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CEREBRAL VENTRICLE MEASUREMENT USING A STANDARDIZED APPROACH: RELIABILITY AND AGREEMENT AMONG SONOGRAPHERS

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ABSTRACT

Introduction: Fetal cerebral ventriculomegaly (FCV), It is an important finding during routine obstetrics sonography since the presence of ventriculomegaly portends fetal anomalies.

Objectives: This work investigates, using a previously described standardized technique that incorporates a scoring system, the interrater variability in the measurement of fetal ventricular diameter (FVD) and compares nomograms obtained via this method with previously reported nomograms.

Materials and Methods: The FVD of two hundred and forty-nine singleton fetuses between 18- and 38 weeks FGA were measured, with the first 30 measured twice by two sonographers. Inter- and intraclass correlation coefficients, repeatability coefficient, and limits of agreement were calculated. Polynomial regression was used to generate a nomogram, which was compared to previous ones.

Results: The mean ± SD of FVD was 0.43±0.14cm, with male fetuses having a significantly higher value than females. Fetal lie and trimester were not associated with FVD measurements. There was excellent and very good repeatability within and between sonographers. The normal range obtained using this technique was lower than previously reported values.

Conclusion: Using the standardized technique earlier proposed, FVD measurements are highly reproducible and repeatable between and within sonographers. Also, the nomogram generated report a mean FCV of 0.43 ± 0.14cm, with an upper limit of normal as 10.2cm.

INTRODUCTION

Fetal cerebral ventriculomegaly (FCV), the commonest fetal anomaly associated with the brain[1,2], is said to be diagnosed sonographically when the posterior horn of the lateral ventricular atrium or fetal ventricular diameter (FVD) measures above 10 mm ——[38]. It is an important finding during routine obstetrics sonography since the presence of ventriculomegaly portends fetal anomalies. In clinical practice, opinions have differed as to the upper limit of normal [9], and there are reported incidences of false-positive and

true negative diagnoses often arising from incongruent initial and second-opinion scans [10]. Different upper limits of normal have been reported by several authors, with some suggesting a range instead of a fixed upper limit. For instance, Chiu and colleagues [11] in a study involving 421 cases, classified ventriculomegaly as mild, moderate, and severe, with a subset falling under a "gray zone". Also, Devaseelan *et al [12]* classified ventriculomegaly as mild (10.1-12.0 mm) and moderate (12.1-15.0 mm). Other authors reported a fixed value as the upper limit of normal. Hilpert *et al* [3] in an old study found a mean value of 6.6mm and suggested an upper limit of four standard deviations from the normal, which is 12mm. More recent findings place the value at 10mm [9].

Though a consensus on the upper limit is important to avoid false positives, the accuracy of the measurements by the sonographers is also important. This is because fundamental clinical decisions such as termination of pregnancy is a frequently considered option even for mild to moderate cases [11,13]. Ultrasound remains an easily accessible and very accurate method of evaluating the fetal ventricles, but results are operator dependent. This could adversely affect the measurements obtained, especially when the clinician requests for a second opinion scan. A study has demonstrated the possibility of measurement errors during FVD measurements, but equally proposed possible corrections. [6]. The effect of measurement errors could be substantially reduced if a standardized approach is used by the sonographers during FVD assessment. In a recent study by Guibaud [14], a method that involved an image scoring system was proposed as a standardized approach towards scanning the FCV and obtaining accurate FVD. [14]. This method, in our opinion could be a highly reproducible technique among sonographers, since it involves an independent image scoring that will ensure that the scan plane used for measurement is reproducible and repeatable. This will in turn reduce the variability of measurements between and within raters. In the clinical work up for FCV, an upper limit of normal and a standardized approach towards scanning and measuring would improve the accuracy of measurements and clinical decisions taken. In this study, we aim to measure the FCV of fetuses using a standardized approach in order to assess the reproducibility of this method within and between experienced sonographers specialized in obstetric ultrasound, and to develop a population specific nomogram of the FVD and determine how the values obtained using the standardized technique compare with previously obtained nomograms.

METHODOLOGY

This is a prospective cross-sectional study involving systematically sampled gravid participants referred for a normal obstetric scan in a federal medical center between May 2018 and August 2019. Ethical clearance was obtained from the ethics committee of a university teaching hospital (No: NHREC/05/01/2008B-FWA00002458-1 RB00002323). Participants included in the study were: (a) singleton pregnancies with completed weeks of FGA from 15 – 40 weeks, (b) estimated fetal weight between the 5th and 95th percentile, and (c) no sonographically detectable fetal abnormality. Participants with current or previously reported case of maternal hypertension, an amniotic fluid index value of more than 27.1 cm [15], and other complications in pregnancy were excluded from the study. The purpose of the study was carefully explained to the participants and a written consent obtained from each of them. Using a 2 – 8MHz variable frequency curvilinear probe (DCN-3 Mindray, Shenzhen, 2012), the fetal lie was established, followed by a general assessment of the fetus for the presence of an anomaly. Following previously recommended scanning protocol [14], a transverse section of the fetal head was first obtained, demonstrating the cavum septum pellucidum to be perpendicular to the ultrasound beam and equidistant from both calvarial margins. Further heeling, rotation and angulation of the probe demonstrated the cavum septum pellucidum anteriorly and the fluid-filled ambient systems posteriorly. The image was adjusted for depth till the rugby ball shaped fetal head filled almost the entire screen (Figure 1). The image was frozen and measurements of the FVD distal from the probe was taken opposite the internal parietal sulcus. The measurement caliper was placed perpendicular to the long axis of the ventricle at the inner surfaces of the proximal and distal walls of the ventricles [16]. In cases where the ventricles were small, the image was zoomed to ensure adequate caliper placement.

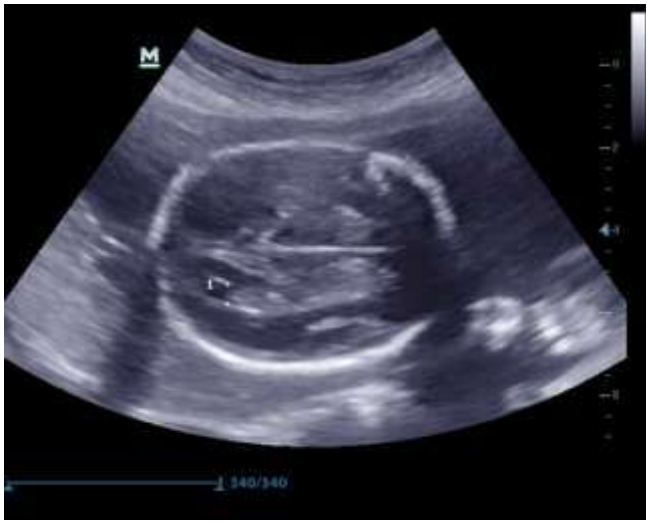

Figure 1: Measurement level of the fetal cerebral ventricles, showing cursor placement

For repeatability and reproducibility studies, the first 30 scans were performed concurrently by two sonographers, each with more than 15 years of clinical experience. The principal sonographer obtained two sets of images: each set taken at the beginning and at the end of the scan. After an interval of 15 - 30 minutes to allow the patient to rest, the second sonographer, blinded to the measurements and images generated by the principal sonographer, rescanned the patient, obtaining similar image sets and measurements. The final measurement for each sonographer was taken as the average of the two measurements each of them obtained, while the principal sonographer completed the rest of the scan. Ancillary parameters obtained include fetal presentation at the time of scan and fetal gender. All the images obtained for measurement was saved and sent to a consultant radiologist with more than 20 years of clinical experience in obstetrics ultrasound scan for scoring using an earlier reported image scoring system [14]. The scoring parameters included three primary and two secondary criteria. The primary criteria were: (i) the midline structures would be equidistant from the proximal and distal calvarial margins and perpendicular to the ultrasound beam, (ii) anterior and posterior landmarks, which respectively are the cavum septi pellucidi or fornix columns and the fluid-filled triangular V-shaped ambient cistern should be visible, (iii) the measurement must be performed opposite the internal parieto-occipital sulcus. Each criterion had a score of 1 to give a maximum score of 3. The secondary criteria were (i) measurement should be perpendicular to the inner and outer border of the ventricle at the junction between the ventricular lumen and ventricular wall, and (ii) the axial transventricular plane should occupy the whole screen with visualization of both proximal and distal calvarial margins. Images with scores of less than 5 were discarded.

All statistical computations were performed using IBM™ SPSS™ (v 24, 2016) and R™ (v 3.2.5, 2016). Prior to data analysis, the Shapiro-Wilk test of normality was used to assess for deviations from normality in the FVD, which were corrected using log transformation. Variability within a sonographer, referred to as 'repeatability', the confidence interval (CI) and repeatability coefficient (C_r). was calculated using the ANOVA model-based intraclass correlation(CC_{intra}).The repeatability coefficient was defined as the maximum difference that is likely to occur between repeated measurements, which can be given as $1.96 \times \sqrt{2} \times s_w$ where S_W is within subject variance. Variations between sonographers, referred to as 'reproducibility', were calculated using and interclass correlation (CC_{inter}) coefficients, but due to few numbers of raters, the CI was not reported[17]. Limits of agreement between and within sonographers were determined using the Bland-Altman's plot. Polynomial regression as earlier described [18], was used to obtain the 5th, 50th, 95th, and 99th centiles, with consistency determined by calculating z scores. All significant p-values were taken to be ≤0.05.

RESULTS

A total of 311 fetuses aged between 18 and 40 weeks were scanned during the period of this study. Forty-nine were excluded as a result of the following: polyhydramnios (n = 11), twin gestation (n = 9), suspected intrauterine growth retardation (n = 11), and refusal of consent (n = 18). The remaining 262 fetal cerebral ventricles were measured. Six of the first 30 scans (two from the principal sonographer and four from the second sonographer) and seven from the subsequent scans sent for scoring were rejected as they returned an image score of ≤5. In the end, a total of 249 measurements were used for data analysis, out of which 30 were used for reliability studies. The FVD ranged from 0.21 – 1.26cm, with a mean ± SD of 0.43 ± 0.14cm. Males had a significantly higher FVD (0.46±0.14cm) than females (0.40±0.12cm) across all FGA, which was not associated with the fetal lie and trimester of scan (η^2: 0.01 *and* 0.03) albeit

weak and negative correlation between FGA and FVD (r = -0.186, p = 0.03).

As shown in Table 1, there was very good reproducibility between sonographers (CC_{inter}: 0.87, C_r: 0.03).

Reproducibility was excellent for the principal sonographer (CC_{intra}: 0.97, C_r: 0.07, CI: 0.96 – 0.98) and very good for the second sonographer (CC_{intra}: 0.89, C_r: 0.10, CI: 0.82 – 0.93). Bland-Altman's plots (Figure 2 and Figure 3), demonstrated good limits of agreement within Bland-Altman's plots (Figure 2 and Figure 3), demonstrated good limits of agreement within (-0.06 to 0.08 and -0.09 to 0.11) and between sonographers (-0.06 to 0.07).

Table 1: Reliability and reproducibility measurements

	Between sonographer	Within sonographer	
		Sonographer 1	Sonographer 2
Patients	30	30	30
Measurements	120	120	120
CC_{inter}	0.87	-	-
CC_{intra}	-	0.97	0.89
C_r	0.08	0.07	0.10
Confidence Interval	-	0.96 – 0.98	0.82 – 0.93
Lower Confidence Limit	-0.06	-0.06	-0.09
Upper Confidence Limit	0.07	0.08	0.11

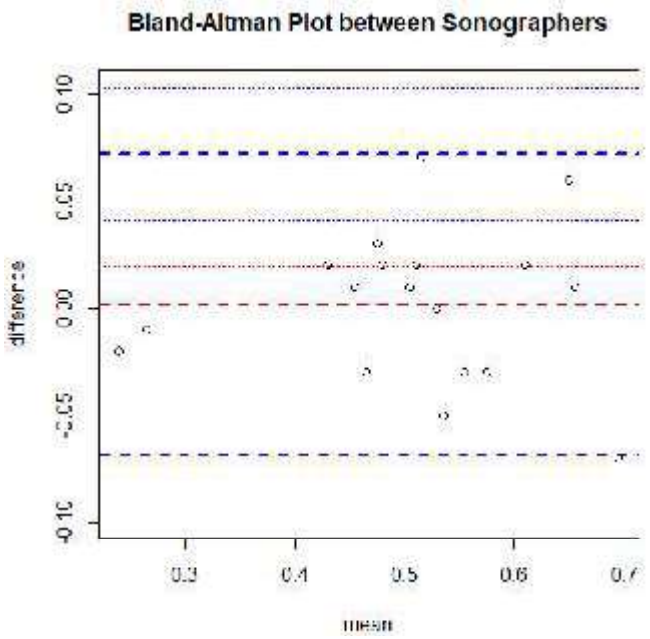

Figure 2: Bland-Altman method of agreement plot between sonographers

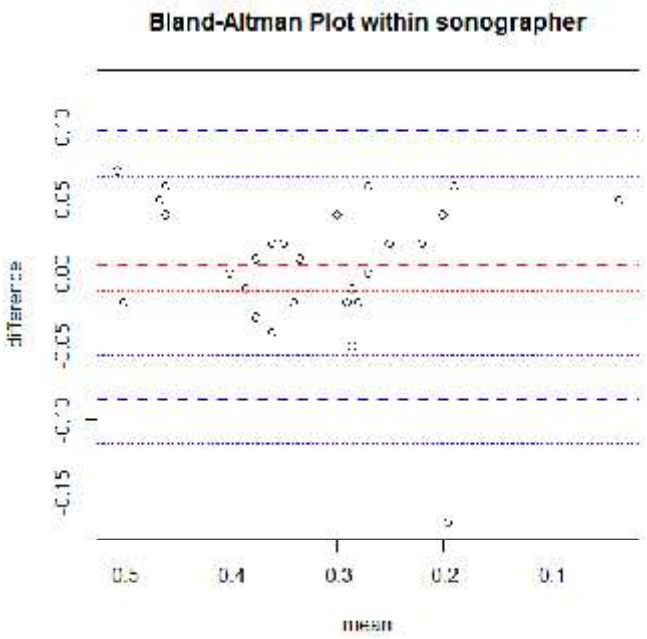

Figure 3: Bland-Altman method of agreement plot within a sonographer

A log-transformed quadratic model fitted the relationship between FVD and FGA, while a linear regression fitted the model for obtaining the standard deviation:

$$\log FVD = 0.381 - 0.053 \times FGA + 0.00089 \times FGA^2$$

$$SD = 0.126 + 0.000252 \times FGA$$

Consistency in the model was checked by calculating the z scores. All the z scores fell within the boundary -1.645 ≤ z ≤ +1.645 (Fig 6), and a Shapiro-Wilk normality plot returned a value of 0.784 ($p<0.05$). The resulting centile values are shown in Table 2, and a comparison of the mean values of our centile charts with other normal ranges ———[4,8,9,1921] are shown in Table 3.

Table 2: Centile charts of Fetal Cerebral ventricle

	Centile values for FVD				
FGA (weeks)	5th	50th (Mean)	95th	99th	SD
18	0.32	0.70	0.85	1.05	0.13
20	0.29	0.64	0.78	0.96	0.13
21	0.28	0.62	0.76	0.93	0.13
22	0.27	0.60	0.73	0.90	0.13
23	0.26	0.58	0.71	0.87	0.13
24	0.25	0.57	0.69	0.85	0.13
25	0.25	0.56	0.68	0.84	0.13
26	0.24	0.55	0.67	0.82	0.13
27	0.24	0.54	0.66	0.81	0.13
28	0.24	0.54	0.66	0.81	0.13
29	0.24	0.54	0.65	0.81	0.13
30	0.24	0.54	0.65	0.81	0.13
31	0.24	0.54	0.66	0.81	0.13
32	0.24	0.54	0.66	0.82	0.13
33	0.24	0.55	0.67	0.83	0.13
34	0.25	0.56	0.68	0.84	0.13
35	0.25	0.57	0.70	0.86	0.13
36	0.26	0.59	0.72	0.89	0.14
37	0.26	0.60	0.74	0.91	0.14
38	0.27	0.62	0.76	0.94	0.14
39	0.28	0.65	0.79	0.98	0.14
40	0.29	0.68	0.83	1.02	0.14

Table 3: Comparison of previous centile charts with present study

FGA	SALOMON (4)	ALMOG (8)	CARDOZA (9)	ALAGAPPAN (21)	FARREL (22)	BASSEY (23)	THIS STUDY
15	-	-	-	-	0.58	0.66	-
16	-	-	-	-	0.58	0.66	-
17	0.7	-	-	0.72	0.58	0.66	-
18	0.7	-	-	0.72	0.58	0.66	0.7
19	0.69	-	-	0.72	0.58	0.66	0.64
20	0.68	0.59	0.76	0.67	0.58	0.64	0.62
21	0.66	0.59	0.77	0.67	0.47	0.64	0.6
22	0.65	0.57	0.77	0.67	0.47	0.64	0.58
23	0.63	0.57	0.77	0.67	0.47	0.64	0.57
24	0.62	0.60	0.77	0.6	0.47	0.64	0.56
25	0.61	0.60	0.77	0.6	0.49	0.64	0.55
26	0.61	0.60	0.75	0.6	0.49	0.62	0.54
27	0.61	0.60	0.75	0.6	0.49	0.62	0.54
28	0.61	0.64	0.75	0.64	0.49	0.62	0.54
29	0.62	0.64	0.75	0.64	0.56	0.62	0.54
30	0.63	0.66	0.75	0.64	0.56	0.62	0.54

FGA	SALOMON (4)	ALMOG (8)	CARDOZA (9)	ALAGAPPAN (21)	FARREL (22)	BASSEY (23)	THIS STUDY
31	0.64	0.66	0.76	0.64	0.56	0.65	0.54
32	0.65	0.68	0.76	0.66	0.56	0.65	0.55
33	0.66	0.68	0.76	0.66	0.55	0.65	0.56
34	0.67	0.72	0.76	0.66	0.55	0.65	0.57
35	0.68	0.72	0.76	0.66	0.55	0.65	0.59
36	0.69	0.69	0.76	0.67	0.55	0.67	0.6
37	-	-	-	-	-	-	0.62
38	-	-	-	-	-	-	0.65

DISCUSSION

The cerebral ventricles develop from the central canal of the neural tube. The fourth ventricle is the first to appear around the 9th week, followed by the third ventricle two weeks later and lastly the two lateral ventricles [22]. Being the most prominent of the ventricles, the two lateral ventricles develop from the primordium of the forebrain, specifically the telocoele, which is the primitive structure representing the neural cavity in the telencephalon. The telocoele divides in the 6th week to form two distinct cavities, becoming sonographically visible in the 13th to 14th week. During rapid cerebral growth experienced in the first and early second trimester, studies show that the FVD surprisingly remains constant [23], a feature that might be of clinical importance in FCV assessment [22]. Intrauterine enlargement of the ventricles is one of the commonest cranial anomalies seen during ultrasound [1], but documented findings in low-risk populations report varying incidences ranging from 1 in 50 to 1 in 1600 fetuses[7,20]. Ventricular maldevelopment, ex vacuo enlargement, and obstructive hydrocephalus are known to be the three major pathologic process that culminates to ventriculomegaly [22], while other disease processes such as Dandy-walker syndrome, aqueduct stenosis, Chiari II malformation and agenesis of the corpus callosum have been identified as major contributors [24,25]. Even though the diagnosis of FCV is a nonspecific sonographic finding, it is however associated with some pathological conditions which can be neural or extracranial [26,27]. It often points to other pathological processes such as dysgenesis of the posterior portion of the corpus callosum and was once believed to be the most sonographically sensitive indicator of maldevelopment in fetuses [6]. Postpartum diseases are also associated with ventriculomegaly, with several authors reporting increase mortality, growth retardation, failure to achieve milestones, and other neurological deficits among live births diagnosed with intrauterine ventriculomegaly [22]. Some studies have sought possible discrepancies between sonographic measurements and a relatively less operator-dependent modality like magnetic resonance imaging, but found no statistically significant difference. Garel [28] and Perlman [29] compared prospective measurements from 106 and 162 fetuses respectively from both modalities and reported excellent agreement, even though slight overestimation by ultrasonography when the ventricles present with thin diameter has been observed[28].

Our findings indicate that the use of the standardized technique for FVD scanning is highly repeatable with a very good agreement within a single sonographer. This was seen in CC_{intra} values of 0.97 and 0.89 for both sonographers. The Bland-Altman plot further illustrated that the maximum and minimum difference between two separate measurements by a sonographer will be 0.08cm and 0.06cm respectively. Additionally, with high CC_{inter} values of 0.87 and a C_r of 0.08, FVD measurements between sonographers would be very well reproduced. Our findings are in keeping with two previous findings on the reproducibility of FCV measurements, both of which reported high reproducibility between sonographers [30,31]. Despite the fact that some authors have pointed to a possibility of different sonographers judging the margin of the cerebral ventricle differently before placing their measurement cursor[31], our study has shown that this does not affect the reproducibility of the measurements. We think that this method that has been described should be used along with the scoring method whenever a

diagnostic work up for possible fetal ventriculomegaly is required.

Furthermore, we report a mean FVD of 0.43 ± 0.14cm, with our upper limit of normal as 10.2cm, which is 2.3SD above the mean (CI: 99%), and beyond which we suggest that FCV can be diagnosed. Generally, 1.0 – 1.2cm is taken as the normal range of FVD. Some authors have suggested 1.0cm as the upper limit of normal, which is between 2 – 4 standard deviations above the mean, while others define ranges for mild, moderate, and severe fetal ventriculomegaly ——[11,12,23,3239] below 1.2cm as mild and above 1.5cm as severe. Our values are similar to the measurements obtained by Farrel [8] between 21 and 28 weeks FGA. However, when compared to measurements from previous studies —[9,19,21,30,40,41], our FVD values were consistently lower by approximately 0.2cm. Almog [9] reported a mean value of 0.63±0.12cm in his study involving 427 fetuses and a pooled mean from 8236 cases of 0.64 ±0.12cm. Population-specific differences or an underestimation of FVD by this standardized technique may be reasons for this. Finally, the CC_{inter} values could have been more robust and reliable if more than 2 raters participated in this study. This was not possible due to the limitation of the length of time each pregnant patient could lie down for a scan. A multicenter study could investigate this.

CONCLUSION

Fetal ventricular diameter measurements using the standardized approach are highly repeatable and reproducible, with an excellent agreement within and between sonographers. We advocate that this standardized approach along with the image scoring system be used whenever the measurement of the fetal ventricles are to be relied upon for cardinal clinical decisions. Finally, we present a nomogram of FCV, reporting a mean of 0.43 ± 0.14cm, with our upper limit of normal as 10.2cm.

Conflict of interest: None declared.

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