Fetal MRI in CNS abnormalities. Relevant issues for obstetricians


INTRODUCTION

The main purpose of prenatal diagnosis is to gather genetic, anatomical, biochemical and physiological information about the fetus to detect potential abnormalities that may have impacts both during the fetal period and after birth. Thus, we can provide families with information, genetic counseling, and/or therapeutic alternatives for any anomalies detected.

Since the first use of magnetic resonance imaging (MRI) in pregnancy reported in the Lancet in 1983 by Smith FW et al (1), over 3,000 articles on fetal MRI have been published.

MRI is a complementary method to ultrasound (US), useful for fetal assessment, which is helpful in formulating prognosis and perinatal management, and can detect occult abnormalities in up to 50% of cases for certain indications (2).

Our aim is to show the safety, advantages, limitations, indications and clinical applications of fetal brain MRI.

SAFETY

Many MRI safety studies have been conducted in animals, but there is a lack of consensus as to the extrapolation of results to human subjects (3). The Safety Committee of the Society for Magnetic Resonance Imaging concluded 17 years ago that fetal MRI was indicated when other non-ionizing diagnostic imaging methods were inadequate or when MRI examination would provide important information on pregnancy. However, owing to the potential risks to the developing fetus and the limitations of MRI, it is advisable to wait until the second trimester. Nevertheless, in 2002, the American College of Radiology, based on a risk-benefit assessment, approved the use of MRI at any gestational age (4).

The use of intravenous contrast is not accepted because gadolinium chelates cross the placenta; they appear in the fetal bladder and then in amniotic fluid, to be subsequently swallowed by the fetus. Furthermore, the half-life of gadolinium in the fetus is unknown (5). Some authors have recently reported the potential nephrotoxicity risk of gadolinium (nephrogenic systemic fibrosis) (6).
ADVANTAGES AND LIMITATIONS

Ultrasound is the method of choice for routine screening in the fetus and for examination of the central nervous system (CNS) anatomy. However, even in expert hands, some abnormalities may be overlooked due to technical problems (reverberation artifacts), maternal or fetal conditions (maternal obesity, inappropriate fetal position, oligohydramnios) or because findings are very subtle.

Fetal MRI has several advantages over perinatal US:
- Improved spatial resolution (due to the use of multi-channel receiver arrays and parallel imaging techniques).
- Direct visualization of both sides of the brain (while on ultrasound, the anterior margin of the cerebral hemisphere is shadowed because of reverberation from overlying structures, there are limitations in the case of oligohydramnios, inadequate fetal positioning for US or acoustic shadowing from the ossifying calvarium).
- More detailed assessment of brain development, including direct visualization of the developing cortex and sulcation pattern, which is extremely difficult, and sometimes impossible, to visualize on ultrasound.

Fetal MRI’s leading limitations include:
- Fetal motion artifacts, reduced with the new ultrafast imaging sequences (images are acquired in less than 1 second) and with maternal fasting 4 h before the study.
- Low spatial resolution at early gestational age because of the small size of the fetus.
- Maternal claustrophobia and discomfort during the scan (particularly at advanced gestational age).

INDICATIONS

As we have previously mentioned, ultrasound is the method of choice for routine screening in the fetus and for examination of fetal brain anatomy. In our centre, we perform MRI as from the second trimester to avoid the period of fetal organogenesis, preferably at 20 weeks gestational age, when the size of the fetus is large enough to obtain good spatial resolution.

MRI should always be performed after an ultrasound examination by a skilled sonographer. Salomon LJ et al report the main indications:
- A history of severe brain abnormality in a previous pregnancy, but ultrasound examination is considered normal; MRI is performed in order to look for subtle signs of recurrence.
- An abnormality identified on ultrasound examination that appears to be isolated (typically ventriculomegaly or corpus callosum agenesis); MRI is performed to look for associated abnormalities that may have been overlooked by ultrasound.
- An abnormality diagnosed on ultrasound examination, but the examination cannot be completed because of technical problems (e.g. maternal obesity or fetal position); MRI is performed to supplement ultrasound.
- A high risk of development of brain abnormality, especially in cases of fetal infection (cytomegalovirus, varicella and toxoplasmosis) or ischemic damage (in-utero death of a monochorionic twin or twin-to-twin transfusion syndrome).

IMAGING PROTOCOL

It is advisable to perform MRIs using a high-field MRI scanner (1.5T) with high spatial resolution arrays to obtain good diagnostic imaging (such as an 8-channel cardiac array); higher magnetic fields are unacceptable. The examination is performed in supine decubitus position, except at advanced gestational ages, when the patient lies in the left lateral decubitus position.

In most centers, the examination is performed with no maternal sedation, given the use of ultrafast imaging sequences. The patient should fast for 4 h before the examination to reduce bowel peristalsis artifacts. Centers that perform fetal MRI with sedation usually administer 1 mg flunitrazepam 20 minutes before the examination.

Written informed consent should always be obtained from the patient. It is advisable that the examination be performed by trained operators. Previous ultrasound information allows better planning of the examination.

Three orthogonal planes with respect to the mother are identified to obtain sagittal, coronal and axial slices of the fetus, always taking as reference the last sequence used to plan the following sequence because of fetal movements.

The main sequences used are:
- **T2-weighted images such as Single Shot Fast Spin Echo T2 (SSFSE T2) and balanced sequences (FIESTA)** are useful to assess fetal anatomy. Balanced sequences or Steady-State Free Precession sequences are less susceptible to fetal movements and cerebrospinal fluid (CSF) artifacts, mainly at early gestational ages. CSF is hyperintense in these sequences.
- **T1-weighted images** (dual echo gradient or Fast Spoiled Gradient Echo T1) allow for identification of hemorrhage, calcification or fat and provide information on myelination. CSF is hypointense in these sequences.
- **Diffusion-weighted imaging:** this sequence is particularly useful in detecting acute ischemic lesions as well as in the differential diagnosis of arachnoid and epidermoid cysts (Fig. 1).

**Relevant imaging parameters:**
- **Single Shot Fast Spin Echo T2 (SSFSE T2):** TR = 1088 ms, TE = minimum (90 ms), matrix = 256 x 256, FOV = 34 cm, bandwidth = 20.83 KHz. NEX = 0.5, slice thickness = 3 mm, spacing = 0 mm.
• **Balanced sequences (FIESTA):** TR = 3.9 ms, TE = minimum (1.7 ms), matrix = 256 x 256, FOV = 35 cm, bandwidth = 125 KHz. NEX = 2, slice thickness = 5.1 mm, spacing = 0 mm and angle = 45°.

• **T1-weighted images (3D dual echo gradient):** TR = 8.5 ms, TE = minimum (2.4 ms), matrix = 336 x 256, FOV = 39 cm, bandwidth = 62.5 KHz, NEX = 0.69, slice thickness = 6 mm, spacing = 0 mm and angle = 12°.

• **Diffusion-weighted imaging:** TR = 2500 ms, TE = minimum (69 ms), matrix = 128x128, FOV = 36 cm, bandwidth = 62-250 KHz, NEX = 6, slice thickness = 4 mm, spacing = 0 mm and b = 1000 s/mm².

**ANALYSIS AND INTERPRETATION**

**Fetal Biometry**

Brain volume estimation is performed using the fronto-occipital, cerebral biparietal and bone biparietal diameters as well as the craniocerebral index and the cephalic index (Fig. 2).

For assessment of the cerebellum, the transverse cerebellar diameter, anteroposterior diameter, and height and surface of the vermis are used (Fig. 3) (10, 11). Ventricular size assessment is performed using the anteroposterior diameter of the fourth ventricle, the width of the third ventricle, and the transversal dia-
meter of the lateral ventricles measured on the coronal slice at the level of the atria (12).

The corpus callosum is assessed using the length of the corpus callosum measured on the sagittal slice from the genu to the splenium.

Cortical sulci analysis

Assessment of cortical sulci is the second step. Sulcal development is an important marker of fetal maturation.
- At 20 gestational weeks, only the lateral sulci (Sylvian fissures) and the interhemispheric fissure will be visible.
- At 25 gestational weeks, the lateral sulci, the interhemispheric fissure, the hippocampal and calcarine fissures, and the cingulate and internal parieto-occipital sulci become visible (Fig. 4).
- At 27 gestational weeks, the lateral sulcus, the interhemispheric fissure, the hippocampal and calcarine fissures, the cingulate, internal parieto-occipital and central sulcus should already be present (10-13).
- At 29 gestational weeks, marginal, pre- and postcentral, intraparietal, collateral, superior temporal and superior frontal sulci should be visible and the central sulcus should reach half of the cerebral hemisphere (10-13)
- At 31 gestational weeks, the inferior frontal sulcus should be visible.
- At 35 weeks, the temporal lobe should have all its sulci, including the inferior temporal sulci and the occipitotemporal sulci. The pattern at this gestational age is the definitive pattern (Fig. 5) (10-13, 14).

Fig. 4 (a) Sagittal SSFSE T2, (b) Axial FIESTA, (c) Coronal FIESTA at 20 gestational weeks, only the interhemispheric fissure (1) and the Sylvian fissures (2) would be visible. (d) Sagittal SSFSE T2, (e) Axial FIESTA; (f) Coronal FIESTA, at 25 weeks, only the interhemispheric fissure (1), Sylvian fissures (2), parieto-occipital sulci (3), calcarine fissures (4), and hippocampal fissures (5) would be visible.

Fig. 5 (a) Sagittal SSFSE T2; (b) Axial SSFSE T2; (c) Coronal SSFSE T2. At 29 weeks, the marginal (6), precentral (7), central (8), postcentral (9) intraparietal, collateral (10), superior temporal (11) and superior frontal (12) and inferior frontal (13) sulci would be visible and the central sulcus would reach half of the cerebral hemisphere in depth. (d) Sagittal SSFSE T2; (e) Axial SSFSE T2; (f) Coronal SSFSE T2; at 35 weeks, the temporal lobe should have all its sulci, including the inferior temporal sulci (14) and the occipitotemporal sulci (15). The pattern at this gestational age is the definitive pattern. Interhemispheric fissure (1), Sylvian fissures (2), parieto-occipital sulci (3), calcarine fissures (4) and hippocampal fissures (5).
Myelination analysis

Myelination is a good indicator of fetal cerebral maturation. The increase in cholesterol and glycolipids accompanying the formation of myelin results in an increase in water, thus leading to a shortening of T1 and T2 sequences, visible as a hypersignal on T1-weighted images or a hyposignal on T2-weighted images.

Such signal changes can be seen in the white matter, starting at 20 weeks’ gestation in the posterior brainstem. At 27 weeks, some myelin is visible in the vermis and the middle cerebellar peduncles. A moderate signal is also visible at the central basal ganglia \(^{(10,13)}\), and at 33 weeks, the myelination of the posterior limbs of the internal capsules occurs, extending progressively to the globus pallidus at 35–36 weeks (Fig. 6) \(^{(14)}\). Myelination of the corona radiata occurs at the end of gestation.

Neuronal migration analysis

The development of the cerebral cortex is divided into 3 stages: cell proliferation, cell migration and, finally, cortical organization.

Neuronal migration occurs between the third and fourth month of gestation and is complete by approximately 24 weeks. Neuronal migration occurs from the periventricular germinal zone to the pial surface in six successive layers. The first neurons occupy the deepest portion within the cerebral cortex, whereas those migrating later occupy the most superficial layers. Migration is regulated by radial fibers and mediators \(^{(15)}\).

In MRI, neuronal migration is determined by the multilayered appearance on T2-weighted images:

- At 16-18 weeks, three layers are observed (inner germinal matrix, intermediate layer of migrating neurons and outer immature cortex).

Fig. 6 Normal myelination of the brainstem in a 25-week fetus. (a) Axial FIESTA T2; (b) Axial FIESTA T2. Myelination has not begun in the supratentorial brain. Myelination of the posterior border of the pons (arrowhead). The signal intensity of the pallidum and the thalamus is similar to that of white matter (curved arrow). (c) Axial SS FSE T2. The signal intensity of the pallidum and thalamus is hypointense in T2-weighted sequences at weeks 27 to 34 (arrow). (d) Coronal FSPGR T1. Myelination of the internal capsule, of the globus pallidus and thalamus increases at 35 weeks with hyperintensity in T1 (arrow).

Fig. 7 (a) Coronal SSFSE T2; (b) Coronal SSFSE T2; (c) Coronal FIESTA; (d) Coronal FIESTA. Three layers: inner germinal matrix (broken arrow), intermediate layer of migrating neurons (black arrow) and outer immature cortex (curved arrow) at 20.4 weeks. Two layers: inner white matter (white arrow) and outer cortex (white arrowhead) at 35 weeks.

Fig. 8 GA: 29 weeks. Corpus callosum agenesis. Diamniotic and bichorionic twin pregnancy. (a) Coronal FIESTA; (b) Axial Single Shot Fast Spin Echo T2 (SSFSE T2); (c) Sagittal SSFSE T2. Total agenesis of the corpus callosum in the twin in left dorsal cephalic position: elevation of the third ventricle connecting with the interhemispheric fissure (white arrow), separated frontal horns (arrowhead) and colpocephaly (curved arrow). The other twin shows no abnormalities.
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- At 34 weeks, two layers are identified (inner white matter and outer cortex) (Fig. 7) [16].

CLINICAL APPLICATIONS

Central nervous system malformations account for one third of fetal anomalies and are found in 75% of dead fetuses. The incidence of CNS malformations is estimated at 1 out of 100 live births. Approximately 10% of brain abnormalities are secondary to chromosomal aberrations, 20% to genetic factors, 10% to adverse effects in the uterus (e.g., infection) and 60% have no identifiable etiology.

We will divide diseases according to the different brain areas involved:

- **Midline abnormalities**: total or partial agenesis of the corpus callosum (Fig. 8), alobar, semilobar or lobar holoprosencephaly (Fig. 9), septo-optic dysplasia, lipoma of the corpus callosum, cysts of the cavum septum pellucidum, of the cavum vergae or of the velum interpositum or absence of the cavum.

  Assessment of the corpus callosum is one of the main indications of fetal MRI. While the diagnosis of total agenesis is usually based on ultrasound, MRI is particularly useful in the investigation of partial agenesis or for the identification of associated abnormalities. MRI should be performed when the development of the corpus callosum is complete, after week 20. In approximately 20% of cases in which callosal agenesis was suspected on ultrasound, MRI was able to demonstrate an intact corpus callosum [17]. In over 63% of cases there are associated abnormalities such as cortical malformations, heterotopia, Dandy-Walker malformation, Chiari II malformations, schizencephaly and encephalocele [17,18].

- **Ventricles**: ventriculomegaly is the most common finding on ultrasound and therefore the most common indication for fetal MRI. It is classified as mild (10–12 mm), moderate (12–15 mm) and severe (> 15 mm). Fetal MRI can detect sonographically occult abnormalities in up to 40-50% of cases, such as neural tube defects (Fig. 10), agenesis of the corpus callosum, Dandy-Walker complex, lissencephaly, polymicrogyria, holoprosencephaly, subependymal heterotopia, intraventricular or subependymal hemorrhage, periventricular leukomalacia or porencephaly [2].
Periventricular area: MRI can detect subependymal heterotopia, small germinal matrix hemorrhages as well as subependymal nodules in tuberous sclerosis (Fig. 11). Non-visualization of subependymal nodules cannot rule out a diagnosis of tuberous sclerosis [19, 20, 21].

Cerebral parenchyma: MRI can detect small brain hemorrhages or ischemic lesions, determining if lesions are acute or not based on diffusion sequence (Fig. 12) [22, 23].

In infectious diseases, MRI allows detection of parenchymatous lesions that may be overlooked by ultrasound, especially cytomegalovirus infection [24, 25].

Cortical surface: The development of the cerebral cortex is divided into 3 stages: cell proliferation (2 to 4 months of gestation), neuronal migration (from 3-4 months of gestation to 24 weeks’ gestation) and cortical organization (from 22 weeks’ gestation to 2 years of age) [26]. Malformations are classified into:

Cell proliferation disorders: decreased proliferation (microlissencephaly), increased proliferation (hemimegalencephaly) and abnormal proliferation (cortical dysplasia).

Disorders of neuronal migration: decreased migration (classic lissencephaly) (Fig. 13), increased migration (congenital muscular dystrophy), ectopic migration (heterotopia).

Disorders of cortical organization: polymicrogyria (patterns I and II), polymicrogyric syndromes (bilateral frontal, bilateral perisylvian, bilateral frontoparietal, bilateral parasagittal parietooccipital and diffuse bilateral) and schizencephaly type I (fused lips) and type II (open lips) (Fig. 14) [26].
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Pericerebral spaces: While enlarged, extra-axial spaces are normally visible on ultrasound, some lesions such as subdural hematoma require further examination by MRI (27).

Posterior fossa: Most abnormalities discovered during pregnancy that involve the posterior fossa have a poor prognosis. MRI allows better visualization of this structure than ultrasound, especially in cases of non-cephalic presentations, when an endovaginal probe cannot be used as a complement. Posterior fossa abnormalities evaluated by fetal MR imaging include Dandy-Walker malformation (Fig. 15), hypoplasia and/or rotation of the vermis (Fig. 16), Blake pouch cyst, mega cisterna magna, arachnoid cyst, cerebellar dysplasia, cerebellar hypoplasia, cerebellar hemorrhage, Walker-Warburg syndrome, Chiari malformation and other less common abnormalities such as the Pascual Castroviejo type 2 Syndrome (PHACE Syndrome) (28, 29).

Special reference should be made to two indications for fetal MRI:

Complications of monochorionic twin pregnancies: Intrauterine death of one monochorionic twin is associated with an increased risk of survival in the other twin because of acute cerebral hypoperfusion secondary to thromboembolic events (30).

Twin-twin transfusion syndrome (TTTS) is characterized by abnormal flow from the time when the donor twin develops oligohydramnios to the time when the recipient twin develops polyhydramnios. The morbidity of TTTS is very high and both twins are at risk for cerebral ischemia. Approximately 50% of surviving twins experience abnormalities (31).

Congenital infections: The most common cause of brain abnormality in cases of infection is cytomegalovirus (CMV) and secondly toxoplasmosis. Other viruses that can also affect the fetal brain include: varicella zoster virus, parvovirus B19, rubella, and lymphocytic choriomeningitis virus. They cause diffuse or focal white matter abnormalities and, with time, cortical

MRI is performed at 6 years of age because of seizures as from 5 years of age, controlled with valproic acid, and mild spastic monoparesis of the left arm. We can see how the open lip schizencephaly has progressed to fused lip schizencephaly with polymicrogyria lining the cleft (white arrowhead). Opercularization occurs between weeks 22 and 38. Associated with subependymal heterotopia in inferior and posterior location (black arrowhead).
atrophy and ventricular enlargement. Hemorrhages are also observed in association with CMV and parvovirus B19. They may be associated with cortical malformations such as lissencephaly, polymicrogyria, and delayed cortical maturation (24, 25, 32).

MRI also allows assessment of spinal and medullar abnormalities: Chiari II with myelomeningoceles, sacrococcygeal teratoma, caudal regression syndrome, myeloschisis, meningocele and lipomeningocele, tethered spinal cord or diastematomyelia.

The most common indication is myelomeningocele associated with Chiari II (Fig. 17); MRI is particularly helpful when ultrasound is limited (in cases of maternal obesity, inadequate fetal position, oligohydramnios). MRI is useful in identifying additional associated anomalies: corpus callosum agenesis or hypoplasia, periventricular nodular heterotopia, cerebellar dysplasia, hydrocephalus, syringohydromyelia and diastematomyelia (33, 34).

Sacrococcygeal teratoma is the most common tumor of the neonate, with an incidence of one in 35,000 to 40,000 live births (35). Malignant degeneration is the primary cause of postnatal death and is rare in utero. The high mortality rate is related to tumor size and associated dystocia, preterm labor secondary to polyhydramnios and placentomegaly (secondary to cardiac failure associated with arteriovenous shunting) (36, 37, 38). MRI is better than ultrasound in assessing the extension of the teratoma. The American Academy of Pediatrics Surgical Section Classification is used:

Fig. 15. GA: 22 weeks. Classic Dandy-Walker complex. (a) and (b) ultrasound; axial planes (c) Sagittal SSFSE T2; (d) Sagittal FIESTA; (e) Axial SSFSE T2; (f) Axial FIESTA. Dandy-Walker with partial cerebellar vermis agenesis (arrow) and hydrocephalus (arrowhead).

Fig. 16. GA: 25 weeks. Hypoplasia and/or rotation of the vermis (a) Coronal FIESTA; (b) Sagittal FIESTA, fetus 1; (c) Axial SSFSE T2 fetus 1; (d) Sagittal FIESTA, fetus 2; (e) Sagittal FIESTA, fetus 3; (f) Coronal FIESTA, fetus 3. Multiple pregnancy in 42-year-old woman with OVODON IVF and transference of 3 embryos. Two monochorionic diamniotic males (fetus 1 in cephalic presentation and fetus 3 in breech presentation) with hypoplasia and rotation of the vermis (white arrow) and open communication of the fourth ventricle and the cisterna magna (arrowhead). The twin in transverse position (female) has a normal vermis (black arrow).
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type I (external component and minimal presacral component), type II (external component and significant presacral component), type III (minimal external component and predominantly intrapelvic component) and type IV (located entirely within the pelvis and abdomen) (Fig. 18) (39, 40).

Finally, another clinical application of MRI is the assessment of craniofacial abnormalities, including: cleft lip, cleft palate (Fig. 19), hypotelorism, hypertelorism, anophthalmia, microphthalmia, nasal bone agenesis or hypoplasia (Down syndrome or fronto-nasal dysplasia) (Fig. 20) or midline abnormalities (maxillary hypoplasia, cyclopia, proboscis, ethmocephaly or ceboccephaly) (41, 42, 43).

CONCLUSIONS

MRI is evolving as a useful complimentary tool to ultrasound that allows assessment of fetal brain development as from the second trimester. It has a more accurate diagnostic capability than ultrasound in the identification of brain development abnormalities or other destructive lesions. MRI is helpful in formulating prognosis and perinatal management, since it can detect occult abnormalities in up to 50% of cases for certain indications.
References


