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TOPIC HIGHLIGHT

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Quantitative magnetic resonance imaging of the fetal brain in utero: Methods and applications

Anat Biegon, Chen Hoffmann

Anat Biegon, Department of Neurology and Radiology, School of Medicine, Stony Brook University, Stony Brook, NY 11794-2565, United States
Chen Hoffmann, Department of Diagnostic Imaging, Sheba Health Center, Ramat Gan 52622, Israel
Author contributions: Biegon A and Hoffmann C solely contributed to this paper.
Correspondence to: Anat Biegon, PhD, Professor of Neurology and Radiology, School of Medicine, Stony Brook University, 100 Nicols Rd, Stony Brook, NY 11794-2565, United States. anat.biegon@stonybrook.edu
Telephone: +1-631-6326228 Fax: +1-631-6326294
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Abstract

Application of modern magnetic resonance imaging (MRI) techniques to the live fetus in utero is a relatively recent endeavor. The relative advantages and disadvantages of clinical MRI relative to the widely used and accepted ultrasonographic approach are the subject of a continuing debate; however the focus of this review is on the even younger field of quantitative MRI as applied to non-invasive studies of fetal brain development. The techniques covered under this header include structural MRI when followed by quantitative (*e.g.*, volumetric) analysis, as well as quantitative analyses of diffusion weighted imaging, diffusion tensor imaging, magnetic resonance spectroscopy and functional MRI. The majority of the published work reviewed here reflects information gathered from normal fetuses scanned during the 3rd trimester, with relatively smaller number of studies of pathological samples including common congenital pathologies such as ventriculomegaly and viral infection.

Key words: Fetal brain; Fetal magnetic resonance imaging; Fetal magnetic resonance spectroscopy; Fetal apparent diffusion coefficients; Fetal functional magnetic resonance imaging; Cortical development

Core tip: This review focuses on the budding field of quantitative magnetic resonance imaging and studies of the fetal brain designed to establish normative databases relevant to regional brain growth, connectivity and function and their application to a deeper understanding of the etiology, diagnosis and prognosis of fetal brain pathologies.

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INTRODUCTION

The history of fetal magnetic resonance imaging (MRI) in utero spans more than 3 decades, beginning with clinically driven T1 and T2 weighted studies at relatively low magnetic field published in the 1980's[1-4]. This was followed by early echo planar imaging of fetal brains attempted in the early 1990s[5,6]. Throughout this period, the mainstay of fetal imaging for all organ systems has been ultrasound, but the better contrast resolution of MRI relative to ultrasound made it especially attractive for studies of the central nervous system (CNS), which is relatively vulnerable to congenital anomalies. Progressive improvements in imaging hardware and software, resulting in shortened scan times and increasingly wider choice of imaging sequences, have made fetal brain MRI an increasingly valuable imaging tool in cases with uncertain

diagnosis of CNS abnormalities[7,8].

The biggest problem in acquiring reliable, reproducible and comprehensive MRI images of the fetal brain has been motion. Early studies attempted to overcome this problem by sedation of mother and/or fetus[9] although this approach has obviously limited the widespread use of the technique in clinical and research settings. The breakthrough came with the development of faster imaging techniques and sophisticated methods for motion correction[10-16]. The Ultrafast sequences which have been developed, including single shot fast spin echo, fast spin echo and the half fourier single shot turbo spin echo require a second or less per slice acquisition. In these studies multiple stacks of slices are acquired at different orthogonal orientations, providing a comprehensive view of the anatomy while allowing for manual adjustment to fetal motion or gating to maternal breathing. The most recent and ongoing developments in image reconstruction and motion correction methods[17-20] have enabled the adoption of all major MR approaches currently used in adults to in utero studies; including diffusion weighted imaging, tractography and MR spectroscopy[21-26] consequently enabling the gathering of unprecedented amounts of information on fetal brain development in utero.

This review focuses on the budding filed of quantitative MRI and studies of the fetal brain aiming at the establishment of normative databases relevant to normal regional brain growth, connectivity and function and their application to a deeper understanding of the etiology, diagnosis and prognosis of fetal brain pathologies.

QUANTIATIVE MRI IN THE STUDY OF NORMAL FETAL BRAIN DEVELOPMENT

Mapping regional and local patterns of normal fetal brain growth

An early study using the Cavalieri method to estimate whole brain volumes in a small cohort (n = 18) of third trimester fetuses[27] described a linear relationship between gestational age and whole brain volume, with a growth rate averaging 2.3 mL/d. The first study to measure volume changes in brain hemispheric parenchyma, cerebellum and ventricles of 27 normal, third trimester fetal brains[28] revealed different, non-linear growth trajectories for the three compartments, with a faster growth of cerebral hemispheres relative to cerebellum and a steady decrease in the ventricular/parenchymal volume with increasing gestational age. Subsequent work by Gholipour *et al*[29] using supervised automated segmentation of brain volumes in fetuses aged 19 to 37 wk compared linear and non linear models and concluded that a quadratic model provided the best fit to the data describing the changes of fetal brain volume with gestational age. Hu *et al*[30] also confirmed that the growth rates of the cerebral volumes are region-dependent, with the frontal and parieto-temporal regions growing significantly faster than other regions. More recent studies have added substantial amount of detail on normal fetal brain growth, with the publication of a spatiotemporal atlas of MR intensity, tissue probability and shape of the fetal brain[31] and detailed descriptions of the growth of the fetal subplate and other regions[32,33]. Corbett-Detig *et al*[32] examined subplate growth in relatively young (18-24 wk old) fetuses and found that the occipital pole, ventral occipito-temporal region, and planum temporale underwent the most statistically significant increases in subplate thickness, while the thickest region during this period was the developing somatosensory/motor cortex.

A more detailed study of volumetric changes in the growing fetal brain was published by Scott *et al*[33] examining volumes of cortical plate, subplate and intermediate zone, germinal matrix, deep gray nuclei, and ventricles from automatic segmentation of motion-corrected, 3D reconstructed MRI scans from 39 normally developing fetuses at gestational age (GA) ranging from 21 to 31. The findings again show region-specific growth trajectories, with the cortical plate having the highest growth rate (18%/wk).

The supratentorial volume, subplate and intermediate zone, germinal matrix and deep gray nuclei exhibited similar growth rates of approximately 15%/wk while the slowest growth rate was found for ventricles (9.2%/wk). Interestingly, the authors did not find sex differences or asymmetries in hemispheric volumes. This could be a group size/power issue but may also indicate that such difference only emerge later in brain development.

Quantitative studies of cortical folding

Hu *et al*[34] provided a regional quantification of cortical shape development from a group of normal fetuses in the gestational age range of 22-33 wk. They report faster shape changes in the occipital lobe than in other regions and conserved patterns of shape changes in gyri and sulci, whereby the gyral surface smoothens, while the sulcal surface becomes more angular, with gestational age. In addition, the authors report that smoothing of gyri is related mainly to the changes in shape of gyral crowns.

Clouchoux *et al*[35] examined *in vivo* fetal cortical folding patterns in healthy fetuses between 25 and 35 wk gestation, providing an explicit delineation of the sulcal pattern as well as surface area and gyrification index. The findings suggest an exuberant third trimester gyrification process and a non-linear evolution of sulcal development.

Employing a younger group (GA 20-28 wk) of fetuses, Habas *et al*[36] and Rajagopalan *et al*[37] have been able to detect early folding patterns and asymmetries in fetal brain development. Their Tensor based morphometry results show that fetal brain development exhibits a distinct spatial pattern of anisotropic growth, with the most significant changes in the directionality of growth occurring in the cortical plate at major sulci. The authors also report significant directional growth asymmetry in the peri-sylvian region and the medial frontal lobe of the

fetal brain.

Studies of water diffusion in the normal developing brain

Regional differences and developmental changes in apparent diffusion coefficients (ADC) have been the subject of several studies conducted and published during the last decade[23,38-47]. All of the published studies report absolute values for ADC in a similar range and detect a trend towards a reduction in ADC with increased GA, which could be explained by progressive myelination. However, the relationship between ADC and GA appears to be region-dependent and non-linear. Thus, whether a specific study reports on significant changes of ADC with GA appears to depend on the range of developmental ages and regions included in the analysis. To illustrate, Righini *et al*[38] reported a mean ADC value of 1.96 ± 0.1 microm^2/ms (SD) in frontal white matter, 1.95 ± 0.1 microm^2/ms in occipital white matter, and 1.56 ± 0.1 microm^2/ms in basal ganglia of fetuses aged 22-35 wk, with a significant negative correlation between ADC and gestational age for basal ganglia, and only a trend for frontal white matter. A subsequent study by another group involving fetuses between 31 and 37 wk gestation[39] reported mean ADC values of 1.8 microm^2/ms in the centrum semiovale, 1.2 microm^2/ms in the splenium of the corpus callosum and 1.1 microm^2/ms in the pyramidal tract, with mean fractional anisotropy (FA) values of 1.1%, 3.8% and 4.7%, respectively. The authors report a significant age-related decrease in ADC and an increase in FA in the pyramidal tract and corpus callosum. Manganaro *et al*[40] measured ADC in the grey matter, reporting mean ADC values from 1.76 × 10^{-3} mm^2/s (at week 19) to 0.89 × 10^{-3} mm^2/s (at week 37), whereas in the white matter, the values varied from 2.03 × 10^{-3} mm^2/s (at week 19) to 1.25 × 10^{-3} mm^2/s (at week 37). Cartry *et al*[42] reported a linear inverse correlation existed between ADC values and gestational age only in the occipital lobes of 22 normal fetuses scanned between 30 and 34 wk gestation. This theme of region-dependent developmental changes in ADC is reiterated in the largest and most recent study of this kind, where Boyer *et al*[43] described a study of 50 normal fetuses between 19 and 37 wk gestation. The authors report that ADC values remained constant in the basal ganglia, frontal, parietal, temporal and occipital white matter and in the centrum semiovale while significant decreases were observed in the cerebellum, pons and thalamus with advancing menstrual age.

Development of regional connectivity

Tractography presents a bigger challenge for in utero fetal imaging relative to other techniques since acquisition times are longer and therefore studies are more susceptible to motion artifacts[21-23]. Consequently, only a few recent studies provide quantitative data from in utero studies of neuronal pathways. Kasprian *et al*[23] examined a group of fetuses ranging in age from 18 to 37 wk and reported that only in 40% of examined fetuses, diffusion tensor imaging measurements were robust enough to successfully calculate and visualize bilateral, craniocaudally oriented (mainly sensorimotor), and callosal trajectories in utero. However, the successful studies resulted in a wealth of quantitative information on fiber lengths, ADC, FA, and eigenvalues at different anatomically defined areas. FA values and the axial eigenvalue [lambda(1)] showed a characteristic distribution, with the highest values for the splenium, followed by the genu, the right and the left posterior limb of the internal capsule. Intriguing evidence for early asymmetry was also obtained, showing that the right-sided sensorimotor trajectories were significantly longer than on the left side, reflecting higher right-sided lambda(1) values.

A more recent publications from the same group[44] reports on successful visualization and delineation of sensorimotor tracts and the corpus callosum as well as smaller fiber bundles, separating the internal capsule fibers into thalamocortical fibers, corticopontine and corticospinal tracts and segregating the thalamocortical fiber system to anterior, superior and posterior radiations. Association fiber tracts connecting ipsilateral cortical areas were also successfully visualized.

Development of brain chemistry using MR spectroscopy

Development of the normal fetal brain in utero using MR spectroscopy (MRS) has been studied by a number of groups. The size of the voxel necessary to acquire reliable information limits the possibility of regional measurements, so these studies mostly reflect whole brain maturation. With this caveat, levels of choline (Cho), creatine (Cr), myo-inositol (Myo-ins) and N-acetyl aspartate (NAA) have been measured in utero in fetuses in the age range of 22 to 41 wk[26,45-48]. Kok *et al*[45] found no change in the absolute level of Cr using an echo time of 135 ms with 35 fetuses between 30 and 41 wk. In a later study[46], the group reported absolute tissue levels of these metabolites resemble values measured in preterm and term babies, especially of relatively more mature brain regions, from which most of the MR spectra have been obtained. Brain maturation between 30 and 41 wk of gestation was most clearly reflected by increasing levels of the neuronal marker NAA. Subsequent studies by Girard *et al*[47,48] confirmed that by 34 wk the fetal brain spectrum is comparable to that of a term born neonate, with dominant resonances of Cho, Cr and NAA at a long echo time and Myo-ins, Cho, Cr and NAA dominant resonances at a short echo time. The authors further report that creatine and phosphocreatine, compounds involved in energy metabolism, both contribute to the Cr peak. In a study of 58 fetuses with a gestational age range of 22-39 wk, the authors reported that Cr levels increased in the fetal brain with increasing gestational age. However, this was only found at a short echo time (30 ms) and not at a longer echo time (135 ms).

Imaging developing brain function: Functional MRI

The feasibility of studying fetal brain activity with functional MRI was demonstrated by Hykin *et al*[49] just be-

fore the turn of the century, reporting on responses to maternal speech. This was followed by additional studies reporting the detection of responses to visual[50] and various auditory[51-54] stimuli, which were detected between 33 and 34 wk of gestation. Functional connectivity (FC) at rest was subsequently investigated by Schöpf *et al*[55] in fetuses from 20 to 36 gestational weeks of age. The authors report a bilateral occipital network and medial and lateral prefrontal activity pattern that involved the future Brodmann areas 9-11 and a hemispheric lateralized network that involved the superior temporal cortical regions (Brodmann areas 22 and 39). Frequency oscillations were in the range of 0.01-0.06 Hz for all networks. Thomason *et al*[56] studied 25 healthy human fetuses in the second and third trimesters of pregnancy (24 to 38 wk of gestation) and reported the presence of bilateral fetal brain FC as well as regional and age-related variation in the strength of FC between homologous cortical brain regions, which increased with advancing gestational age. The authors also observed medial to lateral gradients in fetal functional brain connectivity. Sørensen *et al*[57] examined the fetal blood oxygen level dependent response to maternal hyperoxia, demonstrating an increased oxygenation in a number of human fetal organs while oxygenation of the fetal brain remained constant. These studies, together with findings from other modalities like fetal electroencephalography and magnetoencencephalography[58] are truly revolutionary since unlike information on maturation of brain morphology and microstructure/chemistry which can be obtained postmortem, the development of function can only be studied *in vivo*.

QUANTIATIVE MRI IN THE STUDY OF FETAL BRAIN PATHOLOGY

Fetal ventriculomegaly/hydrocephalus

The first quantitative MRI studies in ventriculomegaly (VM) employed magentic resonance spectroscopy[59,60]. Kok *et al*[59] performed ^{1}HMRS of the brain in 10 fetuses with ventricular dilatation and 36 normal fetuses between 28 and 37 wk and found that the inositol: Cr ratio was significantly lower in fetuses with hydrocephalus. Roelants-van Rijn *et al*[60] examined the brain of six fetuses with ventricular dilation and were able to detect the presence of Lactate (Lac) in two of the six fetuses, two had no Lac and two spectra were un-interpretable due to contaminating lipid peaks.

The first study applying quantitative MRI to the comparison of ventricular and parenchymal volumes in cases referred because of VM and normal controls revealed that fetal VM is not associated with decreases in parenchymal volume[28]. Using conventional T1- and T2-weighted imaging, Erdem *et al*[61] also found that hydrocephalic fetuses had a normal signal pattern in cerebral parenchyma, but their ADC values, derived from diffusion weighted imaging, were significantly lower than those reported for fetuses with normal brain. The largest volumetric study of VM published to date[62], which included postnatal outcomes in more than 300 fetuses, revealed that ventricular, but not parenchymal, volume was a significant predictor of live birth. The association was stronger in isolated VM relative to VM with other anomalies present. Most recently, the absence of changes in parenchymal volume was confirmed in a cohort of mild isolated VM using motion-corrected 3D reconstruction and automatic segmentation[63].

Congenital cytomegalo virus infection

A recently published study[64] examined the maturation of hemispheric and temporal lobe volumes in 27 congenital cytomegalo virus (CMV) infected fetuses relative to GA-matched normal controls, all scanned during the third trimester. Temporal lobe volumes, normalized to whole brain and co-varied with gestational age; were significantly smaller in fetuses infected with CMV compared to uninfected fetuses. Furthermore, Infection during the 1st and 2nd trimester had a more pronounced effect than infection during the 3rd trimester. While Infected fetuses with no MRI findings had significantly lower temporal lobe/whole brain ratios than controls, the lowest temporal lobe/forebrain ratios were observed in fetuses with CMV as well as overt findings such as cysts or gray matter heterotopy. These findings suggest a regional vulnerability to maternal immune activation in the fetal brain, although the relationship between the results and neurological outcome still needs to be established.

Congenital heart disease

Limperopoulos *et al*[65] compared brain volume and metabolism in 55 fetuses with Congenital heart disease (CHD) and 50 normal fetuses (gestational age range 25-37 wk) with the use of 3-dimensional volumetric MRI and proton MRS. they found progressive and significant declines in gestational age-adjusted total brain volume and intracranial cavity volume in CHD fetuses relative to controls, as well as a significantly slower increase in the NAA:Cho ratio. Predictors of lower NAA:Cho included diagnosis, absence of anterograde aortic arch flow, and evidence of cerebral lactate. In a subsequent study[66] of 18 fetuses with hypoplastic left heart syndrome (HLHS, a severe form of congenital heart disease) and 30 control fetuses in the same age range, the authors found a progressive fall-off in cortical gray and white matter volumes as well as subcortical gray matter in fetuses with HLHS. These fetuses also showed significant delays in cortical gyrification, whereby local cortical folding delays were detected as early as 25 wk in the frontal, parietal, calcarine, temporal, and collateral regions and appeared to precede volumetric brain growth disturbances.

Intrauterine growth restriction

Quantitative studies of fetal organ growth in intrauterine growth restriction (IUGR) confirmed the expected relative sparing of the brain. Damodaram *et al*[67] measured peripheral organs and brain volumes in 20 growth restricted and 19 normal fetuses scanned at gestational age

21-37 wk and found a significant reduction in fetal whole body volume and volume of all internal organs except the brain. A brain:liver ratio above 3.0 was associated with a 3.3 fold increase in risk of perinatal mortality. Interestingly, an MRS study[68] detected a lactate peak in the brain of the most severely affected IUGR fetus which was consistent with low oxygen content and high lactic acid concentration in umbilical blood obtained at delivery.

Ischemic stroke

The likelihood of detecting acute hypoxic-ischemic brain lesions by prenatal magnetic resonance imaging is small. However, a published case study[69] reports on a fetus with a vein of Galen arteriovenous malformation in whom prenatal diffusion-weighted magnetic resonance imaging at 33 wk of gestation clearly detected cerebral acute ischemic lesions, associated with remarkable decrease of the average apparent diffusion coefficient.

Environmental toxicity

Quantitative MRI is uniquely suitable for the study of the effects of exposure of pregnant women to environmental toxins and drugs on fetal brain development. A recent study by Anblagan *et al*[70] reported on the effects of maternal smoking during pregnancy on fetal organ growth in 13 smokers and 13 non-smokers examined at 22-27 wk and again at 33-38 wk of gestation. Exposed fetuses showed lower brain volumes at both time points, and the effect size was larger in the 2nd visit, closer to the end of gestation.

CONCLUSION

The adaptation of quantitative MRI techniques to fetal brain imaging in utero is truly revolutionary, embodying the potential to transform this area of basic and clinical research and practice from the subjective, qualitative and arbitrarily dichotomous identification of "lesions" and "abnormalities" to the much richer and promising domain of objective, continuous measurements of salient parameters reflecting different morphological, microstructural and biochemical aspects of brain maturation. It is fair to say that if fetal MRI is in its infancy, quantitative fetal MRI is in its embryonic developmental stage, undergoing an explosive phase of methods development, fine-tuning and validation. Consequently, the majority of the published work reviewed here reflects information gathered from relatively small cohorts of normal fetuses scanned during the 3rd trimester, and the relatively smaller number of studies of pathological samples to date offer very limited or no postnatal follow-up. Further improvements in methodology and safety are needed before these studies can be extended to earlier fetal ages, affording a comprehensive view of fetal brain development in utero. The progressive accumulation of normative data bases and extended postnatal follow-up are essential prerequisite for the future use of quantitative MRI in the diagnosis, prognosis and prenatal treatment[71] of congenital brain disorders.

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