DISCUSSION
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Development of fetal nervous system in the form of brain volume measurement is important as certain genetic defects may be diagnosed at an early stage. This study was planned with aim to assess fetal brain volumes in normal fetuses involving total brain volume of supratentorial cortex, left and right hemispheric volume of cortex, cerebellar volume and thalamic volume.

The objectives of the study were to establish a data to calculate the normal total fetal brain volume, then to compare fetal total brain volume with gestational age and estimated fetal weight to assess right and left hemicortex volume to establish normal cerebellar volume and thalamic volume in fetuses and compare with gestational age. 725 study women were recruited in the present study with inclusion and exclusion criteria. As mentioned earlier in inclusion criteria, for study subject’s help of Hadlock tables was taken for calculating fetal weight. There are certain advantages of using the Hadlock tables. Also most of the sonography machines have Hadlock’s tables preloaded in their software.

Indian population is very large with high variability. What may be suitable for south Indian population may not be suited for Punjab, Hariyana, Rajasthan, Uttar Pradesh and Jammu & Kashmir etc. After going through biometric tables made by Mediscan Systems Chennai and Christen Medical College, Vellore, conversion of the biometric table to weight percentile for that gestational age was not available. Reasons for using Hadlock biometric tables and percentile charts are:

1) These Hadlock tables are pre-installed in all sonographic machines in India.

2) About 90% of the sonologist use Hadlock tables for calculation.

The volume measurements were taken by using 2-DB-mode ultrasound in three orthogonal planes using formula:

\[ \text{Volume} = 0.52 \times (\text{LXAP} \times \text{T}) \]

\[ L = \text{Length AP, Antero-posterior diameter} \]
\[ T = \text{Transverse diameter} \]
6.1 Total brain volume

In the present study 2-D B-mode imaging was used for measurement of supratentorial volume in 3 orthogonal planes. Statistical analysis was done by comparing data with gestational age and estimated fetal weight (EFWT). As evident from the Table 5.1A (1) and Graph 5.1A (1), in which total brain volume measurements of the fetuses under study were plotted against the gestational age in weeks, the total brain volume increased steadily with the gestational age. The observation was linear increase. Fetal brain volume in our study showed positive correlation with the gestational age by the Pearson’s correlation coefficient ‘r’ [Table 5.1A (1)]. From the data, a regression plot was obtained in order to find out the value of brain volume from gestational age. [Table5.1A (2) and Graph5.1A (2)]. The equation thus obtained is as follows:

Total Brain Volume = 11.619(GA) - 202.95

In the study done by T. Du Bose, measurements were taken from outer cranium while in present study measurements were taken from inner calvarium. So expected total brain volume was less but rise of brain volume was comparable which was five times in third trimester. Rise in brain volume is equal as seen in graph. If one applies regression formula from this study for calculating gestational age G.A = 9.5+1.4 square root of Cranial Volume regression from T Du Bose study answer did not match because from our study calculation is done by taking inner calvarial measurements while in study by T Du Bose outer calvarial measurements were taken. Intracranial volume calculation was done by using formula of CV=0.00055><FOD><BPD><VCD.
While in present study has used formula of Volume = 0.52>< (L >> AP >> T )

Roelfsema et al18 used 3-dimensional ultrasound and found that the median brain volume was 34 ml at 18 weeks which increased to 316 ml at 34 weeks. In this study at 34 weeks, the 50th percentile, which roughly corresponds to the median brain volume at 34 weeks, was 193.7ml. This is substantially lower as compared to the Roelfsema et al study. The reason for this might be due to the fact that Indian fetuses are usually smaller in overall size as compared to the western fetuses.68
Chang et al\textsuperscript{17} was the only study which not only correlated the fetal brain volume with the gestational age, but also with the estimated fetal weight. In our study as seen from the Table 5.1B (1) and Graph 5.1B (1), the estimated fetal weight and fetal brain volume correlate with each other very well. We also developed regression formula for the estimated fetal weight and brain volume [Table 5.1B (2) and Graph 5.1B (2)]:

\[
\text{Fetal total brain volume} = 0.0764(\text{EFWT}) + 24.576
\]

Anderson et al\textsuperscript{69} compared 2D sonographic methods with 3D magnetic resonance imaging for assessing brain structure. Though the aim of the study does not match with the present study, the findings of the study showed that 2D ultrasound imaging for cerebral structures produces good reproducibility.

Some of the studies that are done for intracranial volume use 3-dimensional sonography and use virtual organ computer aided analysis that requires special software and training and specialist do offline estimation of volume. Our predefined objective to have nomogram of brain volume and its comparison with gestational age and estimated fetal weight is well achieved.
6.2 Hemispheric volume

Each hemisphere was measured separately. For each hemisphere all the statistical tests were done and regression formula developed. The left as well as right hemisphere correlated well with the gestational age [Table5.2 (1), Graph5.2 (1), Table5.3 (1) & Graph5.3 (1) respectively]. Hemispheric volume among fetus has been studied very rarely the only study conducted by Hering Hanit et al\textsuperscript{41} in 2001, who established cerebral hemisphere asymmetry among fetuses in Israel. The study found that left hemispheric diameter was larger than right hemisphere. There was no sex related difference found between respective hemicortex. As present study did not focused on sex wise differentiation in the measurement of hemicortex, the finding did not involve in our results. A similarity in volumes was observed in the each hemispheric measurement in our study.

Apart from the correlation and regression plots, we also calculated the percentiles for the both hemispheric volumes separately. These are seen in Table 5.2(3) & Graph 5.2(3) for left hemispheric volume and Table 5.3 (3) and Graph 5.3 (3) for right hemispheric volume.

Kivilevitch et al\textsuperscript{26} found that the cerebral atria and the occipital cortex presented an inverse relationship with sex, head biometry, and estimated weight. They concluded that brain asymmetry is a normal developmental phenomenon of fetal brain. It is sex dependent and lateralized in most cases to the left and is more accentuated in males. Here, only the cortical width and mean hemispherical width were calculated and compared with the both side (right and left) and among males and females. Unlike our study, Kivilevitch et al did not measure actual cerebral volumes. In our study sex related observations were not done considering the PCPNDT act\textsuperscript{57}. However, in our study, there were no differences in the volumes measured between left and right hemispheres.

In contrast to the above mentioned studies, a study performed by MRI by de Lacoste et al\textsuperscript{24} found that although the lateralization was evident in the fetal brains, it was right hemicortex that was larger in the males and left was larger in females.
6.3 Cerebellar Volume

Our study shows that there is a good linear correlation between cerebellar volume and gestational age [Table5.4 (1) and Graph5.4 (1)] from which we derived the regression formula [Table5.4 (2) and Graph5.4 (2)] as follows:

\[
\text{Cerebellar Volume} = 0.4754(\text{GA}) - 9.1648
\]

All following studies that are discussed have used 3-D technique and therefore are not really comparable.

Chang et al\textsuperscript{17} formulated a chart of cerebellar size by study on Taiwanese population. The charts of the cerebellar volume provided by Chang et al varied significantly from our study. The values of cerebellum were lower in our study as compared to the study done by Chang et al. Here again the explanation could be that, Indian fetuses having a smaller overall size also might tend to have smaller cerebellar volume\textsuperscript{30}. But more studies need to be done to substantiate this finding.

Toshiyuki Hata et al\textsuperscript{44} in 2007 evaluated growth of fetal cerebellum using 3-dimensional ultrasound among 13 fetuses. There was curvilinear relationship found between gestational age and cerebellar volume which resembled with findings of our study. Authors also suggested that standard curve for fetal cerebellar volume using 3-dimensional ultrasound can play a role in the evaluation of normal cerebellar growth in the fetus.

Araujo et al\textsuperscript{71} showed that fetal cerebellar volume was highly correlated with gestational age (r =0.94; p<0.001) which was analogous with our study finding and the author also concluded that assessment of fetal cerebellar volume by 3-D ultrasonography is an important tool to evaluate fetal growth in utero.
6.4 Thalamic volume

Thalami from both sides (bilateral measurement) of fetus were measured together and it was found that both gestational age and thalamic volume correlated with each other significantly. There was a linear relationship observed between gestational age and thalamic volume [Table 5.5 (1) & Graph 5.5 (1)]. A regression equation was also developed based on the observation which was as follows:

Thalamic Volume = 0.3594(GA) - 5.8454 [Table 5.5(2) & Graph 5.5(2)]

All following studies that are discussed have used 3-D technique and therefore are not really comparable.

Benavides-Serralde A et al\textsuperscript{22} showed that thalamic volume was significantly larger in IUGR fetuses as compared with appropriate for gestational age fetuses. Benavides-Serralde A et al included the patients in gestational age of 28-34 weeks, where the mean thalamic volume was found out to be $1.5\pm 0.9\text{cm}^3$ (0.8-4.5 cm$^3$) in the AGA (appropriate for gestational age) fetuses. As compared to these values our values of thalamic volume seem to be on a higher side. The 90\textsuperscript{th} & 10\textsuperscript{th} percentile for 28 weeks of gestation is 5.17ml & 2.59ml respectively while for 34 weeks it is 10.1ml and 4.9ml respectively. We did not study IUGR patients.

Sotiriadis A et al\textsuperscript{47} in their study observed that the thalamic volume increases with gestational age and there was no difference in the volumes of right and left thalami. The mean volume of each thalamus increased from 0.45 ml at 20 weeks, to 1.39 ml at 28 weeks, to 2.17 ml at 34 weeks. These measurements are for each thalamus (unilateral) and are similar to our study (In our study we have measure the thalamic volume of both the thalami combined). [Table 5.5(3)]

This study may form a basis in predicting neurological problems that are faced in post natal life and in childhood. Problems like autism, below normal intellect; behavioral changes, learning disabilities, schizophrenia, various types of epilepsies etc. that are exhibited in childhood and adolescent have been found to have reduced brain volumes. Epidemiological studies revealed that many neurologically impaired infants belong to the low-risk population that means they seemed to be developmentally normal as fetuses and infants while later in childhood neurological disability was diagnosed. If someone, extrapolates fetal brain volume to post natal outcome in childhood and adolescence then prediction of neurological outcome shall be possible.
Brain development is continuous after birth and years afterwards. The proliferation and migration are completed in a term infant, synaptogenesis is neuronal differentiation and myelination continues very intensively. The development process of the brain is so complex and possibility for their impairment is very high that is why congenital malformations of the brain are among the most frequent malformations. Environmental factors also play role in child development. The basic abnormality of the brain may be present and environment may act as trigger to produce psychological problem.

In first trimester the anatomic landmarks that are used to measure brain volume are not very well developed. Therefore it becomes difficult to measure brain volume before 20 weeks. At about 20 weeks cerebellum is fully developed and that onwards cerebellar volume can be estimated. Landmarks that are used to estimate thalamic volume are also fully developed around 20 weeks of gestation and therefore thalamic volume can be estimated twenty weeks onwards. In late 3rd trimester nearer term as head starts engaging, it becomes difficult to measure brain volume because mid-sagittal plane is difficult to achieve. Therefore gestational age before 20 weeks and after 35 weeks, suboptimal measurements may be taken. That means, between 20 to 35 weeks, one may be able to estimate fetal brain volume.

Further studies will confirm data and statistical analysis and regression formulas shall be established. Once standards are established one may extrapolate this data in children that are suffering from autism, behavioral problems, learning disabilities, schizophrenic disorders, epilepsies, and other mental illnesses. In future one may be able to predict problems in that might arise in childhood or in adult. Along with fetal brain volume if fetal behavior analysis is done such as fetal movements and facial expression, with the use of 4-D for fetal behavior (like smiling, swallowing, crying) and fetal typical movements, one may be able to get more information in predicting childhood psychological problems.

There might be some of methodological and potential limitations need to be mentioned. During 20 to 30 weeks it is easier to get brain volume, hemispheric volume, thalamic volume and cerebellar volume. As gestation advances and fetal cephalus goes nearer to pelvic brim getting mid-sagittal plane may become difficult. Time period for the scanning is also important but with little practice it may take two to three minutes more. If one takes time period for thorough scanning, it is up to 18 to 20 minutes adding
two minutes one shall get more information of brain in adequate planes. This study is done by 2-D B mode most of the studies that were analyzed for estimation of brain volumes were done by 3-D. In these studies after acquiring volume data offline analysis was done by expert. It may reduce scanning time but analysis done offline by an expert may take his time. Secondly image quality from volume data may not be as good as good B-mode image. In our country under the PC PNDT Act only radiologists are allowed to scan and offline analysis may not be possible. Abiding this law I could not differentiated between fetal sex and their brain volumes.

As it may be suggested another study of brain volume will establish validity of present study.