Development of fetal brain of 20 weeks gestational age: Assessment with post-mortem Magnetic Resonance Imaging

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1. Introduction

During fetal brain development, complex events take place including the rapid developmental process of exterior morphology and internal structures, and it is significant to analyze these changes for the assessment of fetal brain development and diagnosis of clinical diseases [1,2].

At present, the developmental process of the fetus in vivo is divided into the first, second and third trimesters, which are closely associated with the different developmental stages of the central nervous system (CNS). In the first and second trimesters, the neurons in the ventricular and subventricular zone migrate to the surface layer, which is almost finished at 20 weeks GA. After that, there is myelination of the white matter, migration of glial cells and deepening and folding of the immature sulci and gyri [1,2]. Therefore, developmental abnormalities can easily take place in this period but may not be easily detected by ultrasonography (US) or MRI in vivo, because the small fetal brain volume and frequent fetal movement after the second trimester may influence image quality. With the development of MRI techniques, especially the application of rapid acquisition with relaxation enhancement sequence, image quality of in vivo fetal MRI is greatly improved [3]. But in vivo fetal MRI is limited by the special scanning field, sequence and thickness, and is influenced by maternal structures, pulse of the maternal artery or structures [4,5], so that the in vivo data may have limitations particularly concerning the resolution of small brain structures at the early developmental phase, such as the tiny sulci on the cortical surface, the basal nuclei, and the cerebellum. Then, in vitro assessment is necessary. In several countries, the latest time point to perform a termination of pregnancy is 24 weeks GA [6], and thus data on brain development before this fetal
age is crucial. But at present, exact anatomical characters revealed by fetal MRI prior to this time point are lacking.

The present research of post-mortem MRI confirms its value in autopsies [7] and contributions to fetal brain development [8]. Images are clearer on post-mortem MRIs than those in vivo because the former, absent of movements artifacts, are not restricted in the scanning field and sequences. In this study, 20 fetal specimens of 20 weeks GA were chosen, and their heads were scanned with 3.0 T and 7.0 T MR. Then the three dimensional visualization model and quantitative measurements were obtained with Amira 4.1 software. It is thought that the results of the present study can serve as guidance in evaluating the condition of fetal brain development and diagnosing clinical diseases in vivo.

2. Experimental procedures

2.1. Samples

35 fetal specimens of 20 weeks GA were obtained from medically indicated or spontaneous abortions (caused by incurable fetal malformations outside the brain, maternal infection, heart failure, shock and uterine traumas caused by accident, uterine myoma, incompetence of internal orifice of the uterus, and unknown causes), and fetal deaths (caused by maternal diseases or without clear reasons) in hospitals of Shandong Province.

The inclusion criteria were as follows: the maternal pregnancy records with absence of a documented fetal chromosomal abnormality, any other stressful intratuerine conditions before the spontaneous abortion occurred, maternal genetic disease in their families, or a history of seizures in the case of eclampsia; results of US and in vivo MRI examinations for the fetus during pregnancy and results of the post-mortem MRI examinations for the specimen indicating an anatomically normal and developmentally appropriate fetal CNS; further validated detailed autopsy combined with neuro-pathological examinations also describing no detectable CNS malformations.

All the 35 cases had US examinations, and 13 fetuses had prenatal MRI scans at the same time. The post-mortem MRI examination was performed by 2 pediatric neuro-radiologists with clinical experience of more than 10 years. The criteria by which a fetus was deemed to be anatomically normal were based on the size of the cerebrum, developmental status of cerebral cortex, lateral ventricle, and corpus callosum. 2 radiologists reviewed all the images to confirm normal morphological features of the fetal CNS. When there were discrepancies between the 2 neuro-radiologists, the fetuses were excluded. Finally, detailed autopsy was performed on all specimens by 2 embryologists, and neuro-pathological examinations were offered by 2 neuro-pathologists to confirm whether there were detectable CNS malformations.

Finally, 20 specimens (10 males and 10 females) with an appropriately developmental fetal brain were reserved for the study. The GA was estimated on the basis of their crown-rump length, head circumference, foot length and/or pregnancy records and expressed as weeks from the last menstrual period [9]. The entire fetus was immersed in 10% formalin for preservation, and was separately reserved in wide mouthed bottle made according to their body size in order to avoid deformation once they were obtained. Then they were scanned with 3.0 T and 7.0 T MR. The time interval between performing the fixation and the scanning was within 2 months.

2.2. MRI protocol

The specimens were first scanned by a GE 3.0 T MR scanner (General Electric, Milwaukee, USA). The eight-channel high-resolution brain array was chosen for scanning all the fetuses. Scanning thickness: 2 mm, slice interval: 1.5 mm. Parameters were as follows: T1 FLAIR sequence: Repetition time (TR): 2580.0 ms, echo time (TE): 23.4 ms, matrix size: 512 × 512, number of excitations (NEX): 1, the acquisition time: 1 min 47 s. T2-weighted: TR: 4600.0 ms, TE: 111.6 ms, matrix size: 512 × 512, NEX: 1, field of view (FOV): 16 cm × 16 cm, and acquisition time: 3 min 56 s.

There were scanned by a BRUKER 7.0T Micro-MR with a maximum gradient of 360 mT (10/16 pharmaScan, Bruker Biospin GmbH, Germany). A rat body coil with an inner diameter 60 mm was chosen to scan all the fetuses. T1-weighted: slice thickness: 0.8 mm, slice interval: 0.8 mm, and the parameters were as follows: TR: 384.4 ms, TE: 15.8 ms, matrix size: 512 × 512, NEX: 1, FOV: 6 cm × 6 cm, and the acquisition time: 14 m 32 s. T2-weighted: slice thickness: 0.5 mm, slice interval: 0.5 mm, and the parameters: TR: 17000.0 ms, TE: 50.0 ms, matrix size: 256 × 256, NEX: 4, FOV: 6 cm × 6 cm, and the acquisition time: 28 m 15 s.

2.3. Structure annotation and reconstruction

Amira 4.1 was used for image segmentation and reconstruction of 7.0 T MRIs. Brain structures were assigned and annotated based on a histological atlas of second trimester fetal brains [10]. The cerebral surface, basal nuclei, lateral ventricles and cerebellum were manually traced out on each image. The segmentation on the cortical surface was performed at the borderline between the cortical plate and the marginal zone (Fig. 1). To check the reproducibility of the manual segmentation, all the brain structures were manually segmented simultaneously twice by two anatomists to obtain a mean. The time interval of each round of manual segmentation was at least 1 week.

2.4. Statistical evaluations

A clear indentation at the surface of the brain was considered the earliest indication of a sulcus, while a slight indentation of the brain surface was defined as an ‘anlage’ of a sulcus. A sulcus was considered to be present or its anlage was present if it was observed in more than 75% of cases, detectable if observed in 25–75% of cases, and absent if observed in less than 25% of cases. A paired t test was used to detect significant differences in genders and hemispheres. All the statistical work was done on SPSS 17.0.

2.5. Ethics

This study was conducted on the basis of the approval from the Internal Review Board of the Ethical Committee at the School of Medicine, Shandong University. Parents' consent to donate the fetal cadaver was obtained.

3. Results

3.1. The sulci on gross anatomy

The sulci could not be observed on the brain surface covered with the cerebral pia mater and there were many vessels lying just above the sulci. After removing the cerebral pia mater, the immature sulci were seen as shallow fossas on the cerebral surface, such as the lateral sulcus, central sulcus, and precentral sulcus. Some sulci were discontinuous, and appeared as a clustering of shallow fossas, such as the superior frontal sulcus and superior temporal sulcus. There were good consistencies in delineating the sulci between the gross anatomy and the reconstructed three dimensional visualization model (Fig. 2).
3.2. The sulci on post-mortem MRIs

The lateral sulcus, central sulcus, cingular sulcus, superior frontal sulcus, parieto-occipital sulcus, calcineur sulcus, posterior part of superior temporal sulcus, and olfactory sulcus were present at 20 weeks GA. The anlage of the inferior temporal sulcus, collateral sulcus, and orbital sulcus were also present. The anlage of the inferior frontal sulcus and precentral sulcus were detected. The postcentral sulcus and intraparietal sulcus were absent. All the sulci were straight, immature and had not developed secondary or tertiary branches. Most of the sulci appeared deeper and more distinguishable in the right hemisphere. The lateral sulcus was the widest and deepest, which appeared as an open fossa on the cerebral surface, and the operculum insulae had not folded. On 3.0 T MRI, the sulci were vaguely shown as punctiform regions with high signal intensities on T1-weighted images, but there were good consistencies with the 7.0 T MRIs on which they were more clearly delineated (Figs. 3 and 4a).

3.3. The laminar organization on post-mortem MRIs

The nomenclature of the laminar organization was used according to the description given in previous studies [11–13]. The parallel laminar organizations were shown with different signal intensities on post-mortem MRIs, which were the most distinguishable in the parieto-occipital part of brain and peripheral regions of the hippocampus (1–7 in Figs. 3, 4a and 5). The layer with high density of cells was seen with high signals on T1-weight post-mortem MRIs, such as the ventricular zone and the marginal zone. However, the layer of low density cells or rich fibers was delineated with low signals, such as the subplate zone and periventricular zone. The subplate was the most obvious, which was described as a wide layer containing two layers of different signals. The lower layer had a high signal while the higher had a low signal (5 in Figs. 3a, 4a and 5a). The periventricular zone (2 in Figs. 3, 4a and 5) and external capsule (white single arrow in Figs. 4a and 5) could be continuously differentiated with low signal intensities on T1-weighted images in the parieto-occipital part of brain. The external capsule fibers, which connected the external capsule (black single arrow in Fig. 3) to the basal nuclei, separated the intermediate zone and the subplate. The intermediate zone (4 in Figs. 3, 4a and 5), a high signal layer on T1-weighted images, appeared wide and typical at this time, with the bilateral sides forwardly linking the bottom part of the external capsule and upwardly linking the inferior part of the subplate. The marginal zone could be observed on 7.0 T MRIs (7 in Figs. 3b and 5b) but it could not be delineated on 3.0 T MRIs.

3.4. The basal nuclei on post-mortem MRIs

The basal nuclei could be clearly described on 3.0 T MRIs. The dorsal thalamus, lenticular nucleus and caudate nucleus, which had high signal intensities on T1-weighted images, could be differentiated (Figs. 3a and 4a). The internal capsule (white single arrow in Fig. 3) was among them and its anterior limb had high signal intensity but the posterior limb had low signal intensity similar to that of the subplate zone. The claustrum, which had high signal intensity, had formed and separated the external capsule and extreme capsule. The signal intensity of the external capsule and extreme capsule were lower compared with that of the internal capsule on T1-weighted sequence. The germinal matrix was the most obvious structure in the basal nuclei which occupied most of the lateral ventricle. It was just above the caudate nucleus with its bilateral sides forwardly connecting with the ventricle zone (Figs. 3, 4a and 5). On 7.0 T MRIs, the basal nuclei and the borderlines could be more clearly described.

3.5. The cerebellum and brainstem on post-mortem MRIs

The cerebellum had higher signal intensity on T1-weighted images compared to other brain regions (Figs. 4a and 5a). It was vaguely described and could not be precisely discriminated on 3.0 T MRIs, but it could be clearly delineated on 7.0 T MRIs (Figs. 4b and 5b). In all the fetuses, the primary fissure, the postero-lateral fissure, tonsilla of cerebellum, and the floccular
Fig. 3. The transverse T1-weighted 3.0 T MRI (a) and T2-weighted 7.0 T MRI (b) of 20 weeks GA. The sulci at the brain surface, such as the lateral sulcus, superior frontal sulcus, parietooccipital sulcus, posterior part of superior temporal sulcus and inferior temporal sulcus are vaguely shown on the former but clearly shown on the latter. The basal nuclei are clearly shown with visible borderlines, and the cerebral cortex is composed of parallel layers with different signal intensities. The white single arrow represents the internal capsule. The black single arrow represents the external capsule. Figure explanations: cgs = cingular sulcus, pof = parietooccipital sulcus, cof = callosal sulcus, sts = superior temporal sulcus, its = inferior temporal sulcus, ots = occipitotemporal sulcus, dt = dorsal thalamus, cn = caudate nucleus, ln = lenticular nucleus, and gm = germinal matrix. 1 is the ventricular zone; 2 is the periventricular zone; 3 is the subventricular zone; 4 is the intermediate zone; 5 is the subplate zone; 6 is the cortical plate; and 7 is the marginal zone.

Fig. 4. The sagittal T1-weighted 3.0 T MRI (a) and T2-weighted 7.0 T MRI (b) of 20 weeks GA. The central sulcus, pre-central sulcus, superior frontal sulcus, parietooccipital sulcus and calcaine sulcus are visible on brain surface on the 3.0 T MRI. The laminar organization is typical in the parieto-occipital part of brain and 6 layers can be distinguished. The white single arrow represents the external capsule fibers, with low signal intensity, separating the intermediate zone and the subplate. The primary fissure, prepyramidal fissure and secondary fissure can be delineated on the 7.0 T MRI. Figure explanations: caf = calcaine fissure, pf = primary fissure, and sf = secondary fissure.

Fig. 5. The coronal T1-weighted 3.0 T MRI (a) and T2-weighted 7.0 T MRI (b) of 20 weeks GA. The laminar organization is typical and clearly shown. The tonsilla of the cerebellum is visible. The white single arrow represents the external capsule fibers. Figure explanations: tc = tonsilla of cerebellum.
The lateral ventricle had developed its common shape with the germinal matrix just lying above it were clearly delineated on the three dimensional visualization model, and they also appeared on the lateral sulcus with the operculum insulae not folded. In some cases of prenatal imaging, the white matter was already present at 20 weeks GA in almost all the specimens, but in post-mortem imaging, the brain surface was grossly smooth except the wide fossa of the lateral ventricle, appearing as a clustering of discontinuous shallow sulci. The sulci or their anlage could be observed on the three dimensional visualization model, and they also appeared on the lateral sulcus, central sulcus, precentral sulcus, superior frontal sulcus and olfactory sulcus. The length, depth and location of the sulci could be clearly delineated on the model (Fig. 7), and it could be dynamically displayed.

3.6. The three dimensional visualization model

The lateral ventricle had developed its common shape with anterior, posterior and inferior cortices. It occupied a large part in the cerebral hemisphere (Fig. 6a and b). The ratio between volume of the lateral ventricle and that of the cerebrum was about 7% in the present study. The dorsal thalamus, lenticular nucleus and caudate nucleus with the germinal matrix just lying above it were clearly delineated on the three dimensional visualization model, and they also occupied a large part in the cerebral hemisphere (Fig. 6c and d). The ratio between volume of these structures and that of the cerebrum was about 3%.

Most sulci or their anlage could be observed on the three dimensional visualization model, such as the lateral sulcus, central sulcus, precentral sulcus, superior frontal sulcus and olfactory sulcus. The length, depth and location of the sulci could be clearly demonstrated on the model. The primary fissure could be observed on the cerebellum surface. The shape and relative relationship of the telencephalon, brain stem and cerebellum could be appropriately delineated on the model (Fig. 7), and it could be dynamically displayed.

Table 1
Measurements of the 20 fetal brains by Amira 4.1.

<table>
<thead>
<tr>
<th></th>
<th>The left (X ± SD)</th>
<th>The right (X ± SD)</th>
<th>The lateral ventricle</th>
<th>The left (X ± SD)</th>
<th>The right (X ± SD)</th>
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<tr>
<td>The brain hemisphere</td>
<td></td>
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<tr>
<td>Surface Area</td>
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<td>44.779 ± 4.337</td>
<td>Volume</td>
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<td>1.181 ± 0.310</td>
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<td>16.385 ± 2.642</td>
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<td>2.506 ± 0.304</td>
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<td>4.613 ± 0.330</td>
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<td>The germinal matrix</td>
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<tr>
<td>Volume</td>
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<td>0.713 ± 0.235</td>
<td>Volume</td>
<td>0.178 ± 0.068</td>
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<td>Height</td>
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<tr>
<td>Volume</td>
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<td>Volume</td>
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<tr>
<td>The cerebellum</td>
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<tr>
<td>Volume</td>
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<td>Length</td>
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</table>

Surface area is in square centimeters. Volume is in cubic centimeters. Height, width and length are in centimeters.

* Measurements of the whole cerebellum.

Qualitative measurements of the brain hemisphere, lateral ventricle, germinal matrix, caudate nucleus, lenticular nucleus, dorsal thalamus and cerebellum were listed in Table 1. There were no sexual dimorphisms or cerebral asymmetries in the measurements (p > 0.05).

4. Discussion

4.1. The landmarks of fetal brain development

Development of the fetal brain is described by changes of several landmark structures. Exploring the developmental sequences of these structures on fetal MRIs can greatly enrich the knowledge of prenatal radiology and benefit the diagnosis of the fetal brain in vivo [1,2,14].

The morphological change of sulci is a stable, ordered and obvious progress which can be recognized as an indicator of brain maturation [15]. In this study, it was found that development of one single sulci starts at several separate regions located on the cortical surface, appearing as a clustering of discontinuous shallow fossas, which later merged together. It was also found that almost all the sulci or their anlagen were present but were shallow at 20 weeks GA, with the neighboring walls straight and wide open. The whole cortical surface is grossly smooth except the wide fossa of the lateral sulcus with the operculum insulae not folded. In some CNS diseases, such as congenital callosal or insula agenesis, congenital agryria and severe hydrocephalus, the present time of the sulci and their appearance will change, which could be recognized as the indication of abnormalities [5].

In the present results, some of the sulci could be visualized earlier on post-mortem MRI than in vivo MRI, such as the central sulcus, which commonly could be visualized on fetal MRI at 24–25 weeks GA [15], but it could be clearly observed on the 3.0T or 7.0T post-mortem MRIs at 20 weeks GA, the same results as Chi at al based on neuro-pathological examinations [16]. It can be concluded that MRI with high Tesla can earlier detect the tiny sulci. There are inconsistencies between the present results and previous research. For example, we found that the superior frontal sulcus was already present at 20 weeks GA in almost all the specimens, but Chi at al described the neuro-pathological appearance of the sulci...
at 25 weeks GA, so the present result is even earlier than that of the neuro-pathological examinations [15,16]. The inconsistencies may be due to the following facts: fluid loss of the fetal brain caused by fetal death or formalin fixation, method of describing the presence of a sulcus (being observed in more than 75% or 50% cases), method of examination (US or MRI of different magnetic strength), different races (Asian or Western) and any other unknown reasons. Because there are differences between post-mortem and in vivo imaging regarding the assessment of sulci and gyri, the shallow sulci detected here may not be detected either by US or in vivo MRI for clinicians. This has to be stated.

Laminar organization, which supplies important information for assessing the perinatal origin of cognitive disorders and illuminating the functions of the preterm cortex, is the transient structures of the developing fetal cerebral cortex [17]. It is formed by migration of neurons and fibers, and also displays age-specific changes [11–13]. The laminar pattern in this study, described as layers with different signal intensities, is consistent with previous findings from histological slides and T1-weighted images [11–13]. In this study, the typical laminar organization is clearly delineated at 20 weeks GA, and the marginal zone can be observed on 7.0 T MRI, but it could not be distinguished on in vivo MRI [18] or in vitro MRI of magnetic strength less than 4.7 T [19]. The periventricular zone and external capsule could be clearly visualized at the parieto-occipital part of brain and peripheral regions of hippocampus in our images. But, on previous post-mortem MRIs of 2.0 T [11,12], the two layers could not be continuously delineated.

The cerebellum is the main structure in the posterior cranial fossa, and its developmental condition can be recognized as an indicator for assessment of the posterior cranial fossa [20]. In diseases or deformities, such as the Dandy-Walker deformity, Chiari deformity and Joubert syndrome, the morphology, volume or other measurements of the cerebellum may change. In this research, the fissures, lobes and vermis including the inner nuclei could be clearly observed on the 7.0 T MRIs.

4.2. The superiority in demonstrating fetal brain structures with post-mortem MRIs of high Tesla and three dimensional visualization

It was found that post-mortem MRIs obtained with high Tesla can more clearly delineate the brain structures, and demonstrate some structures that can not be shown on US or in vivo fetal MRIs, such as the small and immature sulci, the marginal zone, the continuing periventricular zone and external capsule.

US is the first screening choice in the clinical examination for fetuses [21], and fetal MRI has become the most common and valuable complementary examination [22]. It is commonly performed after the first trimester when the main steps of organogenesis are completed, but the low scanning field strength (commonly 1.5 T), small head circumference and big scanning thickness (3–5 mm) will lead to low accuracy in diagnosis for the brains younger than 20 weeks GA. However, in vitro MRI can supply excellent slice resolution [23], largely due to the absence of subject movement, unlimited MRI scanning strength Tesla, and acquisition time. So, post-mortem MRI obtained with high Tesla in our research can supply more anatomic references for in vivo studies about fetal brain development, which will benefit the clinical diagnosis in vivo.

Previous research has confirmed the value of three dimensional visualization in the clinical application and assessments of fetal brain development [8,24]. However, because of fundamental differences in tissue types, tissue properties and tissue distribution between the fetal and adult brain, automated tissue segmentation techniques developed for adult brain anatomy are unsuitable for this data [25], and it is difficult to rebuild the brain based on in vivo fetal MRI because of the big scanning thickness (3–5 mm) and low image resolution. But post-mortem MRIs obtained with high Tesla are of high quality sufficient for segmentation, reconstruction and later quantitative analyses. In this research, the interface between the marginal zone and cortical plate to segment the cerebral cortex during the reconstruction process was chosen, because the shallow
sulci are more obvious at this interface. It is thought that this segmentation method can benefit the delineation of sulci at the initial developmental stage. The three-dimensional model can show all the sulci discriminated at the two-dimensional post-mortem MRIs, and the dynamic demonstration supplies great help for comprehension of the relative location of the inner structures.

After reconstruction, the segmented structures were measured automatically, and the fetal brain of 20 weeks GA was quantitatively described in details. The measurements correspond to those Huang obtained with 11.7 T and 4.7 T post-mortem MRIs [8]. But it is thought that our results are more convincing because they were obtained from a greater amount of specimens of the same GA. The volumetric analyses of the germinal matrix and lateral ventricles also correspond to the results Yoshimasa obtained with 4.7 T post-mortem MRIs [26], but the ratio between volume of the germinal matrix and that of the cerebrum in the present results (4%) is a little smaller than that of Yoshimasa’s (5%). Our results may be more accurate because more specimens were scanned with a higher Tesla in the present study, and manual segmentation is much more precise than automatic segmentation especially for the immature fetal brain.

Quantitative analysis in the present study may provide valuable assistance in modeling normal fetal brain development and extracting rules to detect growth patterns that may be related to an abnormal outcome in the early developmental phase. At present, quantitative data about fetal brain development mainly comes from research on neonates or pre-matures [27–29], and very little is known about the range of normal values of brain growth in the first and second trimesters. The present results may be considered as a valuable reference to determine whether the brain is developing normally or not at 20 weeks GA.

4.3. The significance of studying fetal brain development at 20 weeks GA

The 20th week GA is at the mid-point of the whole fetal brain developmental phase in vivo. A complete analysis of the ranges of normal values and asymmetries of brain structures at this time can supply benefits for the assessment of brain maturation during the first half of gestation.

The 20th week GA is also in the initial phase when MRI can be clinically and legally permitted on the pregnant, which is commonly performed after 18 weeks GA. So, our analysis can help to better understand the in vivo fetal MRI, and supply guidelines for diagnosis. In many countries throughout the world, pregnancy termination is usually possible prior to 24 weeks GA [6]. The present results may be helpful in making some crucial decisions.

Asymmetry of the human brain is a normal developmental phenomenon. It is a continuing biological process that begins in fetal life, maturing and changing during neonatal and adult life. At present, there have been conflicting results about whether sexual dimorphisms and cerebral asymmetries were present in fetal life, maturing and changing during neonatal and adult life. The present results indicate that sexual dimorphisms and cerebral asymmetries may start in the second half of the pregnancy. There are some limitations for this study. First, the fetus is not routinely scanned at this high field strength, which may limit the clinical application of our results. It is thought that although the present results cannot be directly used in clinical setting, they provide certain beneficial information in evaluating the fetal brain and interpreting an MRI examination performed at lower field strengths. Second, the scanned fetuses had undergone formalin fixation, which slightly reduced the volume and increased the width of the sulci and affected the measurements. Third, there are no histological comparisons with high-resolution MRI images.

5. Conclusions

At 20 weeks GA, the sulci are mostly present but are immature; the lamination is typical and delineated as layers with different signal intensities; the basal nuclei, lateral ventricle, and the cerebellum have formed their common shape. All the brain structures can be more clearly shown on post-mortem MRIs obtained with high Tesla and three-dimensional visualization supplies benefits for cognition of the immature brain structures. Sexual dimorphisms and cerebral asymmetries of the fetal brain maybe start in the second half of the gestation period.

Acknowledgements

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