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Assessment of Normal Cerebral Sulcal Development in Foetus Using MRI

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Abstract
Aim*: The timing of the appearance of different types of sulci in a foetus is so precise that neuropathologists consider gyration to be a reliable estimate of gestational age and consequently a good marker of fetal brain maturation. The aim of this study is to provide a standard of reference that can be used to assess normality of fetal sulcation.*
Materials & Methods *: Foetal MRI of 74 ultrasonically labelled normal fetuses of gestational age 22 to 36 weeks is done using standard turbo spin echo sequence (HASTE) by focussing on Foetal brain . Assessment of cerebral sulcation is then done by two experienced radiologists having blinded from gestational age of the foetuses . Total of 17 sulci are analysed e in an orderly manner starting from sulci present in medial cerebral surface,followed by ventral cerebral surface and then those present in vertex . The identified sulci were categorized in to three catagories – present, absent and partially developed.*
Results*: Based on the observation, the gestational age at which each sulci can be identified and gestational age after which each sulci should be visualized are tabulated . Sequential development of the various sulci is consolidated and as a result 6 stages of cerebral sulcal development is proposed*
Conclusion*: This study provide a sequential stages of in utero sulcal development by which the evaluation of fetal brain maturation in relation to gestational age can be done during the second and third trimesters especially to identify early brain anomalies involving neuronal migration and cortical formation . .*
Key Words: *Foetal MRI , Sulcal Development , Foetal Brain ,Normal Sulcation, Foetal Brain Maturation .*

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I. Introduction

Sulcation is a sequential process of disproportionate, rapid development of outer cortical surface to that of the inner white matter so that the cortex ends up in wrapping around and folding over itself , forming cerebral sulci and respective gyri (1) . These sulci and gyri become more evident during the course of foetal development and they constantly occupy relatively same locations ,which itself act as a precise reference (2) .The timing of the appearance of these different types of sulci is so precise that neuropathologists consider gyration to be one of the reliable estimate of gestational age and consequently good marker of brain maturation (3).

Although abnormalities of cortical formation and migration anomalies are felt to be rare ,they are indeed seen in more than 20% of CNS anomalies identified on postnatal MRI (4).They may be either isolated or associated with some other cerebral anomalies .Third trimester MRI shows 80% of lissencephaly ,100% of schizencephaly and 73% of polymicrogyria foetuses whose postnatal diagnosis were the same(5). It has been suggested in literature that abnormal operculization results from underlying cortical dysplasia and those foetuses are at increased risk of refractory epilepsy or developmental delay in postnatal period (6,7,8). Hence knowledge of anatomy and development of the developing fetal brain is essential to detect abnormalities in prenatal imaging ,since some of the brain malformations are associated with severe developmental anomaly which requires early diagnosis (9).

Although ultrasonography remains the modality of choice for evaluation of antenatal foetus , MRI has been increasingly used in second and third trimesters of pregnancy for foetal brain evaluation (10). In contrast to USG ,visualisation of fetus in MRI is not limited by fetal position, maternal obesity or oligohydramnios and also visualisation of brain is not restricted by ossified skull (11,12). MRI is a boon to antenatal foetus through which fetal brain structures such as gyration/sulcation, posterior fossa structures and cerebrospinal fluid spaces can be visualised through its excellent soft tissue contrast resolution (13). Since brain development is a dynamic process ,it is indeed important to recognize the normal MRI appearance of the developing brain and its

sulcations at different gestational ages to avoid misdiagnosis or missing diagnosis. Hence our aim of the study is to establish the normal sulcation landmarks at different gestational age by using in utero MR imaging in South Indian population .

II. Materials And Methods

It is a prospective descriptive anatomical study .The study subjects are antenatal mothers between 22 to 36 weeks of gestation. Totally 74 antenatal mothers were included in the study whose obstetric ultrasound examination of the foetuses shows apparently normal findings . The gestational age of the foetuses were determined by first trimester dating scan age which is enrolled by crown rump length of the fetus . The study subjects of number 74 were selected among our outpatient population who came for routine ultrasound examination in second and third trimester between the study period of August 2016 to June 2017.

All antenatal mothers, underwent screening ultrasound for presence of any other organ anomalies and gross neurological anomalies.The inclusion and exclusion criteria were

Inclusion criteria :

1. Fetuses with gestational age between 22 – 36 weeks who should have done atleast once ,the dating scan in first trimester i.e less than 12 weeks .
2. MRI indicated antenatal mothers with familial history of gyrational abnormalities, family history of epilepsy.
3. Obese mothers in whom usg not useful in assessing foetus, mothers with epilepsy, family history of epilepsy .
4. Antenatal mothers with fetuses showing normal findings on sonographic brain examinations who gives complete informed consent to do foetal MRI.
5. Fetuses having normal cerebral MR findings are included in the study .

***Exclusion criteria* :**

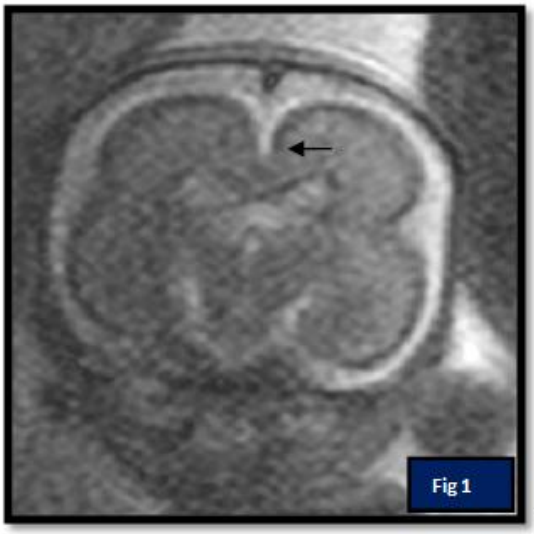
High risk pregnancy with complications like pregnancy induced hypertension ,gestational diabetes were excluded from the study since it may adulterate the assessment of normal cerebral sulcal development due to high possibility of intrauterine growth restriction . Twin gestation also was excluded from the study..

MRI examination is done in the early morning session in overnight fasting status . Mothers were instructed to empty the bladder before MRI examination only to reduce foetal movements to some extent. No other medication or sedation was given .Foetal MRI was performed using 1.5 tesla superconducting magnet SIEMENS SYMPHONY SYNGOMR (no.1006992119) using a phased array torso surface coil .we employed half fourier acquired single shot turbo spin echo sequence **(HASTE)** , which is a type T2 spin echo sequence (single shot fast spin echo sequence) ,So as to reduce the movement artifacts created by foetal movements and to improve image quality .

Initially localizer is obtained with large field of view ranging from 320–400 mm to assess the foetal position in three orthogonal planes . Once scout image was taken ,based on the position of foetal head serial images in all three planes were taken which should set to allign orthogonal to fetal brain using following parameters

1.Slice thickness was kept as 4 – 6 mm .
2.Matrix size 169x256
3.Field of view of 330-360mm
4.Flip angle of 90 degrees with acquisition time of 1 slice per sec .
5. About 9 to 19 slice of images were obtained with interslice thickness of less than 2 mm .

All the images were well scrutinized and examined under the guidence of two eminent radiologists with 5 years of experience in MRI from our department without the knowledge of gestational age of the foetus. All the cerebral sulci (total of 17)were looked for in an orderly manner starting from sulci present in medial cerebral surface,followed by ventral cerebral surface and then those present in vertex . The identified sulci were categorized in to three catagories – present, absent and partially developed . Sulcus which may be seen as a very shallow indentation without a clear CSF space in between are termed as partially developed. Sulcus which is well conspicuous with a clear CSF space in between were termed as present. Each of the sulci may be visualised better in specific orthogonal plane. Those planes at which examination of each sulci were performed at its best are described in the Table 1 . In our study, the side of the sulci and sex of the foetus were not discriminated .



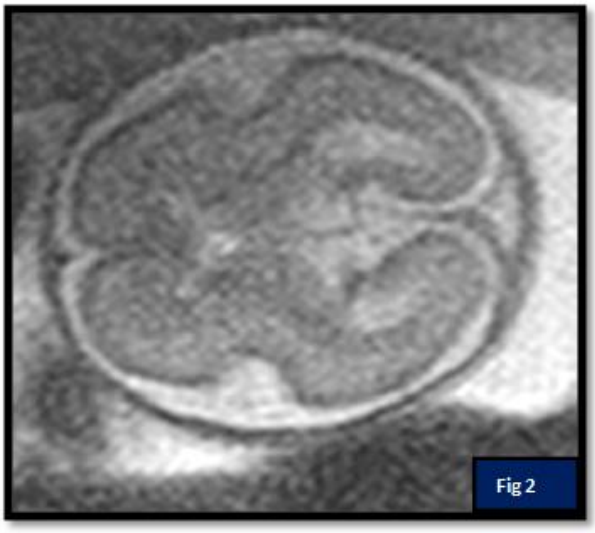
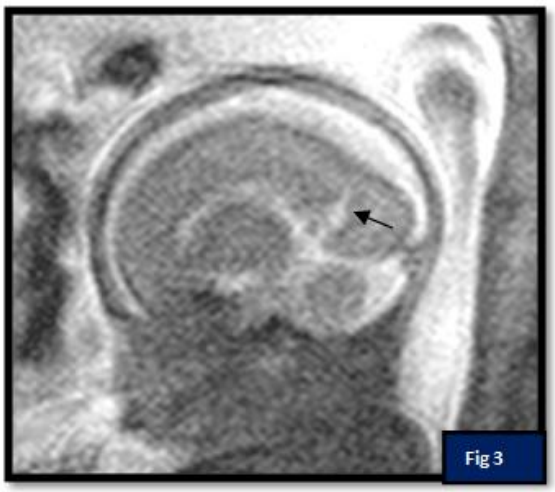


Fig 1,2 shows interhemispheric fissure in coronal and axial sections respectively .
Stage -1 (22-23 wks of gestation)



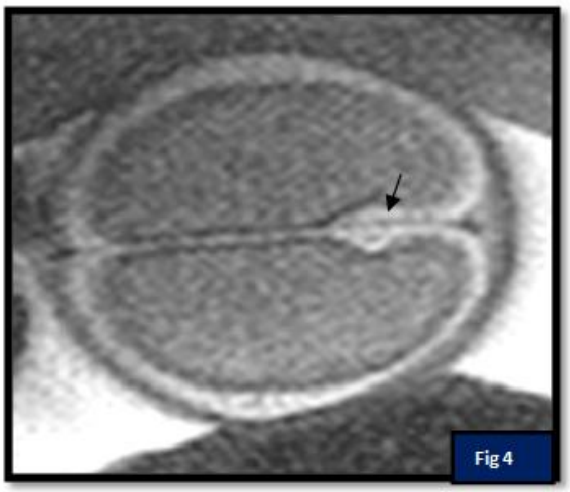
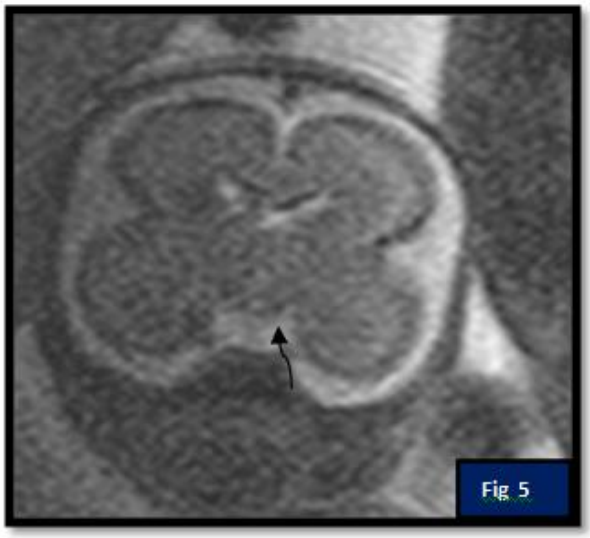


Fig 3 ,4 shows parieto-occipital fissure in sagittal and coronal section . ***Stage 1 (22-23 wks of gestation)***

III. Analysis And Results

Based on the percentage analysis of the categorical variables , the cingular and calcarine sulcus are earlier detectable in 24 and 25 wks of gestation respectively , whereas they ever present after 28 wks of gestational age . Other sulci those present in the medial surface of cerebrum includes Secondary cingular sulci , marginal sulcus and secondary occipital sulci , which are earliest detectable at 31 wks,27 wks,and 32 wks respectively .They present ever after 31 ,28 and 36 wks respectively .Collateral and occipitotemporal sulci of ventral surface of brain begin to be identified by 27 and 29 weeks repectively ,whereas it is fully developed and always well demonstrable after 29 and 33 weeks respectively .



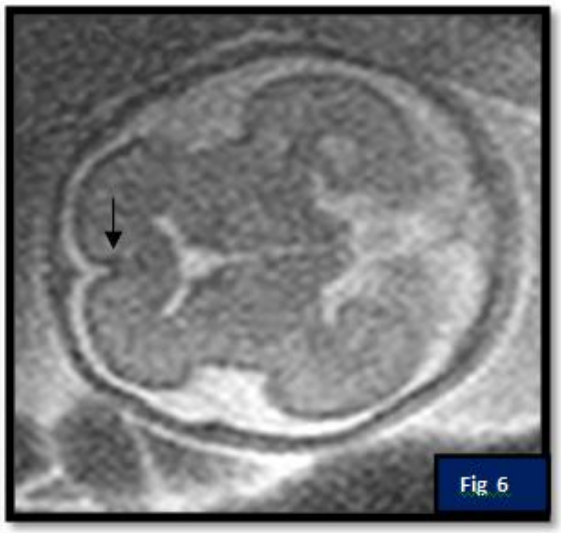


*Fig 5 ,6 shows hippocampic fissure ( ) and interhemispheric fissure ( )in coronal and axial sections .(**Stage 1**)*

Table 1 shows priority of cut sections in which specific sulci can be visualised better

SULCI	**BEST PLANE OF VISULAISATION**
Interhemispheric fissure	CORONAL > AXIAL
Callosal sulcus	SAG > CORONAL
Parietooccipital fissure	SAG > AXIAL > CORONAL
Cingular sulcus	SAG > COR
Secondary cingular sulci	COR > SAG
Marginal sulcus	AXIAL > SAG
Calcarine fissure	SAG > AXIAL > CORONAL
Secondary occipital sulci	COR > SAG > AXIAL
Sulci of the ventral cerebral surface	
Hippocampic fissure	COR > AXIAL
Collateral sulcus	COR > AXIAL
Occipitotemporal sulcus	COR > AXIAL
Sulci of the lateral cerebral surface	
Superior frontal sulcus	COR > AXIAL
Inferior frontal sulcus	COR > AXIAL
Superior temporal sulcus (posterior part)	COR > SAG
Superior temporal sulcus (anterior part)	COR>SAG
Inferior temporal sulcus	COR>SAG
Intraparietal sulcus	COR> AXIAL
Insular sulci	AXIAL > COR >SAG
Sulci of the vertex	
Central sulcus	AXIAL > SAG
Precentral sulcus	AXIAL > SAG
Postcentral sulcus	AXIAL > SAG

Intraparietal , post central ,superior frontal , inferior frontal ,superior temporal (anterior part are earlier detectable in 28-29 weeks of gestation in which intraparietal , post central and superior frontal sulci are 100 % visualised in 30-31 weeks of gestation. Anterior part of superior temporal sulcus is demonstrated in 100% of foetuses in and after 33 weeks of gestation .Inferior frontal sulcus is always by any means present by 31 wks of gestation.. In the gestational age of 30-31 wks, secondary cingular sulcus, inferior temporal sulcus and insular sulcus can be demonstrated at its earliest , whereas 100 % of foetuses demonstrated inferior temporal sulcus by 35 weeks , and insular sulcus by 34 weeks.

Interhemispheric fissure , callosal sulcus , hippocampic fissure already exist in all 74 fetuses starting from 22 weeks of gestation .Parietooocipital fissure also noted in 10 out of 11 fetuses by 22 weeks of gestation and is partially developed in one of those foetuses by 22 wks whereas it is ever demonstrable after 23 weeks of gestation . However the earliest detectable gestational age of all 4 above mentioned sulci could not be covered upon by our study group .

Table 2 shows gestational age group at which each sulcus can be earliest demonstrable and must be demonstrable .

SULCI	EARLIEST DETECTABLE	ALWAYS PRESENT(100%)
CINGULAR SULCUS	24 WKS	27 WKS
SECONDARY CINGULAR SULCUS	31 WKS	31WKS
MARGINAL SULCUS	27 WKS	28WKS
CALCARINE SULCUS	25 WKS	28 WKS
SECONDARY OCCIPITAL	32 WKS	36 WKS
COLLATERAL SULCUS	27 WKS	29 WKS
OCCIPITOTEMPORAL	29 WKS	33WKS
SUPERIOR FRONTAL	28 WKS	29WKS
INFERIOR FRONTAL	28 WKS	31 WKS
SUPERIOR TEMPORAL (POSTERIOR)	27 WKS	28 WKS
SUPERIOR TEMPORAL (ANTERIOR)	28WKS	33 WKS
INFERIOR TEMPORAL SULCUS	31 WKS	35 WKS
INTRAPARIETAL SULCUS	28 WKS	29 WKS
INSULAR SULCI	31 WKS	34 WKS
CENTRAL SULCUS	26 WKS	27 WKS
PRECENTRAL SULCUS	26WKS	28WKS
POSTCENTRAL SULCUS	28 WKS	30 WKS

IV. Discussion

According to Barkovich *et al*., 1988 (14); O'rahilly and Muller, 2001 (15) the progression of myelination and gyral sulcal formation are the indicators of functional maturity in the fetal brain as it can well be correlated with psychomotor development. However in a foetus myelination occurs only partially, starting from the thalamus and brain stem (Yakovlev and Lecours, 1967 (16); Lee *et al*., 1986 (17)). Thus, sulcal development is considered to be more accurate indicator of fetal brain maturation in utero than myelination. As the gestational age advances the sequential development of sulcation also progresses. Hence we attempted to stage the development of sulcation based on the serial appearance of particular sulci in MR images (Table 3) .

Below proposed stages are , based on the fact that there is a sequential appearance pattern of cerebral sulci . Our classification is based on both earliest visualisation of various sulci and its deadline visibility in relation to gestational age, which makes it both more sensitive as well as more specific in detecting neuroanatomical abnormalities . when the classification is solemnly based upon presence of sulci in 100% of fetuess , correlation between the sulcal development and gestational age can only be done after 28 weeks of gestational age . Hence we attempted to classify combining both earliest and deadline visibility of each sulci

The Below table shows that the assessment of sulcal formation and brain maturation can be done most accurately through fetal MRI after 28 weeks of gestation , which appears to be reiterating the MRI findings of Garel et al .

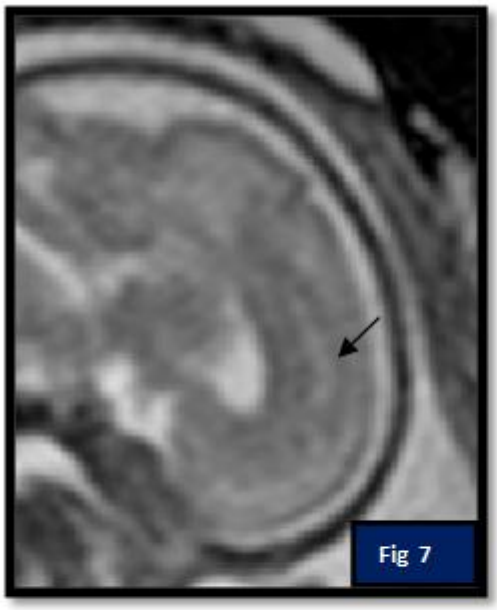
Table 3 shows proposed stages of in utero sulcal development .

STAGES	GA	SULCI
STAGE 1	**22-23 WKS**	i. Interhemispheric fissure, hippocampicfissure ,callosal sulcus , parietooccipital fissure may be present .
STAGE 2	**24-25 WKS**	i. Calcarine and cingular sulcus may be present . i. Stage 1 sulci must be present .
STAGE 3	**26-27 WKS**	i. Marginal ,collateral,central ,precentral ,superior temporal (posterior part) sulci may be present i. Stage 1 ,2 sulci must be present .
STAGE 4	**28-29 WKS**	i. Intraparietal , post central ,superior frontal ,inferior frontal ,superficial temporal (anterior) sulci may be present i. Stage 1,2,3 sulci must be present .
STAGE 5	**30-31 WKS**	i. Secondary cingular ,inferior temporal and insular sulci may be present . i. Stage 1,2,3,4 sulci must be present
STAGE 6	**32-33 WKS**	i. Secondary Occipital Sulci may be present . i. Stage 1,2,3,4,5 sulci must be present .

Mcardle *et al*. (1987) (18) , using MR - T1 images, anatomically classified the cortex development in preterm infants which comprises of five groups. These stages however appears to be more nonspecific. It was based on gray–white matter differentiation , and it was also determined how post conceptional age was related to the development of sulcal formation . As per Garel et al , sulcus formation are best evaluated during the gestational period of 28 to 34 weeks but Mcardle *et al*. categorized this whole period into a single stage . Moreover , the duration of each stage was huge and it varied from 3 to 10 weeks in their classification. Thus, their classification cannot be considered to be too accurate. On the other hand , in our proposed stages,

the gestational period of 28 to 33 weeks was classified into 3 stages . Since beyond 34 weeks no newer sulci appear to emerge it was not considered in our stages. unlike Mcardle's classification each category comprises of only 2 weeks without any overlapping .

Van der Knaap *et al.* (1996) (19) reported and compared MR images of seven regions of brain on prematurely delivered infants and infants expired within one week after birth by evaluating the width of the gyrus and depth of the sulcus in reference to postconceptional age. However, their results show a lag of 2 to 4 weeks than ours for each sulcation stage.



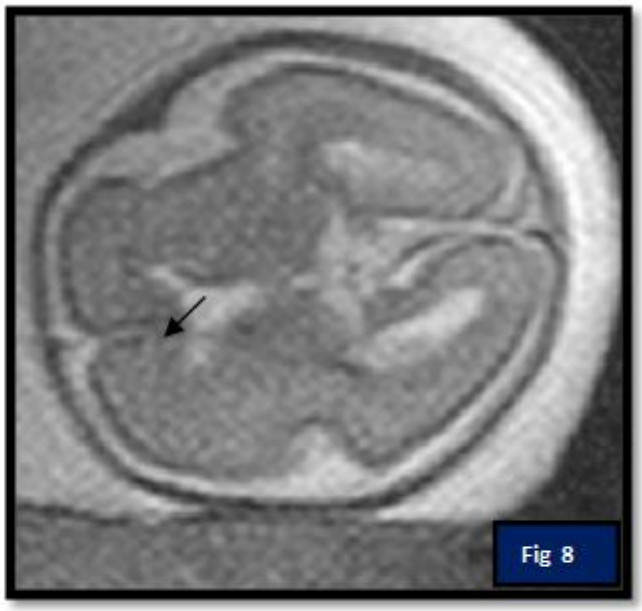
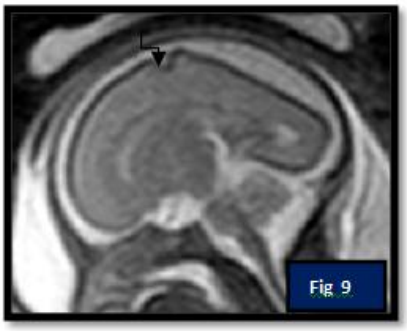
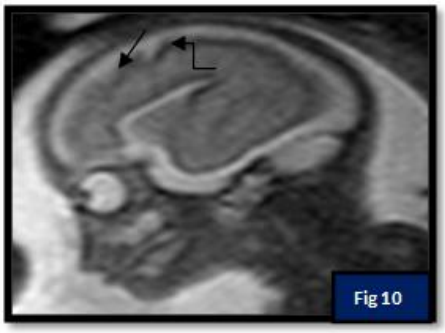
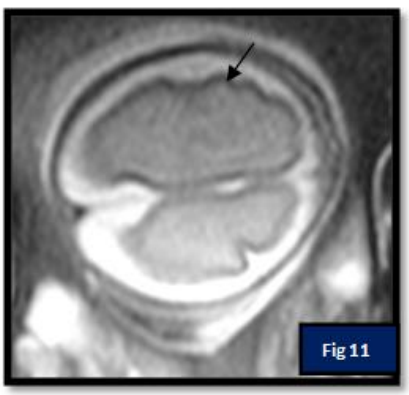


*Fig 7 ,8 shows cingular sulcus (↙) in its sagittal and axial sections which usually starts seen after 24-25 weeks (**Stage 2**)*







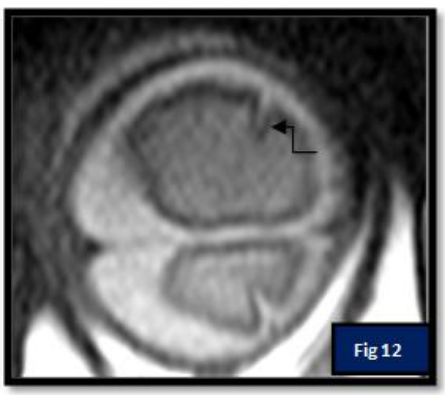


*Fig 9 & 12 shows central sulcus in sagittal and axial section of brain in 26-27 weeks of gestation (**Stage 3**) Fig 10 & 11 shows stage 3 sulcal development where precentral sulcus(↙) , central sulcus (↰) can be seen.*

The possible major reason for difference of opinion could be that vanderkanap study was an evaluation of preterm infants and infants who died within one week of delivery, while ours comprises of normal foetuses who are expected to born at term. Therefore, To estimate the sulcal formation using fetal MR images, we feel that our stages may be more appropriate especially in second and third trimester , usually when antenatal MRI is done if at all for other indications .

Only a few investigators have attempted to study the fetal MR images of sulcal and gyral formation . Among them the first ones were Levine and Barnes (1999) (20) who reported the developmental pattern of sulcal formation in relation to gestational age on MR images. However, most of the study subjects undergone MRI for maternal indications and fetal non neurological indications. Hence ,the image slices were not obtained in the orthogonal plane to the brain in all cases. Whereas in our study, all the antenatal mothers underwent MR imaging specifically to look for foetal brain following a standard protocol for it and also cases in which images were not obtainable in the orthogonal plane to brain were excluded from analysis. In addition, Levine et al included twin gestation mothers in whom a delay of two to three weeks in the development of gyral and sulcal formation occurs when compared to that in a singleton which has been already reported (Chi *et al*.,1977). Whereas in our study only singleton are taken in to account. .

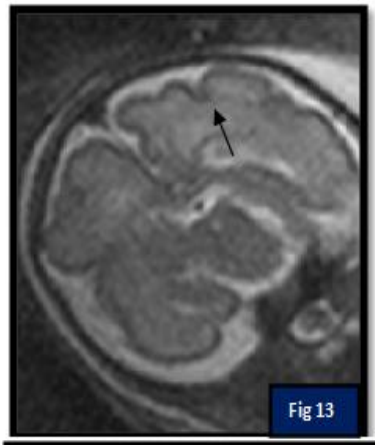
Seiji abe (21) et al , did their assessment on cortical gyrus and sulcus by dividing the study group in to 8 and compared the individual groups to give developmental stages of sulcal and gyral development which comprises of 8 stages .Their stages included only the frontal and temporal lobe sulcal formation leaving behind the parietal and occipital lobes . Hence we feel that our proposed stages would be more reliable and accurate in assessing sulcation in toto .

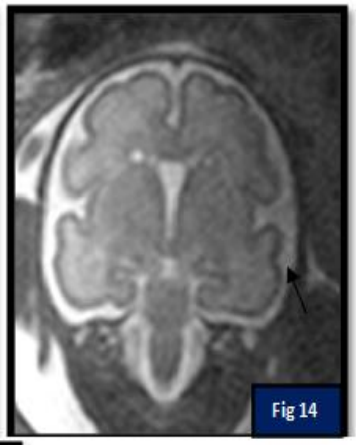
On retrospective correlation (Table 4) with prior antenatal MR study on normal cerebral sulcation done by Garel et al , our study appears to be well correlated with their respective gestational age of presence of particular sulci except for few sulci namely secondary cingular sulci , secondary occipital sulci , occipitotemporal sulci ,, superior temporal sulcus (anterior part) , inferior temporal sulcus and insular sulcus .All these above said sulci are demonstrated 1 or 2 weeks earlier than by those described by Garel et al . According to Garel all the primary sulci appear before 34 weeks, whereas all the primary sulci tend to be present even before 32- 33weeks gestation in our study. This may be attributed to the usage of 1.5 T MRI in our study compared to 0.5 T MRI by Garel et al.

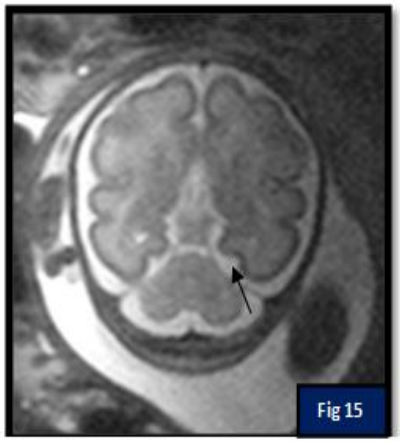
Table 4 correlated findings of our study with neuropathological appearance , garel et al other studies using MRI

SULCI	NP (WKS) APPEARANCE (Chi et al)	GAREL ET AL (WKS)	LAN ET AL (WKS)	GIRARD ET AL (WKS)	OUR STUDY
IHS	10	22-23	-	-	AP
CAL	14	22-23	-	-	AP
POF	16	22-23	26	20	AP
HF	-	22-23	-	-	AP
CIN	18	24-25	-	27	24-25 WKS
SCS	32	33	-	-	30-31 WKS
MS	-	27	-	-	26-27 WKS
CLC	16	24-25	-	24	24-25 WKS
SOS	34	34	-	-	32-33 WKS
COL	23	27	-	-	26-27 WKS
OTS	30	33	-	-	28-29 WKS
SFS	25	29	-	-	28-29 WKS
IFS	28	29	-	-	28-29 WKS
STS-P	23	27	24-26	28	26-27 WKS
STS-A	-	32	-	-	28-29 WKS
ITS	30	33	-	-	30-31 WKS
IPS	26	28	-	-	28-29 WKS
IS	34-35	34	-	-	30-31 WKS
CS	20	27	24-26	24	26-27 WKS
PRE CS	24	27	24-26	24	26-27 WKS
POST CS	25	28	24-26	24	28-29 WKS

.(AP – already present)(IHS - *Interhemispheric Fissure ,CAL- callosal sulcus ,POF - parietooccipital sulcus,HF - hippocampic fissure , CIN - cingular sulcus, SCS- secondary cingular sulcus, MS- marginal sulcus, CLC- calcarine sulcus, SOS - secondary occipital sulcus,COL- collateral sulcus, OTS - occipitotemporal sulcus, SFS - superior frontal sulcus,IFS - inferior frontal sulcus,STS-P - superior temporal(posterior),STS-A - superior temporal (anterior),ITS - inferior temporal sulcus,IPS- Intraparietal sulcus,IS- insular sulci,CS- central sulcus ,PRE CS- precentral sulcus,POST CS-postcentral sulcus)*







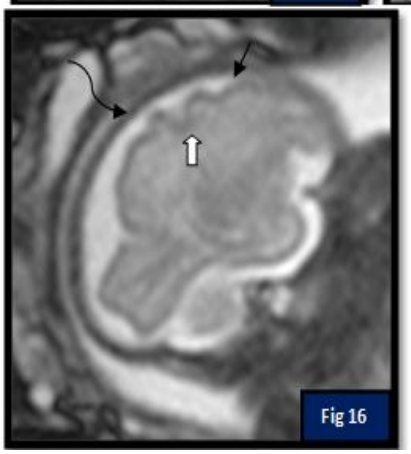


Fig 13 shows intraparietal sulcus , Fig 14 shows superior temporal sulcus (posterior part) , Fig 15 shows occipito temporal sulcus .

Fig 16 shows partially developed post central sulcus ( )with central ( )and precentral ( ) sulcus presence . All of these subjects are in ***Stage 4*** *sulcal development .*

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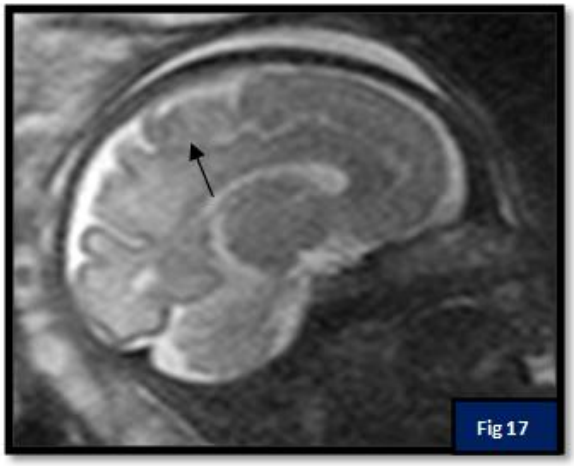
Cortical sulcation was considered to be a appropriate and good marker of fetal brain maturation by neuropathologists(22,23,2); however, even among these neuropathologic researchers , there were lot of discrepancies concerning the time of appearance of cerebral sulci . According to Larroche (23), the superior temporal sulcus was considered to be good morphologic criteria of gestational age and it was described to appear at 28 weeks gestation, whereas Chi et al (2) observed the same sulcus by 24 to 26 weeks gestation. Moreover, the central sulcus was described to be detectable by 20 weeks of gestation as per Chi et al (2) and Larroche (23) where as by 24 weeks of gestation according to Dorovini-Zis and Dolman (22) .

These discrepancies may be due to several factors such as 1. Difference in field strength of the MRI machines used in various studies and difference in sensitivity of sequences 2. Calculation of gestational age, which was not based on the same criteria for all the author - it was calculated by last menstrual period by some authors (2, 23) (which is more unreliable), and some of them calculated by using head circumference, and crown-to-heel length measurements . 3. Sampling size (cohort size) which varied from 30 (23) to 80 (22) to 207 (2) foetuses 4. Different techniques of neuropathological examination such as gross inspection of the brain, photographs of the fixed brains , serial sections of the brain with varying thicknesses . and 5. laterality of brain side and inclusion of twin gestation , which may influence sulcation . These discrepancies emphasize the difficulty in establishing a reliable pattern of sulcation even in the case of neuropathologists with a high degree of precision.

Limitations : We feel that for a formation of standards of reference of normal pattern of sulcal development , there should be considerably large sample size in the study. However due to ethical issues , to include the so called normal foetuses in the research study makes it difficult to gain a large sample size . The sex and side of the brain where the sulci were identified were not included in the study . However there are literature giving evidence (Chi et al) that there is no difference between the sulcal development among male and female foetus.



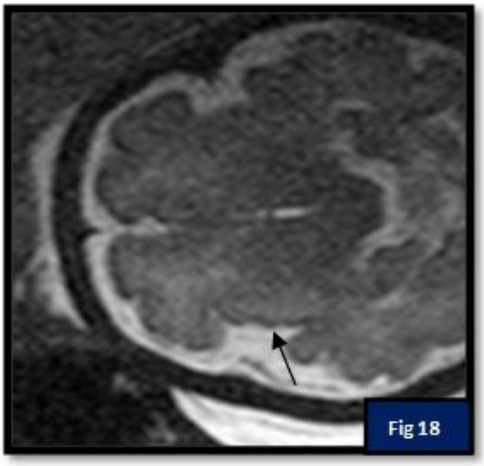
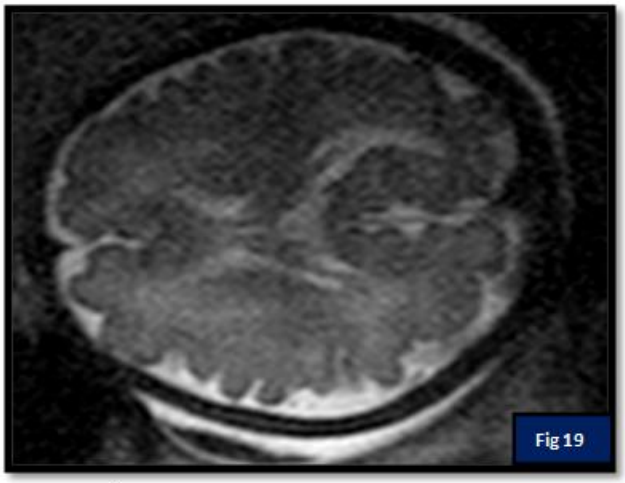


Fig 17 shows secondary cingular sulci with undulations .Fig 18 shows insular sulci . Note the undulations formed in the sylvian fissure which is termed as insular sulci ***(Stage 5)***

Recommendations :

The observations of our study and the stages of the sulcal development derived from it can be made in to a chart and can easily be monitored to evaluate brain maturation of foetuses. Eventhough ,it is a MRI study ,the normal observations made in our study can very well be followed up in ultrasonagram provided acoustic window is favourable to an experienced and eminent radiologist . And we also recommend further studies based on this normogram in early search of brain formation anomalies.



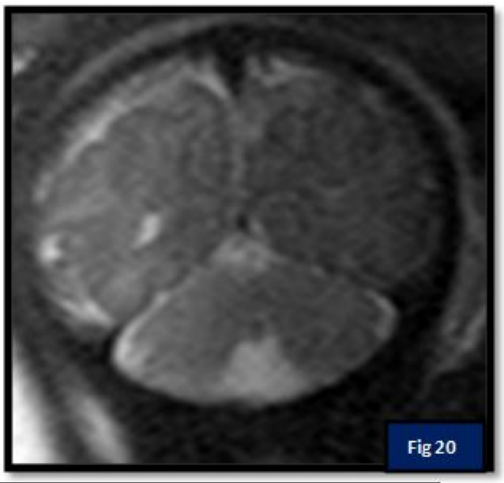


Fig 19 shows partially developed secondary occipital sulci ***(Stage 6)****whereas Fig 20 shows well formed secondary occipital sulci*

V. Conclusion

MRI scores over ultrasound in number of conditions like in having a higher contrast resolution, being not affected by calvarial shadow or by low amniotic fluid volume, and being easily performable using ultrafast T2-w sequences within seconds per sequence . Hence sulcation with sequential stages of its development with respect to gestational age can be efficiently assessed using foetal MRI. Evaluation of the developmental stages of sulcal formation using Foetal MR images in turn evaluates fetal brain maturation in relation to gestational age especially in second and third trimesters. Foetal MRI also aids in early detection of gyral and sulcal formation anomalies and assessment of its severity to make the final management decisions, genetic counselling and sometimes in guiding therapy . Hence Foetal MRI proves to be a potential screening tool in the second and third trimester fetuses who are at risk for brain anomalies .

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