13] Hill, Lyndon M. MD; Guzick, David MD, PhD; Rivello, Dawn RDMS; Hixson, Joyce RDMS; Peterson, Carol RDMS. (1990) "The Transverse Cerebellar Diameter Cannot be Used to Assess Gestational Age in the Small for Gestational Age Fetus." Obstet and Gynecol,75(3), 329-333.
[14] Behrman RE, Lees MH, de Peterson EN, Lannoy CW, Seeds AE. (1970) "Distribution of the circulation in the normal and asphyxiated primate." Am J Obstet Gyneco1.8, 956–96.
[15] Dobbing J, Sands J. (1973) "Quantitative growth and development of human brain." Arch Dis Child, 48, 757-767.
[16] Meyer WJ, Gauthier D, Ramakrishnan V, Sipos J. (1995) "Ultrasonographic detection of abnormal fetal growth with the gestational age-independent, transverse cerebellar diameter/abdominal circumference ratio." Am J Obstet Gynecol, 171(4), 1057-1063.
[17] Campbell WA, Vintzileos AM, Rodis JF, Turner GW, Egan JF, Nardi DA. (1994) "Use of the transverse cerebellar diameter/abdominal circumference ratio in pregnancies at risk for intrauterine growth retardation." J Clin Ultrasound, 22, 497–502.
[18] Prabhat Goel, Mukesh Singla, Rashmi Ghai, Shilpi Jain, Virendra Budhiraja, CS Ramesh Babu. (2010) "Transverse Cerebellar Diameter – A marker for estimation of Gestational Age." J. Anat Soc. India, 59(2), 158-161.
[19] Dhumale H, Pujar YV, Shravage JC, Bellad MB, Sherigar BY, Durdi GS, et al. (2010) "Fetal Transcerebellar Diameter to Abdominal Circumference Ratio (TCD/AC) in the Assessment of Normal Fetal Growth." Donald School Journal of Ultrasound in Obstetrics & Gynecology, 4(4), 448-450.
[20] Dilmen G, Toppare MF, Turhan NO, Ozturk M, Isik S. (1996) "Transverse cerebellar diameter and transverse cerebellar diameter/abdominal circumference index for assessing fetal growth." Fetal Diagn Ther, 11(1), 50-56.
[21] Singhakom N, Chawanpaiboon S, Titapant V. (2004) "Reference centile charts for ratio of fetal transverse cerebellar diameter to abdominal circumference in a Thai population." J Med Assoc Thai, 87(3), 54-58.