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Fetal brain monitoring: Future applications

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Summary Future application of fetal brain monitoring is explored by selecting and analysing articles for information on types of brain damage that can be monitored, where in the brain this can be done, how long after the risk exposure, and with what method of investigation.

A limited number of—mainly—case histories reported that early (cell death and oedema) and late (gliosis) effects of brain damage can be demonstrated before birth with multiplanar ultrasound and magnetic resonance imaging, and that hypoxic ischaemic injury or infection can induce local or widespread brain injury, occurring as transient or longer-lasting changes in age-related predilection areas for which normal features are known.

The antenatal role of risk factors inducing abnormal brain development can be studied longitudinally with ultrasound and magnetic resonance imaging. A multidisciplinary approach will facilitate the introduction of various techniques with adequate know-how of underlying processes, to evaluate the predictive value on neurological outcome and prevent premature introduction into clinical application.

Introduction

Which applications should be used for optimal fetal brain monitoring is a question that cannot be easily answered, as this greatly depends on the purpose of the monitoring. The majority of fetuses have a low risk for developing brain damage and can be monitored with short-term and quick evaluative procedures. The minority of high-risk fetuses needs investigation with methods adequate for assessing possible injury. For example, there is growing evidence that adverse neurological outcome (e.g. cerebral palsy) is only rarely associated with birth asphyxia, and that there may be more important causative factors in the prenatal period. Squier and Keeling[1] found that postmortems of stillborn brains showed prenatal circulatory disorders in 44%. Though increasing technical possibilities for investigating the fetal brain should inform us as to whether certain risks induce damage, many questions related to monitoring arise, relating to the kind of damage that can be monitored, how long after exposure to the risk this should occur, which predilection areas of the brain should be monitored, whether damage is permanent or transient, whether it is with or without influence on the neurological outcome, and whether it is detectable with what method of investigation. Multidisciplinary observational studies are necessary to clarify all of these clinically urgent questions for each prenatal risk identified.

This overview presents a selection of articles describing (1) the developmental aspects of acquired brain anomalies (including risk factors and interval exposure-imaging of the

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damage, age-related predilection areas, and transient or permanent damage), and (2) techniques and age-related normal development of the brain structures. Within the scope of current available literature, advice for fetal brain monitoring is given.

Developmental aspects of acquired brain anomalies

Risk factors and interval exposure-imaging of the damage

The commonest ways of acquiring brain injury are either hypoxia (usually chronic or acute) in any form of uteroplacental insufficiency (e.g. fetal growth restriction, anaemia, injury) or infection (viral and bacterial). The neuropathological processes underlying development of brain injury and methods of brain imaging have already been described in detail.[2–4] In short, hypoxic ischaemic injury (HII) causes individual cells to die, limit damage, or produce scar tissue. The speed and intensity of these cellular responses vary with gestational age, and are responsible for the final patterns of the damage.

Within one week, the first reactions caused by neural cell death can be seen by ultrasound (US) plus T2-weighted sequence magnetic resonance imaging (MRI). Two forms of cell death—necrosis and apoptosis—are described. *Necrosis* is passive cell death leading to cell swelling and the release of its contents, provoking a local inflammatory response. *Apoptosis* is triggered by intracellular enzyme-mediated events leading to cell shrinkage. Promising techniques are diffuse-weighted imaging and diffusion tensor imaging visualizing changes in tissue water content and cytoarchitecture within hours.

After one week, the results are caused by the supporting cells of the neurons. Various cells supporting the neuronal cells arrive in the damaged area during the first week and start tissue repair, not by replacement but by gliosis:

- microglia arrive in the injured area in 2–3 days, remove the dead cells and transport them via the blood vessels, leading to cysts after 8–10 days (US + T2-weighted sequence MRI);
- endothelial cells increase in size and thickness within 2–3 days after the injury and form new vessels in this area by 5–7 days (US + T2 weighted sequence MRI).

Later findings are the result of the following.

- Astrocytes: glial cells which increase in size and number, make fibrillary processes, and replace damaged areas (MRI visualization until many years after the injury).
- Oligodendroglia: glial cells which are hindered in their age-related development of myelin sheets around axons (T2-weighted sequence MRI).
- Deposition of minerals in areas of damage: remnants of nerve cells, axons, and neurons can persist for years (T2-weighted sequence MRI). Localized depositions are found around areas of focal infarcts of affected deep nuclei in case of HII. In viral infections, calcium mineral deposition is widespread throughout the brain or forms a dense periventricular band (US + T1-weighted sequence MRI). Cytoplasm of microglia show depositions of iron as microglia phagocytosed red cells in areas of haemorrhage (histology).
- Reductions of nerve cells result in thinning of brain areas, e.g. corpus callosum (US + T1-weighted sequence MRI or three-dimensional US + MRI).

Age-related predilection areas

HII is considered the reason for the findings of periventricular white matter echodensities in two reports on fetuses exposed to uteroplacental insufficiency in the second and third trimesters.[5,6] It has been demonstrated that the localization of the HII damage is age-dependent and widespread in neonates[2]:

- before 28 weeks: cerebral cortex (laminal necrosis, polygyria), porencephaly, basal ganglia, brainstem;
- between 24 and 36 weeks: periventricular leukomalacia (PVL), intraventricular haemorrhage, parenchymal haemorrhagic infarction;
- after 36 weeks: cerebral cortex, ulegyria (necrosis of depths of sulci sparing gyral crests), basal ganglia;
- at any age: brainstem necrosis, arterial infarction, schizencephaly, hydrancephaly.

Intracranial haemorrhages—mostly intraventricular and in two cases subdural—of varying grade are presented in a report on 33 fetuses.[7] In the neonate they are most frequently intraventricular, originating from germinal matrix, choroid plexus, or cerebral parenchyma, and intraparenchymal from periventricular white matter, thalamus, or arteriovenous malformation.

Toxoplasmosis in the fetal brain has been described as inducing unilateral or bilateral dilatation of lateral ventricles, intracranial calcification, hyperechogenic areas within the white matter, and late and severe microcephaly.[8] Cytomegalovirus (CMV) has been shown to produce a variety of abnormalities in the fetal brain in the second and third trimesters.[9] In findings on eight fetuses, periventricular echodensities were seen in all, and intraparenchymal foci and calcifications were seen in five. Other signs of infection were: intraventricular adhesions (3), periventricular pseudocysts (3), sulcation and gyral abnormal patterns (3), hypoplastic corpus callosum (2), vermis hypoplasia (2), cerebellar calcifications (1), enlarged cisterna magna (4), and signs of striatal artery vasculopathy (1). In one case MRI confirmed the presence of ventriculomegaly, but not the echogenic intraparenchymal foci observed on the sonogram. In the other fetus, MRI added information by demonstrating abnormal signal intensity of periventricular white matter in the occipital and frontal regions. Guibaud et al.[10] emphasized that CMV in the fetus can present encephalitis with focal hyperechogenicities in periventricular areas, mild ventriculomegaly and calcifications without other cerebral, cerebellar or cephalic biometric abnormality. The added value of MRI was compared to US and computed tomography (CT) in 11 neonates aged 34–41 weeks.[11] US showed periventricular calcifications and/or lenticulostriate vasculopathy associated with mild

to moderate ventricular dilatation ($n = 10$). Periventricular (pseudo)cysts were seen in six children: occipital ($n = 4$), temporal ($n = 3$) and fronto-parietal ($n = 1$). The cerebellum appeared to be small in four children. Calcification was better seen using US than MRI. MRI was performed in eight children and provided additional information in six: polymicrogyria in the perisylvian region ($n = 4$), hippocampal dysplasia ($n = 3$), and cerebellar hypoplasia ($n = 4$). Abnormal signal intensity in white matter was seen in four infants. Four died in the neonatal period, four of the seven survivors developed severe adverse neurological outcomes, and five developed deafness.

Trauma during pregnancy has been reported in up to 3% of the pregnancies.[12] It is well recognized that low-velocity car accidents can cause brain damage even if the mother is not significantly injured. Two cases illustrate the risks. One case of fetal death at 30 weeks gestational age occurred due to fetal subdural and subarachnoidal haemorrhages without evidence of placental abruption in a mother with only minor seatbelt and facial injuries as a result of the incident.[13] Another relatively minor accident with subsequent deployment of the airbag sticking in the mother's abdomen resulted in generalized bruising of the abdominal wall and mild contractions in the mother, and intracranial and extracranial haemorrhage as well as traumatic injuries (fractures of parietal skull and clavicles) in the 29-week-old fetus.[12]

Immune thrombocytopenia is a known risk factor for intracranial haemorrhage. This, however, has not been systematically examined despite the prevalence of neonatal intracranial haemorrhage in 10–30% of mothers with alloimmune thrombocytopenia and 1% with autoimmune thrombocytopenia.[14]

Anaemia as a risk factor for brain damage has been studied in two risk groups. Infants from twin-to-twin transfusion syndrome (TTTS) treated with selective fetoscopic laser coagulation had an incidence of cystic PVL of 6%, and 52% were free of neurological complications at 6 months.[15] The same investigators demonstrated that the prevalence of cystic PVL was higher after treatment with serial amnioreduction (14%), and with this treatment fewer infants (31%) were free of neurological complications. Daily monitoring of viable monochorionic fetuses with TTTS is performed via cardiotocography. However, in cases of co-twin death, direct termination of pregnancy can still be too late to prevent brain damage in the survivor.[16] In the described case, the fetus was delivered by caesarean section within 30 min of co-twin death and still developed convulsions 6 h later and ischaemic encephalopathy in occipital and parietal lobes on MRI at 29 weeks. Another case reporting co-twin death at 15 weeks and MRI at 23 weeks revealed polymicrogyria in left frontal and parietal lobes.[17] Hydropic fetuses due to anaemia by red-blood-cell alloimmunization (seven fetuses with mean gestational age of 22 ± 2.5 weeks) underwent multiplanar brain sonography.[18] Abnormalities were found in four: two intracerebellar haemorrhages after the first transfusion, one severe brain oedema before transfusion which later developed cystic PVL, and one unilateral ventriculomegaly after the first transfusion which disappeared. Postmortem neuropathological examination of children with hydrops fetalis revealed cerebral abnormalities originating from the intrauterine period: microcalcifications, cerebral and/or cerebellar hypoplasia, microcephaly, encephalomalacia, cavitary lesions, astrocytosis, polymicrogyria, and severe neuronal loss.[19]

Transient changes or permanent damage

Transient changes in brain imaging without consequences for neurological outcome

Four examples are presented of transient echogenicities in the brain. One demonstrates in fetuses from low-risk pregnancies the presence of mild periventricular echodensities with a density equal to that of the choroid plexus at 26–28 weeks' gestation lasting for a few weeks, without consequences for the neurological outcome. Analogously to data after birth (sonographic, MRI, postmortem), the echodensities were explained by migrating germinal matrix cells and, as such, as a physiological phenomenon.[20] In a second group of fetuses exposed to uteroplacental insufficiency, five out of 26 had unilateral density in the thalamus that disappeared after birth.[5] This was explained as a normal finding caused by reflection of the thalamocaudate notch or by a transient phenomenon of unknown origin. Two of these fetuses, however, developed PVL after birth with neurological abnormalities. Another had grade-II bleeding (rupture of germinal matrix bleeding into ventricle without dilatation) before birth which disappeared after birth with a normal outcome. A third study demonstrated that, after birth, a positive predictive value of serial US brain imaging for cerebral palsy was 48% in preterms $\leq$32 weeks ($n = 1636$) and 83% in preterms 33–36 weeks ($n = 503$). The presence of severe sonographic anomalies in the young preterms without neurological consequences could be explained by brain plasticity.[21] A fourth study reports the prevalence of echogenic vasculature in the basal ganglia of newborns (75/3700), seldom (except in one case of CMV) related to infection.[22] Plasticity of the young neonatal brain is also reported in a case through diffusion-weighted imaging (DWI) and functional MRI. DWI demonstrated a left hemispheric lesion 4 days after term birth. Functional MRI showed absence of visual-stimulated cortical activity at 3 months and recovery at 20 months.[23]

Persistent changes with consequences for neurological outcome

Four studies illustrate continuity in sonographic data and neurological outcome. The first examined periventricular densities in 26 fetuses exposed to uteroplacental insufficiency before and after birth, with neurological follow-up until 24 months.[5] Grade-1A periventricular echodensities (white matter as bright or almost as bright as the choroid plexus) was seen in four fetuses. These densities were also seen within 24 h after birth. All four developed long-lasting grade-1B periventricular echodensities (white matter brighter than the choroid plexus). Neurologically, two developed normally, one had minor abnormalities (clumsiness and fussy behaviour) and one mild tetraplegia. Intraventricular haemorrhage grade II was seen before birth in two of 26 infants. In one case the abnormality persisted and the ventrical system dilated; however, the infant was lost to neurological follow-up. The other had no intraventricular densities after birth and had normal neurological development at 2 years. The second study presented

antenatal periventricular echodensities in 42 out of 63 high-risk pregnancies which persisted after birth in 23.[6] Four developed cystic periventricular leukomalacia and later various grades of cerebral palsy. The third study examining 176 cases of fetal cerebral ventriculomegaly illustrates the importance of following an anomaly over time, including prior to birth, and its effect on neurological development.[24] Examination of the 106 live-born fetuses showed that a normal neurological outcome was found more often when ventriculomegaly improved before birth (92%) than when it remained unchanged (35%) or worsened (21%). The fourth study depicts with US intracranial haemorrhages in 33 fetuses. The eight neonates with adverse neurological outcome had the two most severe forms of intraventricular bleeding (grade III and IV, bleeding from germinal matrix with extension more than 50% into the lateral ventricle and extension into parenchyma respectively).[7]

Techniques and age-related normal development of brain structure

Comparing the two brain-imaging techniques, US and MRI, there are similarities and differences.

Similarities between US and MRI

- Both allow whole-brain examination.[4,25]
- Normal values of various brain structures are available for both (Table 1).
- It is possible to obtain axial, coronal, and sagittal planes; anomalies should be examined in two directions to distinguish between abnormality and artefacts.[4,5]
- Both can achieve three-dimensional imaging.
- The diagnostic possibilities are same in fetuses with suspected brain anomalies.[26]
- Both techniques are considered safe.[27,28]

Differences between US and MRI

- US is a bedside technique and equipment availability allows for repeated examination and for follow-up of abnormalities. MRI equipment has limited availability, and with the technical support needed for organizing the proper coils, sequences, and maternal position, it is much more costly.
- US has a long history of safety, MRI a much shorter one, necessitating further study.[28]
- Exposure to MRI (e.g. acoustic noise) does not seem to affect the fetus, as examined with cardiotocography and movement score, since no alteration in the short-term heart-rate variability or movements was found.[29]
- Technically, the coronal and sagittal planes obtained by US and MRI are not identical. The US coronal and sagittal planes radiate from the fontanel and the MRI planes are parallel. These US planes can be obtained most easily transvaginally through the fontanel. Also this procedure can be performed even in the case of preterm premature rupture of the membranes, since the incidence of maternal infection does not increase.[30] Be this as it may, gynaecologists remain reluctant to apply this procedure.
- US benefits from fetal movements. During real-time scanning, adjustments can be made to find optimal planes. This is in contrast to MRI where sedation is sometimes needed to suppress fetal motility, especially in cases of long exposure times (e.g. in three-dimensional imaging or spectroscopy; see below).
- US can distinguish calcium deposition better than MRI, while MRI is better at examining other aspects as mentioned earlier (e.g. deposition of other minerals, myelinization).
- A classification system for PVL and bleeding, which applies equally before and after birth, has been used for US,[5] whereas the systems differ for MRI. One scoring system for MRI evaluation after birth, covering eight aspects through the brain, looks attractive.[31] There is a small difference in the US classification since before birth the persistence of an anomaly over time is not included. This is described separately when more US examinations are possible before birth.
- MRI allows for the use of other techniques such as functional MRI, volumetry, and MR spectroscopy. Functional MRI has demonstrated in low-risk fetuses that visual and auditory evoked responses can be elicited

Table 1 Fetal brain structures are presented with references for age-related data per axial, coronal or sagittal planes by ultrasound (US) (transabdominally or transvaginally) and magnetic resonance imaging (MRI)

	US	Transvaginal,	Transabdominal	MRI
Ventricles				
Lateral	Sagittal[44]	x		Axial
Lateral + choroid plexus	Coronal: axial[45]		x	
Third	Axial[46]		x	Axial
Fourth	Axial[46]		x	Sagittal[46]
Periventricular area	Coronal, sagittal[20]	x		Coronal, sagittal[31]
Corpus callosum	Sagittal[47]	x		Sagittal[46]
Subarachnoidal space	Coronal[48]	x		Coronal[46]
Vermis cerebelli	Sagittal[49]	x		Sagittal[46]
	Coronal 3-D[50]		x	
Cerebellum	Coronal[49]		x	Coronal[46]
Gyration	Coronal, sagittal[51]	x		Coronal, sagittal, axial[52]

as early as 28 weeks onwards until term by means of magnetoencephalography (MEG).[32] Volumetric three-dimensional MRI demonstrated quantitative changes in children examined at term age but born preterm: cerebral cortical grey matter, deep nuclear grey matter and cerebellum were reduced while cerebrospinal fluid increased,[33,34] MR spectroscopy can assess metabolite contents and as such expands the diagnostic possibilities of early detection of HII lesions. The distribution of the metabolites in the fetal brain have been described in a low-risk population between 30 and 41 weeks gestational age.[35] However, in cases of normal oxygen metabolism, the lactate level in the brain and cerebrospinal fluid is low and cannot be identified, or only in small amounts. Ischaemia stops oxidative phosphorylation, and lactate accumulates. Thus it can be considered as an early sign of HII, but it may persist for over a period of 6 months. Two reports on increased lactate levels were analysed. In one high-risk population for uteroplacental insufficiency, six out of 20 fetuses had abnormal spectral images, of which five had increased lactate values in areas suspected for HII.[36] In another high-risk population of six hydropic fetuses (aging 29—30 weeks), two fetuses had increased lactate levels in the basal ganglia.[37]

Postmortem brain investigations can differentiate between recent and old brain damage

The systematic approach of the Scottish perinatal neuropathology study facilitated careful postmortem examination of the brain in 137 early neonatal deaths. Twenty representative blocks were prepared from the cerebrum of each fetus. To evaluate possible gliosis, the study examined astrocyte hyperplasia, activated microglia, accumulated macrophages, haemorrhage (recent and older), vascular responses, foci of mineralization, and infarction. The study revealed that brain injury predates the onset of labour in a large proportion of neonatal deaths (27/70 in infants born after 24 weeks gestational age who died within 7 days after birth) and even more in asphyxiated infants (26/53) than non-asphyxiated infants (1/17).[38] In cases where postmortem brain examination cannot be performed, postmortem MRI can be performed as an adjunct with a high sensitivity to detect macroscopic abnormalities.[39]

Conclusion

HII is not only a risk factor for developing brain damage in preterm neonates. Today, one to three of every 1000 infants born alive at term experience HII with neurological consequences.[40] The growing awareness of a prenatal onset of neonatal brain damage, even in stillborn babies,[38] is the stimulus for further investigation of fetal brain-monitoring.

The knowledge of timing of the risk factor in relation to the moment of visualization via US or MRI is primarily derived from studies on neonates. No data are available about the time interval between viral exposure and brain damage for CMV, but the adverse effects on the ventricular lining suggest this as an early sign and reduction of brain structures such as cerebrum, cerebellum, vermis, corpus callosum, and calcium deposition as late signs. Understanding neuropathology before birth is of great importance, since we have to take into consideration that fetuses exposed to HII or infection may react differently from neonates. Their brain plasticity can be the difference, either for better or for worse. In high-risk fetuses, transient changes in brain imaging have already been demonstrated.[5,19] Therefore, prevalence of brain anomalies and neurological outcome should be examined prospectively and serially at regular intervals.

Comparison of fetal and neonatal data shows that the few studies on fetal brain damage report localized as well as widespread damage similar to that in the neonate. However, studies on neonates are based on large populations and reveal more extensively spread anomalies requiring study of an increased number of fetuses. The question then arises as to what technique should be used to perform a longitudinal study on a population of fetuses at high risk for damage. Two studies have demonstrated that multiplanar US is equivalent to MRI,[9,26] and that both techniques have additional value. Multiplanar US can reveal widespread early effects (cell death, oedema) and later effects (cavities, reduction of brain tissue, ventriculomegaly) of brain damage. Moreover it shows calcification deposition better than MRI. MRI reveals the same early and late aspects of damage and also late gliosis effects (e.g. deposition of other minerals, disturbance in myelinization). MRI can also visualize metabolic changes in affected areas and elicited functions. Other differences and similarities between US and MRI have been described. The strength in future studies will lie in using both techniques for their unique properties: multiplanar US as a quick bedside technique performed weekly in fetuses at risk for brain damage, and MRI to more extensively evaluate certain aspects once before and after birth.

Future studies should focus on longitudinal examination of fetuses at high risk for brain damage with adequate neurological follow-up to at least 2 years of age and organized in close collaboration with various disciplines. The ideal situation is a team of obstetricians, paediatricians, neonatologists, child neurologists, radiologists, pathologists, and geneticists. Using US and MRI together will facilitate gaining understanding of the prevalence and development of early and late effects on fetal brain structures as well as distinguishing between acquired anomalies and underlying disorders. First and most practical applications of the investigations are changes in obstetrical care based upon knowledge of neurological outcomes, as was the case after the published trial on TTTS demonstrating a lower incidence of PVL after selective fetoscopic laser coagulation than serial amnioreductions.[15]

A promising area for study is fetal brain metabolism to inform where brain damage is. After this, a next step would be limiting damage before birth, for example by influencing the area in the brain where apoptosis occurs. This reaction to damage is energy-dependent. Therefore the exact localization of the affected area may attribute to direct local therapy, by reducing the energy only there.

For related reviews see Kostović and Milošević [41] Lowery et al.[42] and Seghier et al.[43]

Practice points

- Diagnosis in fetuses at risk for brain damage lacks objective measures.
- Serial brain imaging of axial, coronal, and sagittal planes with US elucidates the dynamics of the affected areas, and single MRIs before and/or after birth will provide more detail on certain effects of glioses.
- Age-related normal values of various fetal brain structures (by US and MRI) are available for comparison in fetuses at risk for brain damage.

Research directions

- Antenatal role of risk factors inducing abnormal brain development and adverse neurological outcome.
- Multidisciplinary set-up of a longitudinal study of fetuses exposed to a risk for brain damage.
- The role of various techniques of surveillance in brain structure and function in relation to regular care.

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