Magnetic resonance methods in fetal neurology

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1. Introduction

1.1. Overview

Fetal neurology has been defined as morphological, metabolic and functional assessment of the fetus. Ultrasound has been the primary imaging method for the routine evaluation of the fetus and for the early diagnosis of fetal malformations. To date, morphological and functional information has been acquired mainly by ultrasound, which is still the mainstay of imaging the fetus.

According to its specific physical background, ultrasound is limited to the visualization of only certain aspects of fetal neurological diseases.

Fetal magnetic resonance imaging (MRI) has evolved in the last 25 years since it was first described and has become of increasing importance as an adjunct to prenatal ultrasound, especially when evaluating the fetal brain. Because of its higher tissue contrast resolution than prenatal sonography it allows better visualization of both normal and abnormal tissue and may add important information in three specific ways: by quantification of brain growth and structural abnormalities, by qualitative evaluation of central nervous system (CNS) microstructure and by qualitative assessment of dynamic fetal movements in utero. Thus, using MRI as a clinical adjunct to ultrasound, all three mentioned areas of neurologic evaluation can be approached.

Normal fetal brain maturation can be studied by in-vivo MRI from the 18th week of gestation to term and relies primarily on T2-weighted sequences. Diffusion-weighted sequences have recently gained importance in the structural assessment of the fetal brain. Diffusion-weighted imaging provides quantitative information about water motion and tissue microstructure and has applications for both developmental and destructive brain processes. Advanced magnetic resonance techniques, such as spectroscopy, might be used to demonstrate metabolites that are involved in brain maturation, though their development is still in the early stages. Using fetal MRI in addition to prenatal ultrasound, morphological, metabolic, and functional assessment of the fetus can be achieved.

The latter is not only based on observation of fetal movements as an indirect sign of activity of the fetal brain but also on direct visualization of fetal brain activity, adding a new component to fetal neurology. This article provides an overview of the MRI methods used for fetal neurologic evaluation, focusing on normal and abnormal early brain development.

1.2. Safety of MRI in human studies

It is generally accepted that MRI is safe in pregnancy since no short- or long-term effects of MRI on mother or fetus have been reported. Concerns have been raised in some studies about the level of acoustic noise, biological effects and static field exposure. However, several studies failed to show any adverse long-term
effects of fetal MR in children who were imaged as fetuses, though these studies lacked a sufficient sample size.\textsuperscript{14–17} In 2002, the American College of Radiology stated that pregnant patients can undergo MRI at any stage of pregnancy if, the risk-benefit ratio is acceptable.\textsuperscript{18} However, because of the potential risk of MRI to the developing fetus and the excessive motion of younger fetuses, the policy of our institute is not to start fetal MRI before 18 weeks of gestation. Additionally the patients are extensively counseled upfront and an informed consent is signed. All patients are screened for possible contraindications to MRI before the examination. Usually, during fetal MRI, no sedation or contrast agents are administered.

2. Fetal brain morphology

2.1. Background

Normal structural brain maturation is a prerequisite for regular fetal neurological development. Using MRI, fetal brain maturation can be shown from gestational week 17 onwards.\textsuperscript{19} At this stage, the fetal brain consists of seven layers, which can be displayed by MRI.\textsuperscript{9} Until 36 weeks of gestation the fetal brain undergoes substantial development with neuronal migration and formation of gyri and sulci.\textsuperscript{4} The increasing number and the depth of cortical sulci can be assessed and used as age-related marker of brain development.\textsuperscript{20} Interestingly, it could be shown that cortical folding occurs not at the same time in both hemispheres and that asymmetry is a hallmark of normal brain development.\textsuperscript{21} In the second trimester, the fetal brain shows a laminar appearance with different layers, which are transient by nature and disappear during development, leading to its characteristic neonatal morphology. Premyelination – which is the state of the axons before the onset of myelination – of the internal capsule, and the brainstem, as well as cell density in the primary cortical regions and the basal ganglia can be recognized.\textsuperscript{9} Diffusion-weighted imaging is sensitive to the normal maturational changes and may be of value in the detection of abnormalities of brain development that cannot be detected with T2- or T1-weighted images.\textsuperscript{22}

Infratentorial development, which is regarded as crucial for the generation of normal movement patterns, can be assessed and quantified with in-vivo fetal MRI.\textsuperscript{23} Abnormal brain development may be characterized by focal or diffuse changes of cortical folding. Using MRI, diffuse pathologies such as lissencephalies or polymicrogyria may be recognized even before onset of formation of gyri and sulci, as these syndromes are associated with impaired lamination of the brain parenchyma and/or brainstem abnormalities,\textsuperscript{10,24} and/or abnormal hemispherical asymmetry.\textsuperscript{21} Diffuse abnormalities of cortical formation are associated with developmental delay, motoric impairment and epilepsy.\textsuperscript{25,26} Thus early diagnosis of diffuse disorders of cortical malformation is of prognostic significance.

Focal cortical dysplasia may also lead to epilepsy and/or focal neurological deficits. Their etiology is inhomogeneous.\textsuperscript{25} Due to their small size, they may be missed on MRI before the third trimester. This may be also the case in cortical tubera and/or subependymal nodules in tuberous sclerosis.\textsuperscript{27} Morphological manifestations of acquired brain pathology may show an overlap with malformations, especially if caused by infection such as CMV, that may lead to disorders of cortical development\textsuperscript{28} and may cause structural and profound neurodevelopmental abnormalities,\textsuperscript{29} such as microcephaly or ventriculomegaly and periventricular cystic lesions.\textsuperscript{30} Ischemic or hemorrhagic lesions have inhomogeneous etiologies.\textsuperscript{31}

The cause of fetal ischemia can be of placental, fetal or maternal origin.\textsuperscript{5} Ischemia can be demonstrated shortly after the insult by a hyperintense diffusion-weighted image signal, whereas chronic changes appear as increased signal on T1-weighted MR images, which is caused by subcortical leukomalacia.\textsuperscript{32,33} Spontaneous CNS hemorrhage can be caused by congenital coagulation disorders, vascular malformations and pre-existing tumors\textsuperscript{6} and may result in an obstructive hydrocephalus or abnormalities of brain development and neuronal migration.\textsuperscript{34} MRI is highly sensitive to acute ischemic brain lesions\textsuperscript{35} as well as to different stages of hemorrhage. In addition, grading of hemorrhage may be more accurately possible using MRI compared with ultrasound,\textsuperscript{36} leading to better prognostic information.

2.2. MRI

Fetal MR imaging is routinely performed on 1.5T MR scanners. The mother lies supine or in the left lateral decubitus position during the course of the examination. For optimal image quality, the fetal head must be in the center of the coil, which means a centered positioning of a mobile coil (such as a cardiac coil) around the mother, or in case of the use of the body coil, a proper positioning of the pregnant woman within the magnet. Sequences used for the assessment of normal fetal brain development are selected based on their ability to delineate surface structures and layering, which is best provided by T2 weighted contrast; to show differences in cell density, which may be done using T1-weighted images. Gradient-echo-sequences and echo-planar sequences respectively are sensitive for acute hemorrhage and blood breakdown products. Premyelination may be evaluated using diffusion-weighted anisotropy images.\textsuperscript{33,37}

In general, T2-weighted images, ultrafastspin-echo sequences, T1-weighted gradient-echo sequences, steady-state free precision sequences, and diffusion-weighted sequences are used, with their parameters adjusted to the changing ultrastructural composition of the developing brain. Because fetal MRI is performed without maternal or fetal sedation, image acquisition is susceptible to fetal motion; therefore, fetal MRI is performed primarily using ultrafast MRI techniques known as single-shot, fast spin-echo (SS-FSE) or half-Fourier acquired single-shot turbo spin-echo (HASTE).

MR signals of the different layers of the pallium depend on cellular density and on the amount of extracellular matrix, and the spatial course of ultrastructural elements.\textsuperscript{38,39}

3. Fetal brain connectivity

3.1. Background

Diffusion tensor imaging (DTI) and tractography are non-invasive tools that enable the study of three-dimensional (3D) diffusion characteristics and their molecular, cellular and microstructural correlates in the human brain.\textsuperscript{40} Bundles of myelinated axons create a strongly anisotropic environment with a diffusion maximum parallel to the orientation of the fiber tracts. Computational postprocessing algorithms use the directional diffusion information of each imaged voxel to generate 3D visualized ‘fibers’, which allows the 3D reconstruction and depiction of main white-matter fiber pathways.\textsuperscript{41,42} Tractography has already been used to identify white-matter fiber tracts in healthy preterm\textsuperscript{43} and term newborns,\textsuperscript{44} as well as in postmortem samples of fetal brains.\textsuperscript{45–47} Using specially tailored DTI sequences it has already been shown that it is possible to delineate sensorimotor tracts and the corpus callosum in living, unsedated fetuses in utero and to compare developmental changes in the morphology of these fiber tracts across gestational age.\textsuperscript{40} Thus, this method will be helpful in
diagnosing agenesis or hypogenesis of the corpus callosum or in pathologies where an impairment of the corticospinal tract is suspected. Recently even association fibers have been demonstrated. In the future a better estimation of neuropsychological development might be possible using the information provided by tractography of these bundles.

3.2. MRI

Connectivity can be demonstrated from 18 gestational weeks onwards. At that time, the corticospinal and the frontopontine tracts can be visualized. MR tractography is based on the evaluation of diffusion-tensor images. A diffusion-tensor sequence with 16–32 diffusion-sensitizing directions is used. Then, the color-coded fractional anisotropy maps are superimposed with anatomical images. Regions of interest (ROIs) are drawn in locations where the respective tract passes. A fiber-bundle passing through these ROIs can then be visualized (Fig. 1).

4. Functional MRI

4.1. Background and MRI

Functional magnetic resonance imaging (fMRI) allows detection of the brain areas involved in a task, a process, or an emotion. Thus, fMRI gives insights into the spatiotemporal distribution of human brain networks. Some of these networks can be detected when the fetus is in a resting state, whereas others have been observed in the context of task-focused behavior. Resting state networks (RSNs) are always present: during task performance and at rest, during sleep and anesthesia and across all ages from infants to adults.

It has been shown that structural and functional connectivity of RSNs can be affected by various neurodegenerative, neurological, psychiatric, motor and chronic pain diseases. Moreover it has been hypothesized that RSNs may serve as a classifier or marker for the course and extent of various diseases. The developmental origin of these networks is largely unknown.

However, the recent literature shows that resting-state networks are shaped and detectable in utero (Fig. 2). Further investigations of resting-state measurements in the fetus may therefore allow developmental brain activity monitoring and may provide insights into the early brain function.

5. Metabolic information

5.1. Background

Fetal magnetic resonance spectroscopy (H MRS) is a non-invasive imaging technique that allows in-vivo information about the metabolic status of fetal brain tissue by analyzing the differences in the 1H proton's absorption of specific radiofrequencies in a static magnetic field. Brain H MRS identifies several metabolites, including lactate. Preliminary data show that MRS can be used in the pediatric population, especially for the detection of hypoxic ischemic encephalopathy (HIE), leukoencephalopathies and inborn errors of metabolism. Additionally, it has been reported that impaired fetal brain development associated with ventriculomegaly, intrauterine growth restriction (IUGR), and small for gestational age fetuses can be shown by MRS signal changes.

5.1.1. Brain metabolites seen on MRS

1H MR spectra at short TE of the healthy neonatal brain reveal four main groups of metabolites: N-acetyl (NA), creatine (Cr), choline (Cho), and inositol (Ino). Using additional water suppression pulses in vivo, the spectrum in the brain reveals specific peaks due to the metabolites NAAG and N-acetyl-aspartate glutamate (NAAG); creatine + phosphocreatine (Cr); choline (Cho); Myo-inositol (Myo-ino); glutamine (Gln); glutamate (Glu); glucose (G); taurine (Tau); scylloinositol (Scy-ino); and lactate (Lac). Normative values for the levels of the fetal brain metabolites, Ino, Cho, Cr, and NA, and their ratios are available and can be used as references to examine changes in 1H MR spectra due to pathological conditions of the fetal brain, for example, neuronal damage due to hypoxia.

5.1.2. Fetal brain maturation on MRS

Metabolite levels within the human fetal brain have been shown to change with increasing gestational age during the third trimester. This finding is thought to reflect maturation, in agreement with 1H MRS performed on preterm neonates. At 22 weeks of gestation the MRS is characterized by two prominent resonances assigned to Myo-ino and Cho. The Myo-ino resonance dominates the spectrum at short TE from 22 to 28 weeks of gestation and is significantly reduced with progressing gestational ages in fetuses.

Choline is also prominent on the MRS spectrum at a short TE from 22 to 28 weeks. Cho is involved in synthesis of acetylcholine and membrane phospholipids and is taken up by both glia and neurons. Cho and the Cho:Cr ratio significantly decrease with...
NA signal increases significantly with progressing gestational age. \(^{65}\) Ino shows no significant change in relation to fetal gestational age, which is in agreement with findings in the literature.

Increasing cerebral tissue levels of NA and Cr and decreasing levels of Cho and Ino are observed with the development of the fetal brain. \(^{67}\) Fetal brain maturation on MRS \(^{62,69,72–75}\)

At 34 weeks of gestation, the spectrum of metabolites is similar to that of the neonate. Three dominant resonances — Cho, Cr, and NAA — are observed at a long TE and five resonances — Myo-inos, Cho, Cr, NAA, and glutamine/glutamate — are dominant at a short TE.

Recently, lactate was shown on MRS studies in IUGR fetuses and in patients with gastroschisis. \(^{76,77}\) However, as lactate may be part of the normal metabolic spectrum in premature newborns, \(^{77}\) the pathological significance of a lactate peak found in the fetal brain remains unclear.

5.1.3. Impaired fetal brain development demonstrated by MRS

Impaired fetal brain development may be caused by a primary brain malformation, hypoxic–ischemic injury, infection, or a combination of factors. The literature gives little information about specific metabolic changes in different fetal brain abnormalities, and specific spectroscopic patterns in different brain anomalies have not yet been identified in utero. However, in ventriculomegaly, a lower Ino:Cr ratio has been suggested to result from an abnormal hypo-osmolar state. \(^{79}\)

The recent literature also suggests that the evaluation of gliosis might be made possible by Cr increases, which can be detected in tissue injury and which are not visible by conventional T1 or T2 sequences. \(^{30}\) In the future, the evidence of gliosis might help in the evaluation of the timing of an intratérine injury, as glial reactivity has been found to be associated with developmental steps in the rodent brain. \(^{81}\)

5.1.4. Intrauterine growth restriction

As mentioned before, in IUGR fetuses with normal morphology, proton MRS of the fetal brain shows lactate and a low NAA:Cho index, metabolic markers of starvation/hypoxia. \(^{77}\) This pattern is consistent with the metabolic changes seen in hypoxic–ischemic injury in neonates. A recent study additionally shows a significant increase in Ino:Cho ratio and significantly higher apparent diffusion coefficient (ADC) values in the pyramidal tract of small for gestational age fetuses compared with age-matched normal fetuses. \(^{82}\)

5.1.5. Infection

In a fetus with cytomegalovirus infection, MRS may show an increased concentration of lipids, Myo-inos, and possibly alanine, although the white matter may appear normal on conventional sequences. It has been speculated that this may correlate with an increase in amino acids, which is associated with brain infection. \(^{11}\)

5.2. MRI

MRS is usually acquired using spin echo Point-RESolved Spectroscopy (PRESS, SE) or STimulated Echo Acquisition Mode (STEAM, ST) sequences with short and long echo times (TE = 20–35 and 144 ms). For an optimal signal-to-noise ratio a minimum nominal volume of interest (VOI) size of 3.4 cm\(^3\) (15 mm \(\times\) 15 mm \(\times\) 15 mm) should be used, with the VOI as close to the receiver coil as possible. Care should be taken to avoid inclusion of extracranial structures within the VOI. \(^{11}\) The acquisition time for a single spectroscopic sequence may take between 2 and 7 min. The measurement of all necessary spectra can take up to 15 min.

If fetal movements complicate the examination, it is advisable to repeat scout MR images between spectral acquisitions to ensure the placement of spectroscopic VOI within the chosen brain region. The fetal head should not move significantly during the acquisition time period. \(^{11}\) Spectroscopy can be done without sedation. However, maternal premedication with flunitrazepam administered orally 15 min to 1 h before the MR examination has been recommended. \(^{83}\) Short TE acquisitions are used to detect fetal brain metabolites with short spin–spin relaxation times, such as glutamine, glutamate, glucose, taurine and lipids.

Resonances of N-acetyl aspartate (NAA), choline and creatine are also visible in short echo spectra. However, because of the longer relaxation time, a quantification is far more accurate if the TE acquisitions are longer (135, 144 and/or 270 ms). Longer TE acquisitions are also used to discriminate between lactate, alanine and lipid resonances in the spectral region around 1.35 and 1.55 ppm.

6. Observation of fetal movement patterns

6.1. Background

Fetal motor activity is a conspicuous feature of prenatal development. The human fetus moves on average once per minute and is motorically active up to 30% of the time. Spontaneous motor activity starts in the embryonic period and motor patterns become increasingly complex with continuous pregnancy. \(^{84}\)
Fetal behavior is characterized by spontaneous and reflective movements, which require a certain neuromuscular development and a normal metabolic state of the CNS. Thus, evaluation of fetal movements may add accuracy to the overall assessment of the fetal CNS.

The first fetal movements consisting of flexion and extension of the vertebral column occur around the 8th week of gestation. Coordinated movements involving the whole body are observed from 9 weeks of gestation. At this time the movements are not influenced by cerebral input, as the cortical areas, which are important for targeted-oriented behavior and the functionally important subcortical areas, are not developed until 19 weeks of gestation. From the 14th gestational week the movements become more organized and at around 20 gestational weeks the fetus shows bilateral movements, whereas the hands are held preferably near the face. Between gestational weeks 26 and 32, the fetus starts to move extremities independently following a distal proximal pattern. At later gestational weeks between weeks 37 and 38, the movement frequency decreases, and the back of the hands rest against the uterine wall.

Fetal mouth movements may occur as pure mouth movements (opening and closing, swallowing, protruding the tongue, etc.) or as so-called mouthing movements, which are mouth movements characterized by a specific rhythm and frequency. Mouthing is increasingly seen later in pregnancy, after 34 weeks of gestation, and occurs preferentially during fetal rest (Fig. 3).

Knowledge about the MRI characteristics of the fetal musculature is limited and there are only a few reports in the literature. Compared with prenatal MRI, several studies in pediatric populations have documented the role of MRI in the visualization of neuromuscular disorders. Muscular atrophy on fetal MRI may also present with T2 signal hyperintensity and has been attributed to fatty replacement secondary to chronic denervation. The specificity of this finding is unknown. Furthermore, MR spectroscopy might be able to measure abnormal metabolism in fetal muscle tissue, but currently there are no data on this.

Dynamic steady-state free precession (SSFP) sequences using four to six images per second may show gross fetal movements and intrinsic movements, such as mouthing and swallowing. The dynamic SSFP sequence may be applied five times at 5, 10, 15, 20, 25 and 40 min to study fetal movements and to detect fixed contractions. An observation period of $3 \times 30$ s during an MRI examination time of 30–45 min is estimated to be sufficient to show fetal general movements. However, absence of fetal movement patterns during this time period is not necessarily indicative of a fetal developmental abnormality.

6.2. MRI

Using fetal MRI in addition to prenatal ultrasound, morphological, metabolic, and functional assessment of the fetus can be achieved. The latter is not only based on observation of fetal movements as an indirect sign of activity of the fetal brain but also on direct visualization of fetal brain activity, adding a new component to fetal neurology. Future research will contribute significantly to our understanding of early normal and abnormal cerebral development.

7. Conclusion

Fetal MRI has become established as a clinical adjunct in the evaluation of the developing CNS and has the power to confirm or change decisions at critical points in daily clinical practice.
Practice points

- Normal fetal brain maturation can be studied with MRI from the 18th week of gestation to term
- The interpretation of the findings is based on a knowledge of the histological background, the temporal appearance of transient structures and their characteristic presentation on MRI
- Using fetal MRI in addition to prenatal ultrasound, morphological, morphometric, and functional assessment of the fetus can be achieved.

Research directions

- Normal fetal brain development can now be readily assessed in different periods of gestation
- Extending the “conventional” fetal MR-sequences with new imaging techniques, such as diffusion tensor imaging (DTI), tractography or functional fetal MRI may provide important morphological and functional insights into normal and abnormal fetal brain development.
- Further investigations are needed to prove the diagnostic potential of these new imaging techniques.

Conflict of interest statement

None declared.

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