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Imaging of the embryonic and fetal central nervous system

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Introduction

The past decades have seen enormous progress in the ability to visualize the developing fetal and embryonic central nervous system (CNS) with ultrasound (US) and MRI (magnetic resonance imaging). The purpose of this article is to provide a review of the available literature, and to detail some recent research into the topic.

US imaging started in the 1960's with A-mode US (Pasto and Kurtz, 1986). This yields a one-dimensional display of a graph representing the distance between structures producing echoes and the amplitude of these echoes. Imaging of the fetal CNS with this was limited to the measurement of the fetal biparietal diameter and visualization of the cranial midline. Today, A-mode US is used mainly in ophthalmology where precise measurements are required. The development of B-mode US made it possible to visualize fetal structures in two dimensional (2D) cross-sectional planes with a two-dimensional display. This led to an explosion in knowledge of US of embryonic and fetal development to such an extent that it is impossible to imagine practicing obstetrics or fetal medicine without the support of US imaging. Initially, axial images of the fetal brain were used for screening and diagnosis. Coronal and sagittal views are increasingly used, and essential for a complete fetal neursonographical examination (Malinger *et al.*, 2007). With the arrival of three dimensional (3D) US, three orthogonal planes could be displayed simultaneously, planes which might otherwise have been inaccessible could be visualized, and volumes could be measured more accurately (Kalache *et al.*, 2006).

During the same time, magnetic resonance imaging (MRI) developed from a technique which could provide "tissue characterization information that complements the superior anatomic detail of US (McCarthy *et al.*, 1985) in the mid eighties, to arguably "the optimal method for depicting the specific abnormalities that characterize each type of malformation of the brain in the fetus" (Raybaud *et al.*, 2003). It is certainly being argued with great heat whether US or MRI is the optimal method of fetal brain imaging (Malinger *et al.*, 2004). Theoretically, the two modalities should be synergistic, as the physics behind image generation is completely different. US generates images by means of the US waves reflected at the interface between areas with different US conductivity, and MRI contrast depends on the relative fat, water and proton content of tissues (Bitar *et al.*, 2006). In practice, it is difficult to determine the relative merit of either technique from the literature which is often clouded by an implicit or explicit bias for either modality. Also, imaging does not equate diagnosis, and several publications confirm the value of a multidisciplinary approach to the diagnosis of fetal central nervous system abnormalities (Hagmann *et al*, 2008; Malinger *et al.*, 2004). Both techniques are operator-dependent (Brugger *et al.*, 2006), and both techniques are deemed to be safe in pregnancy (Abramowicz, 2007; Kanal, 1994).

Physiology

First trimester

MRI has very limited applicability in the first trimester – not so much because of safety concerns as the lack of resolution. On the other hand, it has been possible to visualize the structure of the embryonic central nervous system with US more than two decades ago (Timor-Tritsch *et al.*, 1988). A decade later, the first three dimensional (3D) reconstructions were done with experimental transducers (Blaas *et al.*, 1998). It is now possible to obtain two dimensional (2D) and 3D images of the embryonic ventricular system from eight weeks of (postmenstrual) gestational age. These can be visualized in orthogonal planes or with 3D rendering techniques. With inverse mode rendering, hypo-echogenic structures

(such as ventricles) are rendered, and with automated volume calculation (AVC) the volume of these ventricles can be calculated automatically (Fig. 1). The single three-dimensional sweep used to obtain these images as well as images which could be used for crown rump length measurement and further anatomical evaluation could also minimize the exposure of the rapidly developing embryo to US energy (Pistorius *et al.*, 2009). The applicability for screening remains to be evaluated in greater detail, but several reports have appeared of holoprosencephaly diagnosed during the first trimester with these techniques (Kim *et al.*, 2008; Timor-Tritsch *et al.*, 2008).

Ventricle size and symmetry: second and trimester

Screening for ventriculomegaly later in pregnancy is well established. A simple cut-off of 10mm for the ventricular atrium as measured on an axial view has been used as a screening test for ventriculomegaly throughout the second half of pregnancy. This cut-off had been developed from cross-sectional data more than twenty years ago (Cardoza *et al.*, 1988), but has stood the test of time (Malinger *et al.*, 2007). On the other hand, there is little information on the prenatal prevalence of physiological asymmetry of the lateral cerebral ventricles. Postnatally, there is significant asymmetry in more than 40% of infants (Shen and Huang, 1989), but it has been reported in only 0.2-0.4% of fetuses (Achiron *et al.*, 1997). This might be a true difference, or might reflect an ascertainment bias, as the proximal hemisphere is often obscured with reverberation artefacts during antenatal US imaging (Monteagudo, 1998). Evaluation of both left and right lateral cerebral ventricles can be improved by obtaining the midcoronal view on 2D US and using volume contrast imaging (a modality of 3D US). Despite adequate visualization of both lateral ventricles, we demonstrated asymmetry of the lateral ventricles in only 4% of examinations in a longitudinal study of 28 fetuses (unpublished observations). It would be interesting to examine the difference between antenatal and postnatal asymmetry prospectively a group of infants before and after delivery.

Cortical development

The prenatal development of the cerebral cortex has been described on anatomical (Chi, 1977) and MRI studies (Garel, 2004; Levine and Barnes, 1999). However, these were all cross-sectional, rather than longitudinal, studies, and fetuses were examined for a variety of maternal and fetal indications. Despite popular belief that it is difficult to ascertain fetal cortical development with US, several publications have demonstrated clearly that fetal cortical development can be demonstrated well with US (Cohen-Sacher *et al.*, 2006; Monteagudo and Timor-Tritsch, 1997; Toi *et al.*, 2004). These include well-designed, longitudinal studies, but it is still difficult to translate these findings into practice. Typically, the first appearance of sulci and gyri were typically described, rather than the development over time, and with little attention to interindividual variation. Another limitation of the available literature was the lack of a systematical description of physiological asymmetry. It is possible to modify a scoring system used in MRI imaging (van der Knaap *et al.*, 1996) to score the progression of cortical folding by US (Fig. 2). In a prospective study of 28 fetuses between 20 and 40 weeks, a good intra- and inter-observer agreement was achieved when grading cortical development with this simple scoring system. Asymmetrical cortical development was seen in a third of fetuses between 24 and 28 gestational weeks (unpublished data). This scoring system now needs to be evaluated prospectively to determine whether it is useful to detect fetuses with malformations of cortical development.

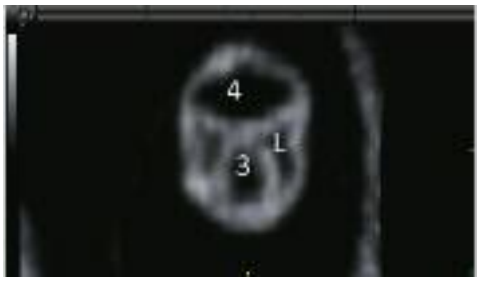
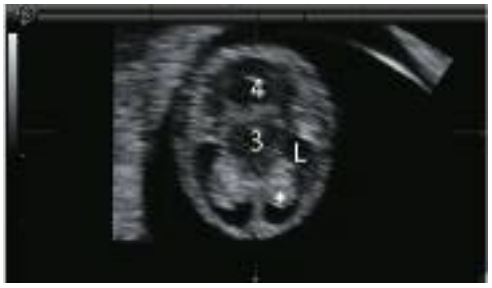
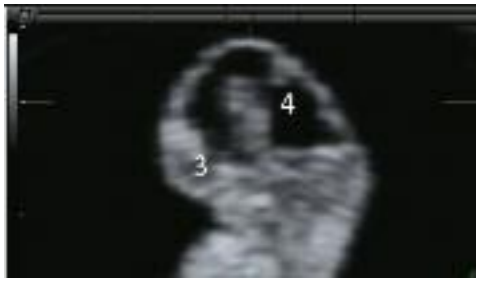
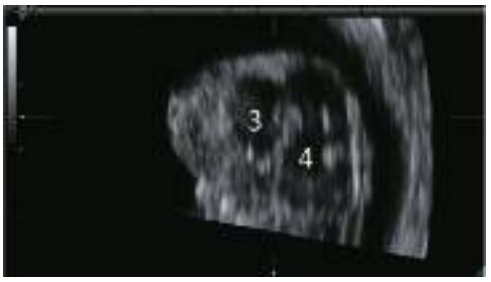
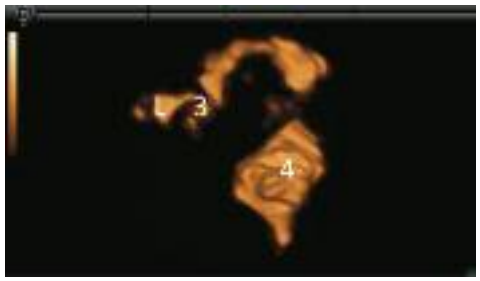
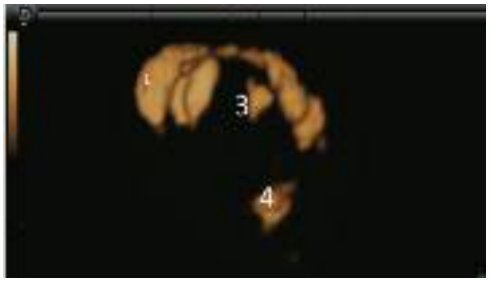
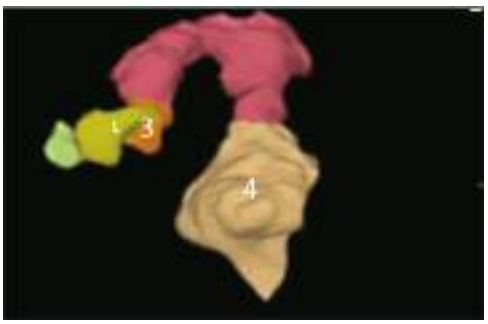
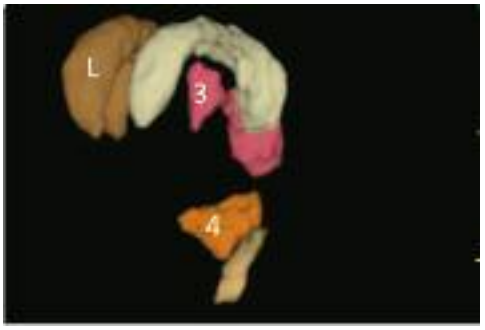
Cerebellar volume

Asymmetry of the fetal cerebellar volume was also found in our longitudinal study of cerebellar volume measured with antenatal US (Rutten *et al.*, 2009), especially before 32 weeks, when the left cerebellar volume can be up to 54% greater than the right and the right cerebellar volume can be up to 6% greater than the left. Both multiplanar and VOCAL™ techniques had a good intra- and inter-observer variability, and yielded similar results when calculating the cerebellar volume. As is the case with the cortical scoring system, it remains to be evaluated whether measurement of the cerebellar volume, rather than a one-dimensional measurement such as the transverse cerebellar diameter, is more sensitive and specific to detect syndromic (McCann *et al.*, 2005) or acquired (Johnsen *et al.*, 2005) cerebellar abnormalities.

Pathology

Spina bifida

To determine whether the parameters visible on prenatal imaging could predict future prognosis, we followed up infants who were antenatally diagnosed with spina bifida until demise or five years of age. Multivariate regression analysis in this group of 41 infants showed that a higher lesion level and head circumference at or above the 90th percentile were independent predictors of demise. None of the US

	Crown rump length 22 mm 8w3d	Crown rump length 28 mm 9w3d
Axial view		
Sagittal view		
Inverse mode rendering		
AVC rendering		

L = lateral ventricle; 3 = third ventricle; 4 = fourth ventricle; * = choroid plexus (note appearance at 9 postmenstrual weeks).

Fig. 1. — Embryonic brain ventricles

features were associated with motor or mental functioning at five years of age. The accuracy of the prenatal US prediction of the anatomical lesion level within one level of the postnatal findings was 50% performed between 1997 and 2002, and 89% between 2006 and 2007 ($p < 0.01$). This improvement in the accuracy of US is offset by a difference between the functional level of neurological deficit and the anatomical lesion level which still limits the ability of US to predict motor function (Vossen *et al.*, 2009).

Hydrocephalus and middle cerebral artery Doppler US

Doppler indices of cerebral blood flow are used postnatally to diagnose raised intracranial pressure in infants with hydrocephalus (Hanlo *et al.*, 1995).

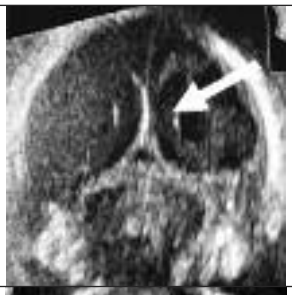
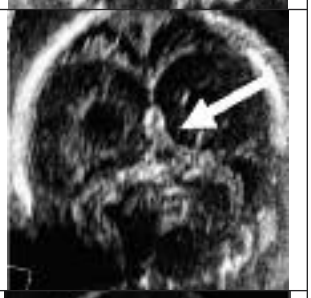
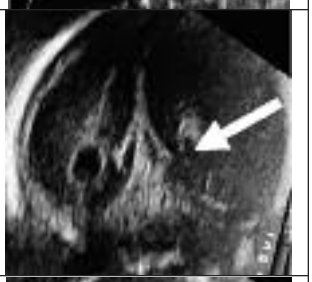
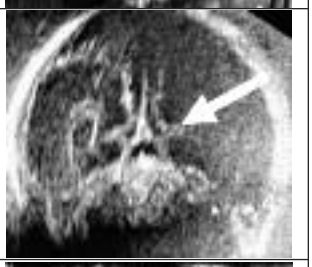
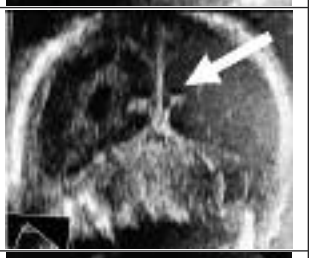
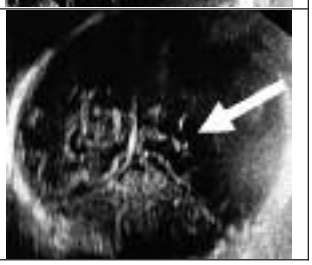
Grade and description of sulcus	Image
0. None visible	
1. Shallow indentation or echogenic dot	
2. Broad V-shape	
3. Narrow V-shape	
4. I- or J-shaped	
5. Branched	

Fig. 2. — Cortical grading (calcarine sulcus used as example)

This raises the question whether measuring middle cerebral artery (Fong *et al.*, 2004) flow is of prognostic value in a fetus with ventriculomegaly, and we investigated the relationship between the mca pulsatility index (PI) and outcome in a retrospective study. A rise in mca PI was seen in four out of 29 fetuses with ventriculomegaly. Two of these four fetuses suffered a perinatal death, and the other two

had subsequent severe neurodevelopmental abnormalities (unpublished observations). An abnormal mca PI therefore seems too insensitive to serve as a useful parameter to aid the timing of delivery in fetuses with ventriculomegaly.

Parvovirus B19 and malformations of cortical migration

It is well known that prenatal infection with Parvovirus B19 can lead to fetal anemia due to a transient aplastic crisis (Anderson *et al.*, 1985). If severe and untreated, this could in turn lead to the development of hydrops and fetal demise. Until recently, it was assumed that successful treatment with intrauterine transfusion was associated with normal neurodevelopmental outcome (Dembinski *et al.*, 2002). We described a case of a fetus that developed malformations of cortical development after requiring intra-uterine transfusion for a severe Parvovirus B19 infection. Antenatal MRI demonstrated mild unilateral ventriculomegaly. Polymicrogyria and heterotopia were confirmed on postnatal MRI (Pistorius *et al.*, 2008). Recent literature also reports mild to severe neurodevelopmental delay in five out of sixteen Parvovirus B19 hydrops survivors (Nagel *et al.*, 2007).

Comparison between US and MRI

Although there are many articles comparing the diagnostic capabilities of prenatal US and MRI, many are hampered by an obvious bias by comparing a diagnosis made in primary care on US with a tertiary diagnosis by MRI, with only few trying to compare like with like (Malinger *et al.*, 2004; Nagel *et al.*, 2007; Levine *et al.*, 2003). It is also difficult to distinguish between the effect of MRI and that of a multidisciplinary discussion (Malinger *et al.*, 2002). This is important, as a multidisciplinary discussion has been shown to be important in improving the accuracy of diagnosis of fetal central nervous system abnormalities (Hagmann *et al.*, 2008).

A previous study in our unit demonstrated additional value of MRI in the diagnosis of fetal (CNS) abnormalities where US examination yielded uncertain or limited results (Gerards *et al.*, 2001). We therefore decided to analyze our subsequent results to compare the accuracy of US, MRI and the additional value of a multidisciplinary discussion with the postnatal diagnosis in a retrospective cohort of patients where an MRI of the fetal central nervous system was performed between 2000 and 2008. We also compared the accuracy of standard US examinations with that of neurosonograms, and found that the diagnosis made during the multidisciplinary discussion was accurate in 62% before and 73% of patients after MRI. The diagnosis remained unchanged in 23 out of 28 patients. The accuracy of the diagnosis improved in four patients and decreased in one patient after MRI. Standard US examinations were accurate in 42% of patients, and neurosonograms in 63% of patients. The highest accuracy of prenatal diagnosis of fetal CNS lesions (78%) was obtained with a multidisciplinary discussion after neurosonography and MRI (unpublished observations). No improvement in accuracy after MRI was seen in patients with neural tube lesions, and the biggest improvement was seen in patients with an US diagnosis of ventriculomegaly.

A review of the available literature on US and MRI imaging of the fetal CNS indicated that MRI does occasionally provide additional information which is not available on detailed neurosonography.

US imaging of the fetal central nervous system seems preferable for screening or repeated examinations, examinations before 20 weeks of gestation, fetal movement assessment in the first and second trimester, evaluation of cerebral blood flow, evaluation of associated (extracranial) abnormalities and where MRI is contra-indicated or has failed.

MRI seems preferable in cases of a difficult US, the assessment of posterior fossa abnormalities, schizencephaly, acute fetal asphyxia or severe microcephaly, for evaluating fetal movements in the late third trimester, detecting and determining the age of intracranial bleeding, detecting intracranial tuberous sclerosis and for postmortem brain imaging.

A synergistic effect between US and MRI can be expected in fetuses suspected of cerebellar telangiectasis, cytomegaloviral infection, intracranial tumors or trauma, vein of Galen abnormalities, germinal matrix and intraventricular bleeding, hemimegalencephaly and septo-optic dysplasia.

In the second half of pregnancy, either modality could be used to diagnose suspected holoprosencephaly, abnormalities of the corpus callosum, ventriculomegaly or craniosynostosis.

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