DISCUSSION
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This study was undertaken to evaluate the contribution of signal intensity measurements towards diagnosis of fetal CNS anomalies. One hundred and ten fetuses who were referred for suspected or proven anomalies and for placental abnormalities over the past 5 years were subjected to MRI. Only 101 could be taken up for the study as 9 of them had destroyed brain like anencephaly, encephalocele, porencephaly. (It becomes impossible to obtain signal intensity of a region in brain if that part is destroyed)

Maternal age: The age group ranged between 19-39 years (mean-25.5 years). Out of the 101 pregnant women, 84 (83%) belonged to third decade and 11 (10%) belonged to fourth decade (Table 1).

Parity: Primigravida accounted for 64% of the pregnant women examined and Para 1 accounted for 28% (Table 2).

Gestational age: The gestational age ranged between 18-38 weeks (mean-26.9wks). The commonest gestational age group examined was 21-24 (31%) followed by 25-28 weeks (22%) (Table 3)

Liquor: Out of the 101 pregnant women, 86 (85%) had normal liquor, 12 (12%) had polyhydramnios and 3 (3%) had oligohydramnios (Table 4)
System involvement: Fifty (49%) fetuses had Central nervous system abnormalities while twenty (20%) of them had genito urinary system abnormalities (Table 5). Thirteen (13%) had thoracic abnormalities while four (4%) fetuses had gastro intestinal abnormalities. 14 (14%) were found to be normal after all the required investigations even though 5 of them were suspected to have anomaly in the initial USG scan. These included fetuses with suspected ventriculomegaly, colpocephaly, spinal anomalies. 9 were referred for placental / lower abdominal pathologies (fibroids, lower abdominal pain) complicating pregnancy - Placenta percreta-3, lower abdominal pathologies -6.

In a study of 66 fetuses, Levine states that MR is useful in further assessing ventricles. Spinal anomalies due to abnormal fetal posture can be ruled out with MRI. This finding correlates with our study. Out of the nine excluded fetuses 5 had CNS anomalies with destroyed brain. The other 4 had CNS and abdominal anomalies with destroyed brain. In a study of 27 fetuses, by Mary Frates et al, CNS anomalies were seen in 17 fetuses followed by thoracic anomalies in 6 fetuses, genito urinary anomalies in 4 fetuses. The relative system distribution correlates with our study.

Controls and Correlation: In the 101 fetuses, 51 had normal brain and 50 had abnormal brain (Table 6). In the 51 fetuses that had normal brain, 42 were managed conservatively and 9 had to be terminated due to anomalies in trunk. The correlation of the normalcy of the brain was based on clinical examination
In 36, USG in 6 and autopsy in 9. The 51 fetuses that had normal CNS were used as controls. They had thoracic or abdominal anomalies or were normal.

In the 50 fetuses that had abnormal brain 18 were managed conservatively and 32 had to be terminated. The correlation of the abnormalcy of the brain was based on Clinical / Physical examination in 15, USG in 14, MRI in 2 and autopsy in 19.

Hydrocephalus was the commonest CNS abnormality, seen in 18 fetuses (Table 7). Arnold Chiari malformation was seen in 15 fetuses (13 had associated hydrocephalus). Thirteen fetuses had isolated ventriculomegaly with lateral ventricle diameter >10mm. Partial agenesis of corpus callosum was seen in 5 fetuses. Other CNS anomalies like suprasellar cyst, isolated meningoceles and Megacisterna magna were seen in 13 fetuses.

**SIR in controls:** Though MR images were obtained in three orthogonal planes, only the transverse images were used for placing the Region of Interest (ROI) cursors. ROIs of size 0.20cm² were placed in the following tissues and signal intensities of the tissues were measured.

- Vitreous humour
- Thalamus
- Corona radiata
- Genu of corpus callosum
- Cerebellar vermis
- Frontal white matter
- Periventricular region
- Grey matter

The lateral ventricle diameter of the fetuses were also obtained.
The ROI was kept at 0.20cm$^2$ for all the cases to ensure comparison. Mild change in the ROI size from 0.20cm$^2$ will not significantly change the signal intensity measurement. However a tiny ROI is susceptible to variabilities. A large ROI is susceptible to volume averaging. A ROI of 0.20cm$^2$ was considered optimal. Akiyama et al (1993)$^{15}$ used similar method to quantitatively evaluate the course of neonatal and infantile myelination by measuring the signal intensities. Seiji et al (2004)$^{17}$ used ROI size of 0.22cm$^2$ to evaluate the development of myelination based on MR signal intensity measurements in 101 normal fetuses.

In our study we analysed the SIR. This is because the absolute signal intensity in the ROIs varies depending on the slice position$^{17}$; ie, it varies among individual images, which makes it impossible to compare the absolute signal intensity between subjects. Therefore, the SIR in the ROIs relative to the intensity of the vitreous allows standardization and comparison between subjects. Signal intensity of a tissue depends on its distance from the receiver coil. A ratio comparing the signal intensity of the brain with another structure of similar depth like vitreous could provide a correction factor$^{17}$. Hence the Signal Intensity Ratio of the tissue : vitreous was obtained (SIR). Akiyama et al, Seijbe et al$^{15, 17}$ used similar sites while assessing the signal intensity in 26-39 weeks fetuses. Vitreous humour was chosen as reference point because$^{38}$: (1) It is unrelated with brain growth. (2) It is composed of glycosaminoglycan and type II collagen and does not change significantly from 12-40 weeks.
Normative values (control values) of the designated regions were obtained for the 18-40 weeks fetuses (Table 8, Figure 5.1). The inter observer mean variability ranged between 2-3.3% (Table 9). Variability in previous study done by Seiji Abe assessing SIR was similar (2-3.8%) 17.

The signal intensities of the designated regions decreased after 34 weeks. This is due to onset of myelination at 33-36 weeks 39. Hence to derive the control values we made two groups (1) fetuses between 18-34 weeks gestation and (2) fetuses between 34-40 weeks gestation. Subsequently, we calculated the mean of the signal intensity measurements of each region in each group. Further, most of our fetuses with CNS anomalies were less than 34 weeks old (48 out of 50).

In 18-34 weeks control fetuses, the signal intensity ratio was 0.6 to 0.7 in vermis (mean 0.68), corpus callosum (mean 0.63), thalamus (mean 0.64) and periventricular region (mean 0.62). This declined to 0.4-0.6 after 34 weeks.

In 18-34 weeks control fetuses, the signal intensity ratio was 0.7 to 0.85 in frontal white matter (mean 0.78) and corona radiata (mean 0.74). This declined at 34 weeks. In grey matter the SIR was 0.5-0.65 (mean 0.59) which showed a shallow decline after 34 weeks.

The decline in SIR is due to onset of myelination during 33-36 wks. This correlates with the previous study done in 26-40 week fetuses by Seijbe et al 17. Previous pathological studies 39 attribute onset of myelination in the 33-36
week period. Iai et al\textsuperscript{39} who examined the time of onset of myelination using immuno staining, reported that myelination began at 33-36 weeks.

In the present study, the SIR of thalamus, grey matter and vermis was lower than that of cerebral white matter. This is because myelination has already started at 26 weeks\textsuperscript{40, 41, 42}. Counsell et al\textsuperscript{41} reported that in addition to myelination the maturation of astrocytes and neurons may also contribute to the reduction of SIR. The decline is shallow in grey matter and thalami where the myelination progresses slower\textsuperscript{17}.

Signal intensity ratio measurements in controls compared with the following conditions and statistical analysis was done by Independent Samples T test

- Fetuses having hydrocephalus
- Fetuses having Arnold Chiari type 2 Malformation
- Ventriculomegaly
- Partial agenesis of corpus callosum
- Fetuses with miscellaneous CNS anomalies
SIR IN FETUSES WITH HYDROCEPHALUS:

Hydrocephalus is characterised by dilatation of ventricles. This may be associated with obstruction in CSF pathway at various levels. Fetus with lateral ventricular diameter > 10 mm had more propensity to develop hydrocephalus

- The SIR of cerebellar vermis was higher than controls whenever the obstruction was beyond the IV ventricle. In aqueduct stenosis SIR of vermis did not increase. By this we can predict the level of CSF flow obstruction (Table 11, Figure 5.2, Plate 4)

- The SIR of periventricular region was higher than controls

- SIR in other regions are not useful

**Vermis SIR:** Values > 0.75 had 87% sensitivity and 99% specificity towards hydrocephalus in the appropriate clinical set up (Table 12, Figure 5.3)

**Periventricular SIR:** Values > 0.75 had 89% sensitivity and 99% specificity towards hydrocephalus in the appropriate clinical set up
SIR IN FETUSES WITH ARNOLD CHIARI MALFORMATION:

Arnold Chiari malformation is characterised by tonsillar herniation meningomyelocele.

Brain anomalies like hydrocephalus may be present

- The SIR of cerebellar vermis was higher than controls (Table 13, Figure 5.4, Plate 5, 6)
- The SIR of periventricular region was higher than controls
- SIR in other regions are not useful

Vermis SIR: Values > 0.75 had 86 % sensitivity and 97% specificity towards Arnold Chiari malformation in the appropriate clinical set up. (Table 14, Figure 5.5 )

Periventricular SIR: Values > 0.75 had 86 % sensitivity and 95% specificity towards Arnold Chiari malformation in the appropriate clinical set up

SIR IN FETUSES WITH VENTRICULOMEGALY:

SIR in isolated non progressive ventriculomegaly was studied. Dilated ventricles due to hydrocephalus and Arnold Chiari malformation-2 were excluded. Dilatation of ventricles - may be a normal variant or associated with agenesis of corpus callosum, atrophy or hemimegalencephaly. (Table 15)
SIR in all the designated regions were similar to controls (Table 16, Figure 5.6, Plates 7, 8)

It is useful to differentiate hydrocephalus from ventriculomegaly

Seiji et al (2004) in their study on myelination in 101 normal fetuses have attributed signal intensity changes depending on the tissue, water content and myelin. Water increases and myelin decreases signal intensity. Maezawa et al (1993) worked on the signal intensity measurements in brains of 87 children postnatally have also said that water increases and myelin decreases signal intensity.

In cases of hydrocephalus and ACM-2, previous pathological and radiological studies have identified CSF flow obstruction with resultant increased interstitial edema in vermician and periventricular region. Hence we can attribute the increase in SIR in vermis and periventricular region in hydrocephalus and ACM-2, to the increased water content resulting from increased interstitial edema. In aqueduct stenosis, the SIR of vermis did not increase as there is no interstitial edema. In ACM-2 there is tonsillar herniation causing some amount of CSF flow obstruction with resultant increased interstitial edema in vermician and periventricular region. Fetal evaluation is done by Fast sequences and may not show the edema. Signal intensity comes handy in assessing the presence of interstitial edema though morphologically there is no edema. Thus it is useful in predicting the level of obstruction. In physiological ventriculomegaly there is no interstitial edema. Hence the SIR values were similar to controls.
SIR IN FETUSES WITH PARTIAL AGENESIS OF CORPUS CALLOSUM:

- The SIR of genu of corpus callosum was higher than controls. (Table 17, Figure 5.7, Plate 9)

- SIR in other regions are not useful

**Genu of Corpus callosum** SIR Values of > 0.75 had 80% sensitivity and 100% specificity towards PACC in the appropriate clinical set up (Table 18, Figure 5.8)

In Partial agenesis of corpus callosum, there is dysgenesis and only the anterior part is present. Altered myelination is also seen. This could explain the altered signal intensity. As the number of patients is small (5), further evaluation is needed.

SIR IN FETUSES WITH OTHER CNS ANOMALIES

Those studied were arachnoid cyst, meningomyelocele, megacisterna magna. (Table 19)

- No significant difference seen in the signal intensity ratios in these fetuses when compared to controls (Table 20, Figure 5.9, Plate 10)
In schizencephaly and heterotopias, there are islands of grey matter which may be difficult to diagnose on conventional fast sequences. SIR at the suspected regions may be helpful. (Plate 11)

When diagnosing abnormal myelination or edema based on SIR, comparison with gestational age matched cut off values in control group becomes indespensible. In this respect a SIR value < 0.7 in vermis, periventricular region and genu of corpus callosum had more propensity towards normalcy in 18-34 weeks fetuses. This finding will help in further studies on fetal brain maturation, myelination, and brain edema.

We feel that SSFSE (HASTE) sequence is optimal to assess the brain maturation, myelination and SIR antenatally. SSFSE does not employ any motion correction and images are obtained as it is at that point of time. Hence it is suitable to get SIR. Previous studies done by Seiji et al (2004) 17, Lee Brewerton et al 37(2005) support this. Seiji et al used HASTE to evaluate the development of myelination based on MR signal intensity measurements in 101 normal fetuses and found it acceptable and reproducible. Lee Brewerton et al in their study on 157 fetuses using HASTE images presented the normograms of Lung to Liver Signal intensity Ratio. They concluded that there is a potential role for Lung to Liver Signal intensity Ratio in the antenatal diagnosis of lung hypoplasia, especially after 25 weeks.

ULTRASOUND VERSUS MRI
In our study, MR imaging provided more number of confident diagnoses in fetal CNS and thoracic anomalies (Table 21). Due to the cranial and rib shadowing with increasing gestational age, structures posterior to them are not well visualized on US. However they are well demonstrated on MRI.

MRI had higher sensitivity and specificity than USG in detection of CNS anomalies (97%, 98 % vs 72%, 88% - Table 22). In CNS, MR imaging was helpful in the confident diagnosis of agenesis of corpus callosum, posterior fossa anomalies and ventriculomegaly. Its inherent soft tissue contrast was helpful in the diagnoses of parenchymal abnormalities like schizencephaly. Its ability to cover a large field of view and demonstrate tissues deeper to bone was useful to assess the head and spine

Mary Frates et al 12 found that in a study of 27 fetuses (28 diagnoses) MR imaging provided additional information in 10 cases. They also reported that MR diagnosis was incorrect and US diagnosis was correct in four cases. US and MR diagnosis were both incorrect in seven cases. US and MR imaging diagnosis were both correct in seven cases.

Levine et al 8 reported that MR imaging provided more information in central nervous system in 10 (55%) of 18 fetuses, which changed pregnancy care in seven (39%) mothers. Additional findings seen on MR imaging after US by Levine et al in their series were agenesis of corpus callosum, cerebellar hypoplasia and cerebral cortical abnormalities.
MRI had higher sensitivity than USG in detection of Chest anomalies (85% vs 100% -Table 22). However both the modalities showed high specificity of 100%. MR imaging was very useful to assess lung hypoplasia in congenital diaphragmatic hernia and the spine in mediastinal cysts. Levine et al \(^{35}\) reported that MR imaging provided more information in the thorax in 28 (38%) of 74 fetuses, which changed pregnancy care in six (8%) mothers \(^{35}\). Rypens et al \(^{34}\) estimated lung volumes by MR imaging in 336 fetuses. Calculation of lung volume is useful in fetuses at risk of lung hypoplasia as in congenital diaphragmatic hernia.

With respect to gastrointestinal and genitourinary anomalies, there was no significant difference between the two modalities. The number of patients in gastrointestinal subgroup is small. A bigger population size is needed for better assessment. A fetus which had autosomal recessive polycystic kidneys at 20 weeks could only be diagnosed on US and not on MR imaging. This could be due to the tiny size of the micro cysts in kidneys. Cassart et al \(^{36}\) found that MR imaging provided additional information in urinary tract anomalies in 5 of 16 third-trimester fetuses, which affected pregnancy care in 4 mothers. However, Poutama et al \(^{24}\) concluded that in cystic kidneys, MRI does not provide more information than sonography.

The limitation of this study is that the radiologist reading the MR images was informed about the region of interest: head - neck, trunk or both. This could promote a bias towards the diagnosis.
Ultrasound is inexpensive, readily available, and has real time capability\textsuperscript{7,8}. Fetal cardiac activity, biophysical profile, fetal biometry and cardiac-limb anomalies are part of every US examination whereas currently, MR imaging has a very limited role in the evaluation of these parameters\textsuperscript{8}. Hence, as of now, for the total evaluation of a fetus, US is mandatory. MR has inherent soft tissue contrast and shows the anomalies, especially of head and trunk with ease. MR increases the confidence of diagnosis in congenital anomalies.