Fetal Magnetic Resonance Imaging (MRI): A Tool for a Better Understanding of Normal and Abnormal Brain Development

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Fetal Magnetic Resonance Imaging (MRI): A Tool for a Better Understanding of Normal and Abnormal Brain Development

Sahar N. Saleem, MBBCh, MSc, MD

Abstract
Knowledge of the anatomy of the developing fetal brain is essential to detect abnormalities and understand their pathogenesis. Capability of magnetic resonance imaging (MRI) to visualize the brain in utero and to differentiate between its various tissues makes fetal MRI a potential diagnostic and research tool for the developing brain. This article provides an approach to understand the normal and abnormal brain development through schematic interpretation of fetal brain MR images. MRI is a potential screening tool in the second trimester of pregnancies in fetuses at risk for brain anomalies and helps in describing new brain syndromes with in utero presentation. Accurate interpretation of fetal MRI can provide valuable information that helps genetic counseling, facilitates management decisions, and guides therapy. Fetal MRI can help in better understanding the pathogenesis of fetal brain malformations and can support research that could lead to disease-specific interventions.

Keywords
anomaly, syndrome, genetic, malformation, fetal, MRI

Brain malformations include some of the most severe developmental fetal anomalies that require early diagnosis. Knowledge of the anatomy of the developing fetal brain is essential to detect abnormalities in prenatal imaging and to understand their pathogenesis. Although ultrasonography remains the predominant modality for evaluation of the fetus, magnetic resonance imaging (MRI) has been increasingly used in the second and third trimesters of pregnancy. In contrast to ultrasonography, MRI visualization of the fetus is not significantly limited by maternal obesity, fetal position, or oligohydramnios, and visualization of the brain is not restricted by the ossified skull. Through its superior soft tissue contrast resolution, MRI is able to distinguish fetal brain structures such as sulcation/gyration, posterior fossa structures, and cerebrospinal fluid spaces. Because brain development is a dynamic process in fetal life, it is important to recognize the normal MRI appearance of the brain at different gestational ages to avoid false diagnosis or miss brain abnormalities. During the second trimester, cerebral malformations can present with morphologic features that are different from those that are seen in a more mature brain.

In this article, we aim to discuss the clinical and research aspects of MR imaging of the fetal brain. We emphasize the optimal MRI technique to study the fetal brain. We highlight milestones of brain development in the second and third trimesters of pregnancy and point the common errors of interpreting normal fetal brain MRI that could cause misdiagnosis of abnormalities. We include the in utero MRI appearances of a wide spectrum of isolated and syndromal brain malformations. The expanding role of fetal MRI as a research tool in describing new brain syndromes and its support for research studies is also highlighted.

Fetal MRI Safety and Ethics
MR imaging is a noninvasive diagnostic examination that does not involve ionizing radiation with no known associated negative side effects or reported delayed sequels. However, the considerable majority of data to date comes from research involving magnetic fields of 1.5 Tesla or less, with less information regarding the potential safety issues that can exist at higher field strengths. The American College of Radiology white paper on MR safety states that pregnant patients can be accepted to undergo MRI at any field strength.

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stage of pregnancy if the risk-benefit ratio to the patient warrants that the study be performed and only if other nonionizing diagnostic imaging methods are inadequate. It could be prudent to wait until around the 17th week of gestation before performing fetal MRI because of the limitations created by the small size and excessive motion of younger fetuses. A written informed consent is usually required from the pregnant woman prior to fetal MRI.

Technical Aspects of MRI of Fetal Brain

Development of ultrafast sequences and improvement in scanner and coil technology have led to an increased use of fetal MRI. Fetal MRI studies are typically performed on a 1.5-T system using torso or cardiac phased array surface coils. However, if the patient will not fit into the magnet with a surface array coil, then a body coil can be used. For optimal signal intensity in the subsequent sequences, the fetal brain (region of interest) should be within the center of the coil; if this is not the case, the coil has to be repositioned.

An initial localizer in 3 planes orthogonal to the maternal body shows the fetal position relative to the mother and determines fetal situs. Following scout acquisition, a series of images are obtained orthogonal to the fetal brain. Fetal MRI is an interactive scanning procedure, with each acquisition serving as a scout for the subsequent one in order to avoid misregistration caused by fetal movement. A variety of MRI sequences is used to image the fetus in utero (Table 1). The most widely used sequence in fetal imaging is T2-weighted single-shot fast spin-echo, and balanced steady-state free precession (Figure 1). Both single-shot fast spin-echo and balanced steady-state free precession sequences provide comparable image quality, especially in the second trimester; however, the axonal myelination in the third trimester is better delineated by the latter. Additionally, balanced steady-state free precession is a preferred sequence for visualization of the fetal vascular structures and heart. A series of T2-weighted images are obtained in the axial, sagittal, and coronal planes orthogonal to the fetal brain. Optimal slice thickness is 3 mm with no gap or with slice overlap. In some patients, a 4- to 5-mm slice thickness could be needed because of signal-to-noise considerations.

T1-weighted images are typically acquired using ultrafast gradient echo sequences or turbo fast low-angle shot. Compared to single-shot fast spin-echo acquisition schemes, gradient echo sequences are more prone to degradation by motion artifacts and have lower spatial resolution. Although fetal neuroanatomy is less commonly depicted by T1- than T2-weighted images, T1-weighted image is helpful for detection of hemorrhage, microcalcification, fat deposition, and myelination. Fetal pituitary, thyroid, liver, and meconium within the bowels are also characterized by T1-weighted image hyperintensity.

Additional sequences are usually adapted to the suspected brain pathology. These sequences can include fluid-attenuation inversion recovery, diffusion-weighted imaging, diffusion tensor imaging, and magnetic resonance spectroscopy. Fluid-attenuated inversion recovery sequences can provide supplementary information on the content of cystic lesions and in staging of hemorrhage. Diffusion-weighted imaging can occasionally be performed for evaluation of developmental and destructive brain processes by providing quantitative information on the water motion and tissue microstructure. Recently, diffusion tensor imaging using 32 noncollinear diffusion gradient encoding directions has been applied in utero, allowing demonstration of major fiber tracts of the fetal brain. Magnetic resonance spectroscopy has been applied to further assess the fetal brain in certain indications such as detection of gliosis and assessment of the risk of hypoxia through the detection of increased creatine content. Although the long duration of magnetic resonance spectroscopy (up to 5 minutes) without sedation can interfere with its acquisition, readable spectra can be obtained in 73.3% of cases.

No maternal sedation or fetal sedation/paralysis is necessary when the protocol is optimized. Currently, fetal MRI lasts about 15 to 45 (average 20) minutes; however, future sequences can further reduce the scan time.

Indications for MRI of Fetal Brain

According to the American College of Radiology guidelines, the primary indications for MRI of the fetal brain include but are not limited to

1. Congenital anomalies of the brain suspected or not adequately assessed by sonography.
2. Screening fetuses with a family risk for brain abnormalities.
3. Vascular abnormalities of the brain suspected or not adequately assessed by sonography.
4. Neural tube defects suspected or not adequately assessed by sonography.
5. Complications of monochorionic twins.
6. Before and after in utero surgery or intervention for a fetal abnormality.

MRI of Normal Fetal Brain Development

In utero MRI can help to understand the normal brain development starting at 16 weeks of gestation. Gestational age is expressed in this article on the basis of the time of the last menstrual period in weeks. Although menstrual weeks are convenient for obstetrics imaging, it is to be noted that gestational age is about 2 weeks earlier than the proper postconception fetal age.

The brain is developed from a simple brain-tube. In consequence of differential growth, the brain tube exhibits 3 dilations (vesicles): forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon). The midbrain is separated from the hindbrain by a narrow segment (the isthmus). The forebrain differentiates into the telencephalon and diencephalon, whereas the hindbrain divides into metencephalon and myelencephalon.
# Table 1. Parameters of Magnetic Resonance Imaging (MRI) Sequences of Fetal Brain.a

<table>
<thead>
<tr>
<th>Sequence scientific name</th>
<th>Sequence generic names in: Philips/GE/Siemens</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>FA degree</th>
<th>NSA</th>
<th>Matrix</th>
<th>FOV (mm)</th>
<th>Thk/gap (mm)</th>
<th>Slices number</th>
<th>Time (s)</th>
<th>How often it is done/indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSFSE</td>
<td>T2-SSH-TSE/ T2-SSFSE/ HASTE</td>
<td>15 000</td>
<td>120</td>
<td>90</td>
<td>1</td>
<td>169/256</td>
<td>200</td>
<td>4/0-0.4</td>
<td>18</td>
<td>19</td>
<td>Always/brain and body imaging</td>
</tr>
<tr>
<td>T1- GRE</td>
<td>Ultrafast GRE: TFE/FMPSPGR/ turbo-FLASH</td>
<td>940</td>
<td>250</td>
<td>90</td>
<td>1</td>
<td>255/512</td>
<td>300</td>
<td>4/0.4-4</td>
<td>17</td>
<td>16</td>
<td>Always/ brain hemorrhage</td>
</tr>
<tr>
<td>b-SSFp</td>
<td>b-FFE/RIESTA/True-FISP</td>
<td>3.5</td>
<td>1.7</td>
<td>80</td>
<td>2</td>
<td>256</td>
<td>300-400</td>
<td>4-6/0</td>
<td>25</td>
<td>25</td>
<td>Sometimes/brain and heart</td>
</tr>
<tr>
<td>DWI</td>
<td>DWI (b: 0 and 700 s/mm²)</td>
<td>1470</td>
<td>125</td>
<td>90</td>
<td>1</td>
<td>108</td>
<td>240</td>
<td>5/0.1</td>
<td>16</td>
<td>19</td>
<td>Sometimes/brain hypoxia</td>
</tr>
</tbody>
</table>

Abbreviations: b-FFE, balanced fast field echo; DWI, diffusion-weighted images; FIESTA, fast imaging employing steady-state acquisition; FLASH, fast gradient echo sequences with low flip angle shot; FMPSPGR, fast multiplanar spoiled gradient-recalled acquisition in the steady state; FOV, field-of-view; GE, General Electric, Medical Systems Milwaukee, Wisconsin; GRE, gradient echo; HASTE, half Fourier acquired single shot turbo spin echo; mm, millimeter; ms, millisecond; NSA, number of excitations; Philips, Philips Medical Systems, Best, Netherlands; s, second; Siemens, Siemens, Erlangen, Germany; SSFP, Steady State Free Precession; SSFSE, single shot fast spin-echo; SS-TSE, 0.5 signal acquired single-shot half spin-echo; TE, echo time; FFE, Turbo field Echo; Thk, thickness; TR, repetition time; True-FBP, Fast Imaging with Steady Precession.

*aModifications of the parameters could be required for different MRI systems.*
Normal development of fetal brain and its corresponding MRI appearance are discussed, for convenience, under the following subheadings: cerebral parenchyma, ventricular system, corpus callosum, and posterior fossa. Table 2 includes a schematic approach of detecting normal MRI appearances of the developing brain features, pitfalls in diagnosis, and recommendations to avoid misdiagnosis.

**Cerebral Parenchyma**

**Parenchymal Layering.** The primitive cerebral hemispheres develop at about 5 weeks of gestation as bilateral vesicles. The cerebral vesicles grow and expand as neuroepithelial cells, located in the germinal ventricular zone, divide and differentiate into glial cells and neuroblasts. The cortical plate begins to appear after the seventh gestational (fifth post-conception) week, in the lateral aspect of the hemispheric wall. Normal cerebral cortical development passes into three stages: proliferation, migration, and organization. As neuronal migration begins, the germinal ventricular zone gradually regresses. By 26 weeks of gestation, migration to the developing cortex is almost complete and the germinal zone disappears, resulting in the differentiation of only 2 layers: the cortex and the white matter.

Myelination occurs predominantly postnatal in a craniocaudal and centrifugal fashion. Myelination can be detected on MRI of fetal brain as high signal intensity on T1-weighted images, in the tegmentum at 22 weeks of gestation, in the middle cerebellar peduncles at 28 weeks of gestation, and in the posterior limb of the internal capsule at 30 weeks of gestation. Diffusion tensor MRI technique allows 3-dimensional reconstruction of the tissue microstructure and can quantify white matter maturation and development.

**Deep Gray Nuclei.** Thalami are derived from germinal matrix lining the diencephalon, whereas globus pallidus, caudate, and putamen arise from the germinal matrix of the ventral forebrain.
<table>
<thead>
<tr>
<th>Normal developing brain feature</th>
<th>MRI plane and sequence</th>
<th>MRI appearance</th>
<th>Pitfall in diagnosis and recommendations to avoid misdiagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal layering</td>
<td>Axial T2-weighted imaging</td>
<td>Before 26 weeks of gestation: 3 layers: germinal and cortex are hypointense; in between them is an intermediate layer. After 26 weeks of gestation: germinal disappears, leaving 2 layers: cortex and white matter.</td>
<td>–</td>
</tr>
<tr>
<td>Myelination</td>
<td>Axial T1-weighted imaging, diffusion-weighted imaging</td>
<td>From 22 weeks of gestation, myelin appears as hyperintense areas.</td>
<td>–</td>
</tr>
<tr>
<td>Ventricular system</td>
<td>Axial T2-weighted imaging</td>
<td>Lateral ventricles are symmetrical in size and shape. Atrial diameter normally measures less than 10 mm.</td>
<td>Physiologic prominence of lateral ventricles early in gestation could be misdiagnosed as ventriculomegaly but atrial diameter measurement is normal.</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>Sagittal T2-weighted imaging</td>
<td>C-shaped hypointense structure. By 15 weeks of gestation, all of its parts are formed.</td>
<td>Apparent anteroposterior progression is due to disproportionate growth of frontal lobe.</td>
</tr>
<tr>
<td>Cavum septum pellucidum</td>
<td>Coronal and axial T2-weighted imaging</td>
<td>Between frontal horns of lateral ventricles</td>
<td>It is normally present in fetuses between 18 and 37 weeks of gestation.</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Axial and Sagittal T2-weighted imaging</td>
<td>The pons has a convex anterior border (flexure).</td>
<td>–</td>
</tr>
<tr>
<td>Cerebellar hemispheres</td>
<td>Coronal and axial T2-weighted imaging</td>
<td>Transverse cerebellar diameter increases during gestation.</td>
<td>Cerebellar hypoplasia cannot be ruled out before 25 weeks of gestation.</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>Sagittal T2-weighted imaging</td>
<td>Develops in craniocaudal direction. Inferior vermis develops at 17-18 weeks of gestation</td>
<td>MRI is recommended after the 20th week of gestation to rule out diagnosis of inferior vermian agenesis.</td>
</tr>
<tr>
<td>Cisterna magna</td>
<td>Axial and sagittal T2-weighted imaging</td>
<td>Normal anteroposterior diameter of cisterna magna &lt; 10 mm</td>
<td>A normal cisterna magna can be reassuring in fetuses at high risk for posterior fossa anomalies.</td>
</tr>
<tr>
<td>Biometry of skull and brain</td>
<td>Coronal and sagittal T2-weighted imaging</td>
<td>Measuring skull and brain at occiput-frontal diameter and biparietal diameter and comparing with norms at the same gestational age.</td>
<td>Actual brain size measurements eliminate errors linked with broadening of pericerebral space.</td>
</tr>
</tbody>
</table>
Early in gestation, deep gray nuclei appear isointense to white matter on MRI. However, with advancing of development (after 28 weeks of gestation), the nuclei become more hypointense on T2-weighted images, more hyperintense on T1-weighted images, and have less mean diffusivity on diffusion-weighted images. Sulcation.

MRI of the normal fetal cerebrum is characterized initially by the presence of a smooth surface and large ventricles, an appearance that resembles lissencephaly (a neuronal migration disorder). But as the brain matures, sulci form in a predictable manner. The degree of sulcation on fetal MR images is used as an indicator of gestational age–related cortical development. In Figure 5, we suggest a scheme for detecting maturation of fetal cerebral sulcation on axial, sagittal, and coronal MR images. By 34 weeks of gestation, all primary and some secondary sulci are visible on fetal MRI (Figure 4). Follow-up fetal MRI later in gestation (ideally after 28 weeks of gestation) is recommended to exclude malformations of cerebral cortical development.

Ventricular System

Early in gestation, the lateral ventricles appear prominent because of the relative paucity of brain parenchyma relative to ventricular size (Figure 3). Physiologic disproportionate enlargement of the occipital horns in relation to the frontal horns of lateral ventricles is also noted on fetal MRI until 23 weeks of gestation; thereafter, they gradually become smaller. Prominence of lateral ventricles early in gestation can be misdiagnosed as ventriculomegaly. Ventriculomegaly is diagnosed when the width of atria measure more than 10 mm in the posterior aspect of the choroid plexus glomus on a midthalamic axial plane. Unlike ventriculomegaly, measurements of the atrial diameter of normal lateral ventricles remain constant from 15 to 35 weeks of gestation and do not exceed 10 mm. Moreover, the lateral borders of the lateral ventricles are convex in hydrocephalus, as opposed to concavity in normal cases.

Septum pellucidum is a thin vertical membrane walled off by the corpus callosum above and the fornix below, separating the frontal horns of the lateral ventricles. Septum pellucidum derives from the commissural plate, with close developmental association with the corpus callosum. During fetal development, the septum pellucidum is filled with cerebrospinal fluid and is termed as cavum septum pellucidum.

Corpus Callosum

The corpus callosum is the largest commissure connecting the cerebral hemispheres. It develops from the laminae reunions...
Corpus callosum has 2 embryonic parts: anterior and posterior. By 15 weeks of gestation, all parts of the corpus callosum are fused and complete. Corpus callosum grows by addition of fibers until after birth. The notion that corpus callosum grows anterior to posterior is incorrect. Apparent anteroposterior progression is due to a disproportionate growth of the frontal lobe, which causes anteroposterior relative displacement of the splenium and hippocampal fissure. The corpus callosum is detected on the midline sagittal T2-weighted images as a C-shaped hypointense structure at the superior margin of the cavum septum pellucidum (Figure 6). The corpus callosum increases in length, width, and thickness with gestational age. Kasprian and colleagues were able to demonstrate fetal corpus callosum using diffusion tensor MRI.

**Posterior Fossa**

The cerebellum and the brainstem form at about sixth weeks of gestation and continue until about 6 months after birth; the pontine flexure develops at the same time as the cerebellar hemisphere. Fetal MRI determines the global volume of the posterior fossa and shows the position of the tentorium cerebelli (Figure 6). MRI also enables morphologic and biometrical analysis of the fetal posterior fossa structures. Cerbellar parenchyma appears multilayered with central lower signal on T2-weighted images that represents the nuclei. The primary fissure is evident on midsagittal MRI at 25 weeks of gestation. The transverse cerebellar diameter increases during gestation and can be measured on axial and coronal MRI then compared with established norms. The fetal cerebellar vermis can be detected on midsagittal and coronal MRI. Because of craniocaudal development of the vermis, inferior vermis develops later at 17 to 18 weeks of gestation. Fetal MRI before 18 weeks of gestation could be misdiagnosed for inferior vermian agenesis (Figure 6). In the presence of a proband, fetal MRI is recommended after the 20th week of gestation to rule out the possibility of vermian agenesis recurrence. Unlike vermian agenesis, cerebellar hypoplasia cannot be ruled out on basis of normal fetal MR images before 25 weeks of gestation. Demonstration of a normal cisterna magna is reassuring in high-risk pregnancies for posterior fossa abnormalities. Detection of an enlarged cisterna magna with an anteroposterior diameter that exceeds 10 mm should prompt a detailed examination of the fetal brain.

During normal development of fetal brain, folding of brainstem occurs between the third and eighth weeks to form 3 flexures: mesencephalic, pontine, and cervical. MRI can demonstrate the morphology and signal intensity of fetal brainstem. The isthmus is the junction between the midbrain and pons. The pons has a convex anterior border (flexure). The dorsal part of the midbrain and pons appear as low signal intensity on T2-weighted images and as high signal intensity on T1-weighted images after 24 weeks of gestation (Figure 6). The ventral part of the midbrain and pons maintains a high signal intensity.
appearance on T2-weighted images and low signal intensity on T1-weighted images until birth.1,32

Skull and Brain Measurements

Biparietal diameters of skull and brain are measured at the greatest diameter of skull and brain, respectively, in the coronal plane at the level of temporal horns of the lateral ventricles. Fronto-occipital diameter can be measured on the midline sagittal image as the distance between the extreme points of the frontal and occipital lobes. Measurements are compared with established norms.5 MRI enables estimation of the actual brain size and eliminates measurement errors linked with broadening of peri-cerebral space.1,5 With these 2 measurements, it is possible to determine variations in cerebral shape and skull contour such as dolicocephaly or brachycephaly.6

MRI of Abnormal Development of Fetal Brain

It has been proved as useful to look at the fetal brain on MR studies following a certain scheme, in order to recognize any change that might contribute to an accurate diagnosis.36 We will discuss fetal brain abnormalities and their corresponding MRI appearances under the following subheadings: cerebral parenchyma, ventricular system, corpus callosum, and posterior fossa.

Cerebral Parenchymal Abnormalities

Fetal cerebral parenchymal abnormalities include hemorrhage, gliosis, and white matter edema.7 Fetal intracranial hemorrhage has been observed after trauma, in cases of maternal coagulation disorder, congenital infection, and fetal intracranial vascular malformation.5 Fetal brain regions with high vascular density, such as the ganglionic eminences of the ventricular zones, are the main sites of bleeding. Hemorrhage can extend to the cerebral ventricles (intraventricular) or manifest as subdural hematomas.37 T1-weighted images and T1-weighted fluid-attenuated inversion recovery sequences can reveal intracranial hemorrhage as high signal intensity; this MRI appearance is secondary to the presence of intracellular or extracellular methemoglobin.7 Supratentorial ventricular hemorrhage can lead to hydrocephalus due to impaired cerebrospinal fluid circulation induced by the
blood clots (Figure 7). Gliosis and white matter edema appear as hyperintense and hypointense lesions on T2-weighted image and T1-weighted image sequences respectively. However, it must be stressed that it can be very difficult to detect small variations in white matter signal intensity because of reduced contrast between the lesion and normal fetal parenchyma. Diffusion-weighted imaging can facilitate detection of local edema as a sign of acute infarction. Infarctions are more often seen in their chronic form as cystic lesions or enlargement of one or both lateral ventricles.

Cortical malformations are identified in MRI by noting alteration of the normal sulcation pattern from a fetus particular gestational age (Figure 8). They can be identified as too many sulci in a less mature fetus (as in polymicrogyria), or too few sulci (as in lissencephaly) or abnormally deep or abnormally located sulci (as in schizencephaly) in a more mature fetus. In order for the diagnosis of lissencephaly to be made using MRI, the examination must be undertaken late in pregnancy at least after 28 weeks of gestation when most of the primary sulci have already appeared. Thin MR slices should be obtained in several planes so as not to miss focal cortical malformations as in schizencephaly and heterotopias. Subependymal heterotopias appear as nodules along the ventricular walls that are iso-intense relative to the germinal matrix. Heterotopias should be distinguished from subependymal tubers of tuberous sclerosis. Tubers appear hypointense on T2-weighted images and hyperintense on T1-weighted images. Subependymal giant astrocytoma is a rare brain tumor that is nearly always associated with tuberous sclerosis. Subependymal giant astrocytoma occurs typically in the wall of the lateral ventricle near the foramen of Monro (Figure 9). Detection of other manifestations of tuberous sclerosis, such as cortical tubers, and cardiac rhabdomyoma could help to arrive at the correct diagnosis.
Figure 6. Normal midsagittal magnetic resonance imaging (MRI) anatomy of the fetal brain. (A) Midsagittal balanced fast field echo of a normal fetal brain at 27 weeks of gestation shows the corpus callosum as a C-shaped hypointense structure that extends from the rostrum anteriorly (white arrowhead) to the splenium posteriorly (white arrow). The image shows the normal appearance of the position of tentorium cerebelli, the size of posterior fossa and its structures. The normal morphology of the brainstem is shown: the midbrain, the pons with its anterior flexure (black arrow), and medulla oblongata. The dorsal part of the brainstem is relatively hypointense. The fourth ventricle lies between the brainstem anteriorly and the cerebellar vermis posteriorly (black arrowhead). (B) Midsagittal balanced fast field echo of a normal fetal brain at 16 weeks of gestation shows development of the superior part of the cerebellar vermis (arrowhead). Physiological nondevelopment of the inferior vermis at this age should not be misdiagnosed as inferior vermian agenesis.

Figure 7. Magnetic resonance imaging (MRI) appearance of fetal intracranial hemorrhage. (A) Axial balanced fast field echo of the brain of a fetus at 32 weeks of gestation shows hypointense germinal matrix hemorrhage with intraventricular extension (arrow) that causes hydrocephalus. The arrowhead points to associated cerebral parenchymal high signal intensity caused by local edema/injury. (B) Axial T1-weighted images from the same fetus: although the neuroanatomy is not well depicted, the intracranial hemorrhage can be detected as hyperintensity (arrow).
Ventricular System and Midline Structures Abnormalities

Ventriculomegaly is one of the most common referrals for fetal MRI. Congenital ventriculomegaly is a heterogeneous disease for which genetic, infectious, ischemic, and neoplastic causes have been implicated. Ventriculomegaly is diagnosed when the atrial diameter is more than 10 mm. Venticulomegaly due to ischemic or infectious events that cause cerebral atrophy can be associated with porencephaly. There is frequently enlargement of the extra-axial spaces with cerebral atrophy. When ventriculomegaly is isolated, it is associated with lower morbidity and mortality relative to that in non-isolated cases. However, in 84% of fetuses with ventriculomegaly, other associated central nervous system abnormalities have been diagnosed with invariably poor postnatal outcomes. Venticulomegaly caused by a lack of tissue has to be differentiated from hydrocephalus occurring as a consequence of impaired cerebrospinal fluid circulation. The shape of the dilated lateral ventricles can indicate the underlying cause: colpocephaly is associated with corpus callosum agenesis, pointed posterior horns are seen in Chiari II malformation, and widened posterior horns combined with a widened V-shaped third ventricle occur in aqueduct stenosis.

The midline septum pellucidum is occasionally destroyed as a consequence of hydrocephalus; an appearance that can resemble absent septum pellucidum, or holoprosencephaly. The midsagittal fetal MR image enables direct visualization of the corpus callosum and diagnosis of anomalies. Indirect signs of complete agenesis of corpus callosum can also be detected in axial and coronal MR images. Indirect signs of complete agenesis of corpus callosum include absence of cavum septum pellucidum, mild ventriculomegaly with disproportionate enlargement of the occipital horns (colpocephaly), straight and parallel lateral ventricles, high riding third ventricle, unaformed cingulate sulcus with radial orientation of medial sulci, and widening of the interhemispheric fissure.

Partial agenesis of the posterior part of the corpus callosum is commoner than missing the anterior part; this fueled incorrect speculation that the corpus callosum grows in an anterior to posterior direction. However, the MRI finding of a callosal body without a recognizable genu (Figure 12b) is not explained by the anteroposterior theory of callosal development; if the genu were the first structure to develop, the body of the corpus callosum could not be present without a genu. It is to be noted that the MRI diagnosis of agenesis of corpus callosum should be made with caution prior to 20 weeks of gestation.

Isolated agenesis of corpus callosum is infrequent; brain malformations, such as sulcal and infratentorial abnormalities, are commonly associated with agenesis of corpus callosum. Presence of sulcation delay in most fetuses with agenesis of corpus callosum could suggest an associated global white matter dysgenesis. Future studies using diffusion-weighted and diffusion tensor MRI techniques could give an insight into the structure of white matter in fetuses with agenesis of corpus callosum. Moreover, confirmation of presence of Probst bundles by diffusion tensor imaging can secure the diagnosis of partial or complete callosal agenesis. Probst bundles are the fibers that would otherwise form the corpus callosum but become misrouted within each cerebral hemisphere. The bundles run parallel to the interhemispheric fissure, lateral to cingulate gyri, and medial to the lateral ventricles. Each bundle indents the medial border of the adjacent lateral ventricle.

Posterior Fossa Abnormalities

Fetal MRI can detect pathologic changes of the cerebellum that include hypoplasia and dysplasia. Significant reduction of the transverse cerebellar diameter is seen in cases with cerebellar
agenesis and hypoplasia. Absence of the inferior cerebellar vermis after 18 weeks of gestation on fetal MRI indicates inferior vermian agenesis (Figure 12). In cases with pontocerebellar hypoplasia, fetal MRI can accurately assess the severity of cerebellar hypoplasia and detect the small-sized pons with its flattened anterior part. A dysplastic brainstem could assume a z-shaped appearance on MR images (kinked brainstem); this is an indicator of severe neurodysgenesis arising early in gestation and carries poor prognosis. MRI can diagnose dysplastic brainstem as well as any associated anomalies in utero and assist in pregnancy counseling. In all of the previously mentioned cases, the posterior fossa has a normal size and the tentorium cerebelli is in the correct position (Figure 14).

Dandy Walker malformation is diagnosed by an enlarged cisterna magna that communicates to the fourth ventricle through a defect in the cerebellar vermis. Global widening of the posterior fossa, with ascent of the tentorium cerebelli and torcular herophili, is the central pillar of the diagnosis of Dandy Walker malformation. Prenatal imaging factors, indicative of poor postnatal diagnosis of Dandy Walker malformation, should be looked for systematically: ventriculomegaly, other central nervous system malformations (as cephalocele), and extra–central nervous system malformations. Recurrence risk and incidence of chromosomal abnormalities are high when Dandy Walker malformation is associated with another anomaly (Figure 15).

Obliteration of the cisterna magna is the most consistent finding in Arnold-Chiari malformation; other findings include obliteration of the fourth ventricle and downward herniation of the cerebellar tonsils (Figure 16). Obliteration of the cisterna magna should suggest a neural tube defect as myelomeningocele is almost associated with Chiari II malformation.

**Neural Tube Defects**

Neural tube defects are a heterogeneous group of malformations resulting from failure of normal neural tube closure early in embryologic development. In addition to spina bifida and anencephaly, neural tube defects include cranial presentations, such as anencephaly and cephaloceles. Cephaloceles are diagnosed when contents protrude through a skull defect. Fetal MRI shows well the location and extent of the skull bony defect as well as the size and contents of the protruding sacs (Figures 15 and 16).

**Vascular Malformation**

Fetal MRI can help in assessment of pathologic intracranial vascular structures; the most common of these is the vein of Galen aneurysmal malformations. Anomalous choroidal arteries drain into the vein of Galen. Because of the high blood flow, the vein dilates and resembles an aneurysm. Drainage usually occurs via dural sinuses, which will eventually become enlarged. Other manifestations of the vein of Galen aneurysmal malformations can include non-immune hydrops, hydrocephalus, intracranial
hemorrhage, and congestive heart failure. The prognosis of the vein of Galen aneurismal malformations depends on the severity of the heart failure (which depends on the size of shunt) as well as on associated cerebral parenchymal injury. Prenatally, the vein of Galen aneurysmal malformations is commonly evaluated by ultrasonography. However, fetal MRI also has been used to study the vascular structure and to identify any associated structural cerebral damage (Figure 17).

Fetal Central Nervous System Syndromes

A syndrome is a set of signs of any morbid state occurring together. Fetal syndromes can be classified according to the main body system involved; central nervous system syndromes involve mainly the brain and/or spinal cord. MRI provides multiplanar imaging as well a large field of view, facilitating examination of fetal brain as part of a complex anomaly or a syndrome. Fetal MRI proved useful in diagnosing selected central nervous system syndromes in the second trimester. Joubert syndromes and related cerebellar disorders are autosomal recessive diseases characterized by cerebellar vermis hypoplasia/dysplasia and a brain deformity at the pontomesencephalic junction that appears as a molar tooth sign on axial MRI. In utero ultrasonographic diagnosis of Joubert syndromes and related cerebellar disorders is usually suggested through demonstrating nonspecific brain abnormalities or other associated extracerebral features such as polydactyly. However, fetal MRI can detect the pathognomonic molar tooth sign and diagnose Joubert syndrome as early as 17 to 18 weeks of gestation (Figure 18).

Meckel Gruber syndrome is a lethal disorder characterized by brain malformations (usually posterior fossa encephalocele) associated with cystic kidney disease, congenital liver fibrosis, and polydactyly. Because of renal affection, a fetus with Meckel Gruber syndrome is usually associated with an oligohydramnios pregnancy. Unlike prenatal ultrasonography, oligohydramnios does not hinder fetal MRI assessment and diagnosis of Meckel Gruber syndrome.

Fetal MRI appearances of brain abnormalities enables better understanding of the pathogenesis of new central nervous system syndromes with in utero presentation. Fetal MRI helped in describing novel central nervous system syndromes such as pseudo–toxoplasmosis, rubella, cytomegalovirus, and herpes simplex syndrome of microcephaly, polymicrogyria with intracranial calcification, as well as a new syndrome of microcephaly, cerebellar hypoplasia, and defective heart conduction. In both of these syndromes, MRI at 25 weeks of gestation identified small-sized brains (microencephaly) associated with...
Figure 12. Magnetic resonance imaging (MRI) appearance of fetal semilobar holoprosencephaly. (A) Axial balanced fast field echo image of fetal brain at 29 weeks of gestation shows noncleavage of the cerebrum anteriorly (arrow), fused frontal horns of the lateral ventricles with absent septum pellucidum (arrowhead); the more posterior areas of the cerebrum are cleaved. (B) Midsagittal balanced fast field echo of the brain of the same fetus shows partial anterior agenesis of the corpus callosum (arrowhead). Only the superior part of the vermis is present (black arrow) and the cisterna magna widely opens in the fourth ventricle through the deficient inferior vermis (black arrow).

Figure 13. Fetal magnetic resonance imaging (MRI) appearance of agenesis of corpus callosum. (A) Sagittal balanced fast field echo image of the brain of a fetus at 29 weeks of gestation documents absence of corpus callosum, unformed cingulate sulcus, and radial orientation of the medial sulci (arrowhead). (B) Axial balanced fast field echo of the same fetus shows parallel orientation of the lateral ventricles and disproportionate enlargement of the posterior horns (colpocephaly) (arrow).
In utero diagnosis of microencephaly, especially in association with cortical malformation, could suggest a genetic etiology (Figure 19).

**Figure 14.** Fetal magnetic resonance imaging (MRI) appearance of pontocerebellar hypoplasia.

Midsagittal fast-field echo image of the brain of a fetus at 29 weeks of gestation shows normal location of tentorium cerebelli and normal size of the posterior fossa. Enlargement of cisterna magna (arrow) is a consequence of hypoplastic cerebellum. The brainstem has a dysplastic kinked appearance (arrowhead); a finding that indicates severe dysgenesis and carries poor prognosis. Note the associated ventriculomegaly and the thin corpus callosum.

**Impact of Fetal MRI on Genetic Counseling of Fetal Brain Abnormalities**

Genetic counseling is a process of communicating medical aspects about a genetic disorder, especially the information regarding risk of occurrence/recurrence of the disease in the family and prognosis. Genetic counseling helps the family to decide between prenatal therapies, postnatal therapies or the interruption of the pregnancy. Thus, accurate diagnosis of fetal abnormalities is of paramount importance. The use of fetal MRI, in addition to prenatal genetic testing and sonography, has the potential to improve prenatal diagnosis of genetic brain disorders. Fetal MRI can help in determining the etiology, prognosis, recurrence risk, and options of pregnancy management of brain abnormalities suspected at ultrasound. MRI is used to examine the fetal brain in cases at increased risk for brain lesions such as in patients with a history of a prior child/fetus with developmental brain abnormalities even when the prenatal ultrasound is normal, because many brain abnormalities can be missed with ultrasonography.

Fetal MRI proved to be a potential screening tool in the second trimester of pregnancies with a family risk for brain syndromes such as Joubert syndrome, microencephaly with simplified gyral pattern, tuberous sclerosis, and corpus callosal dysgenetic syndromes.

Counseling management decisions for parents of a fetus diagnosed with fetal brain abnormalities is multifactorial. It depends on the gestational age at diagnosis, the severity and type of the abnormality, the presence of multiple anomalies, as well as social and religious views. For expectant parents who choose termination of pregnancy because of fetal brain malformation, fetal MRI gives insight into its diagnosis, cause, and recurrence risk. However, despite the abnormal prenatal imaging findings that suggest an affected fetus, expectant parents can opt to continue pregnancy. Precise prenatal diagnosis prepares family for the birth of an affected child and suggests delivery in a tertiary care hospital with a specialized neonatal care unit for management of any anticipated problems of the newly born.

**Applications of Fetal MRI in Brain Research**

In addition to clinical evaluation of fetuses with detected or at risk for brain abnormalities, fetal MRI is also used in research studies of normal and abnormal brain development.

The significant technical progress in fetal MRI contributes to the growth of application of this modality in brain research. Advances in fetal MRI post-processing allow the formation of 3-dimensional images from conventional T2-weighted images which allows the study of brain development in utero. The automated tissue segmentation steps allow morphometric analysis of the developing fetal brain using techniques that quantify tissue volume, surface folding, and cortical thickness.

Research studies of fetal MRI of normal brains at different gestational ages allow establishing of normative measures that can be used in early identification of developmental brain abnormalities. The normative mean diffusivity values of the fetal brain during the second and third trimesters have been established by using diffusion-weighted MRI sequence. Mean diffusivity is a quantitative marker of in utero brain development as it reflects cellularity, neuronal maturation, and myelination. Preliminary studies showed that diffusion tensor MRI can depict certain white matter fiber tracts in the fetal brain such as the corpus callosum. Future studies using diffusion weighted and diffusion tensor imaging are needed to characterize and identify normal and abnormal brain in utero.

Functional MRI studies on fetuses during the third trimester, by the application of an auditory or visual stimulation of the maternal abdomen, have shown fetal brain activation in response to the stimuli. However, functional MRI in utero is still limited by susceptibility motion artifacts that require future development of correction algorithms.

Research investigations continue to identify an increasing number of specific gene defects for brain malformations. The efficient delivery of genetic material to the developing fetal brain represents an innovation in studying brain development.
Figure 15. Fetal magnetic resonance imaging (MRI) appearance of Dandy Walker malformation. (A) Axial balanced fast field echo image of brain of a fetus at 30 weeks of gestation shows an enlarged cisterna magna (arrow) communicating with the fourth ventricle through a defective cerebellar vermis. (B) Midsagittal balanced fast field echo image of the brain of the same fetus documents deficient cerebellar vermis and shows the large size of the posterior fossa with ascent of the torcular herophili (arrow). The association of a posterior meningocele (arrowhead) to Dandy Walker malformation points to a poor prognosis and a higher incidence of recurrence risk and chromosomal abnormalities.

Figure 16. Fetal magnetic resonance imaging (MRI) appearance of Chiari II malformation. Sagittal balanced fast field echo image of the head and spine of a fetus at 30 weeks of gestation shows a small posterior fossa with crowded structures within and obliteration of the cisterna magna and fourth ventricle. Note the consequent supratentorial hydrocephalus (white arrowhead) and the associated defective posterior neural arches of the lower dorsolumbar spine (black arrowhead).

Figure 17. Fetal magnetic resonance imaging (MRI) appearance of vein of Galen aneurysmal malformations. Axial T2-weighted single-shot fast spin-echo image of the brain of a fetus at 33 weeks of gestation shows signal void appearance of the dilated vein of Galen (white arrow) and the draining straight sinus (black arrow) as well as associated ventriculomegaly and hyperintense cerebral parenchymal insults (black arrowhead).
Fetal MRI, especially with using new sequences, has the potential to define structural, physiological, and metabolic aspects of brain malformations that can support research of gene therapy that could lead to treatment or prevention of these diseases. Human fetal MRI aided in a research with an animal model of Joubert syndrome; the study resulted in gene treatment that improved the phenotype in Joubert syndrome mice.

**Conclusion**

MRI allows excellent detailed visualization of the brain in utero. By using a systematic approach, fetal MRI is useful in understanding brain development, early detection of fetal brain abnormalities, and evaluation of complex lesions. Prenatal MRI can facilitate genetic counseling for brain abnormalities, describe novel brain syndromes with in utero presentation, and participate in brain research studies.

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