The Combined Use of 2D/3D Ultrasound and Fetal MRI for a Comprehensive Fetal Assessment in Congenital Cardiac Disease

1. Background

Congenital heart defects (CHDs) are the most common congenital anomaly with a birth prevalence of approximately 5–10/1000 live births, and the leading cause of infant death.\textsuperscript{1,2} Approximately 25% of infants with CHDs will have serious defects requiring surgery within their first year.\textsuperscript{3} Most cardiac lesions are isolated and at present, approximately 50–60% of cases are detected antenatally through those local and national screening programmes which incorporate routine anomaly screening.\textsuperscript{4–7} There is an association with other anomalies, including karyotypic and genetic abnormalities, which accounts for approximately 15% of all cases of CHD.\textsuperscript{1}

The definition of CHD varies significantly. Mitchell et al.\textsuperscript{8} define CHD as ‘a gross structural abnormality of the heart or intrathoracic great vessels that is actually or possibly of functional significance’. This definition includes a significant group of clinically relevant defects, which have been the focus of surgical advancement in recent decades, and is therefore subject to rapidly changing outcomes that require further reporting.\textsuperscript{4} In accordance with this definition, abnormalities of the systemic veins, systemic artery branches, valvular abnormalities, cardiomyopathy and congenital arrhythmias are excluded,\textsuperscript{3} and the CHD abnormalities defined by Mitchell et al. are the predominant focus of this paper.

In only 15–30% of all cases of CHD is a cause identified, in the remainder the cause is unknown.\textsuperscript{1,9} Chromosomal aneuploidy is a well recognised cause accounting for approximately 10% of all cases of CHD, with a number of definitive examples. For example, the prevalence of CHD in Down syndrome is approximately 45%.\textsuperscript{1} Other chromosomal aneuploidies include trisomy 13 and 18, Turner syndrome and DiGeorge syndrome.\textsuperscript{10} Single gene defects account for a further 3–5% of cases of CHD, including Alagille syndrome, Holt–Oram syndrome and Noonan syndrome.\textsuperscript{11–13} Nonchromosomal or genetic causes include some well recognised associations, such as maternal diabetes, phenylketonuria, maternal obesity, rubella infection, alcohol use and drug exposure (e.g. retinoic acid, thalidomide and organic solvents).\textsuperscript{1,4,15} In the remaining cases of CHD the aetiology appears multifactorial, with a suggestion of interaction between genetic and environmental factors. Although the evidence base is limited, the recurrence risks observed in families with CHD suggest a multifactorial interactive model.\textsuperscript{1} The recurrence risk of nonsyndromic CHD in a family with one affected sibling is approximately 1–6% increasing to 3–10% in cases of two affected siblings.\textsuperscript{1,6–9} The risk to the offspring of inheriting CHD from an affected parent is higher at approximately 4%, and two- to three-fold higher in cases of maternal CHD compared with paternal CHD.\textsuperscript{1,10} Nutritional factors have also been implicated; in a meta-analysis\textsuperscript{10} on the effect of prenatal folic acid–fortified multivitamin supplementation and the risk of congenital anomalies, there was an observed reduction in the risk of CHD.

Recent decades have seen a significant advancement in cardiothoracic surgery and cardiac care. The focus on immediate surgical morbidity and mortality is now being re-evaluated. In the 2016 National Congenital Heart Disease Audit of UK centres,\textsuperscript{21} the 30-day survival rates associated with surgical interventions were over 97.5%, depending on the complexity of the cardiac lesion. The survival rate in the first year of life is approximately 85%.\textsuperscript{2,22} Of these infants, more than 90% will be alive at the age of 16 years. Data from a national registry in the Netherlands\textsuperscript{24} have reported the mean age of 34 years in patients with CHD and 85% of patients registered are below the age of 45 years.\textsuperscript{1} In some cardiac lesions, there has been a reported 50–70% decrease in mortality in the past two decades.\textsuperscript{25}
The improvement in survival has been coupled with an increase in the prevalence of neurological deficit in this group, which mainly includes patients with transposition of the great arteries (TGA) and hypoplastic left heart (HLH). There are now robust data that the prevalence of these deficits can be up to 50%, highlighting the need to focus on neurodevelopmental deficits as primary outcomes in patients with CHD. A list of potential causative and contributory factors has been proposed. Many CHD patients require corrective or palliative surgery in the neonatal period, and the use of cardiopulmonary bypass, deep hypothermic circulatory arrest, and various surgical and postoperative factors have all been implicated in contributing to adverse neurodevelopmental outcomes. Other genetic factors, for example expression of neuroprotective apolipoprotein E, may help to modulate brain injury following surgery in certain patients. Socio-economic and parental factors will also influence later intellectual development.

Increasingly, however, preoperative and prenatal brain dysgenesis, immaturity and white matter injury are being recognised in patients with CHDs. There is substantial clinical evidence of neurological developmental deficits prior to surgery in these infants, with this association more established in some cardiac defects, such as HLH. There is a higher prevalence of microcephaly in infants with HLH and the effect of surgery on further neurological deficit in this group is unclear. In addition to global delay, localised neurological deficits have been observed in all domains. Evidence from the neuroimaging literature demonstrates that more than half of newborns with CHD (in high risk groups of HLH and TGA) have evidence of brain injury, which include ischaemic lesions, white matter injury and periventricular leukomalacia. Furthermore, studies incorporating magnetic resonance imaging (MRI), magnetic resonance spectroscopy and diffusion tensor imaging (DTI) on fetuses have revealed abnormalities of brain microstructure and metabolism before delivery, as well as soon after birth and before surgery. The origin of these changes is almost certainly multifactorial, with congenital brain abnormalities, intraterine haemodynamic alterations and acquired brain injury all implicated. With continuing advancement in prenatal screening and diagnosis incorporating modalities, such as 3D and 4D ultrasound reconstruction, MRI and fetal genotyping, including array comparative genomic hybridisation, there is now an opportunity to improve fetal characterisation, with a particular focus on neurological development, to inform counselling, perinatal management and neonatal care and surgery.

2. Fetal assessment and antenatal diagnosis

2.1 Ultrasound including 3D

The challenge for all those involved in prenatal diagnosis, namely the fetal medicine and fetal cardiology specialists, and the multidisciplinary team, which can be comprised of clinical geneticists, paediatric neurologists and neuroradiologists, is to obtain an accurate diagnosis that allows women to make informed decisions about their pregnancy. Assessment of the fetal central nervous system (CNS) is complex; a good understanding of developmental anatomy and an appreciation of the spectrum of the postnatal course is necessary for a given diagnosis. Indeed, it is noteworthy that approximately 20% of CNS-related anomalies lead to late termination of pregnancy due to late and progressive abnormalities in CNS development.

The mainstay of fetal screening and assessment is transabdominal scanning (TAS), which permits routine views of the fetal intracranial anatomy (in both the transthalamic and transcerebellar planes) enabling the detection of anomalies such as ventriculomegaly, severe cerebellar hypoplasia, holoprosencephaly and the Arnold-Chiari malformation. Indeed, from approximately 18 weeks of gestation, fetal cortical development as assessed by ultrasound correlates closely with that obtained by MRI. Furthermore, advances in ultrasound technologies has led to improved visualisation of the
fetal cerebral architecture; for example, with colour Doppler flow imaging and higher frequency probes.40–42

In 2000, Carroll et al.43 documented the difficulties in establishing a correct diagnosis of posterior fossa anomalies; this has been confirmed in later studies.44,45 Crucially, improved detection rates and accuracy of diagnosis have been achieved by the use of transvaginal scanning (TVS) and 3D assessment.46–48 The advent of 3D and 4D ultrasound has also led to the acquisition of volumetric datasets for off-line assessment; this has been particularly useful for assessment of gyria and sulcal formation from 20 weeks of gestation.49

Fetal MRI is often used as an adjunct to search for associated anomalies that may have remained undetected by ultrasound scan, including foci of infarction, and cerebellar and cortical abnormalities.50,51 Furthermore, newer MRI technologies, including DTI tractography and connectomics, may aid in diagnosis and prognosis.52,53 However, it is important to note that MRI is not the gold standard and that each modality has its own merits; in one small series,54 ultrasound was found to be superior to MRI in 3/26 cases.

Ventriculomegaly is an example of an ultrasound diagnosis that may have many aetiologies, including acquired injury, and hence, the rate of associated malformation ranges from 10% to 76%.55 While the ultrasound diagnosis of ventriculomegaly is straightforward, the accurate inclusion and exclusion of additional intracranial anomalies is more challenging. Numerous studies from the early-2000s indicated that additional information is found in up to 44% of cases of mild ventriculomegaly using MRI.56,57 However, other data have shown that by using just conventional high-frequency 2D ultrasound scanning (either TAS or TVS), the amount of additional information drops to 5–17%.58,59 Presumably, with the advancement of other modalities (colour Doppler imaging, 3D and 4D, etc.) this may improve further. The main additional abnormality missed by ultrasound is agenesis of the corpus callosum.60 Other diagnoses, such as intraventricular haemorrhage and subependymal heterotopia, often secondary to in utero ischaemic injury, are best made by MRI.61 The exclusion of additional anomalies using MRI can also provide reassurance.

Proliferation disorders may be secondary to environmental insult.62 The initial concern is often revisited later in gestation by the presence of microcephaly (head circumference more than three SD below the mean).62,63 The necessary assessment for gyral anomalies is best performed by MRI. In 2013, the first in utero use of the combined modalities of ultrasound scanning and MRI, the so-called MRI ultrasound fusion, was reported.64 This proof of concept demonstrated the potential of the technique to enable real-time ultrasound scanning views to be superimposed on MRI images.

2.2 Fetal MRI assessment in CHDs

Brain imaging has a major role in the detection of injury or aberrations in development and follow-up studies of such patients are necessary to determine the clinical significances of the findings. In a meta-analysis27 of 13 studies (n = 425 cases) reporting on brain abnormalities either preoperatively or in those who did not undergo congenital cardiac surgery, and nine studies (n = 512 cases) reporting preoperative data on neurodevelopmental assessment, the prevalence of brain lesions on neuroimaging was 34% (95% CI 24–46; I² = 0%) in TGA, 49% (95% CI 25–72; I² = 65%) in left-sided heart lesions and 46% (95% CI 40–52; I² = 18.1%) in mixed/unspecified cardiac lesions, while the prevalence of neurodevelopmental delay was 42% (95% CI 34–51; I² = 68.9%). In many instances, brain abnormalities will be detected on postnatal imaging performed either prior to, or post, surgical procedures. MRI is now an established, safe imaging technique to assess the fetus, providing complimentary information to ultrasound. In a fetus with a confirmed or suspected congenital cardiac defect, MRI may be used to assist in the detection of additional fetal anomalies, with the usual
emphasis being on the brain. Conventional MRI techniques may identify overt brain anomalies, not previously detected on ultrasound, suggesting or increasing the likelihood of a specific underlying diagnosis. MRI has an improved capability over ultrasound to detect previously undetected agenesis of the corpus callosum, cerebellar defects, cortical abnormalities, such as polymicrogyria, and migration abnormalities, such as subependymal heterotopia. Ultrasound guidelines suggest reserving MRI examination to those fetuses where there is a suspicion of abnormality on ultrasound. The ability of MRI to detect abnormalities not seen on ultrasound in this group of patients is as yet unknown, although evidence for other cohorts suggests that significant abnormalities may be detected.

The majority of fetal MRI is still being acquired at 1.5 T, but several units are using 3 T for research and clinical practice. Fetal MRI is usually acquired without resorting to maternal sedation, but maternal contraindications including claustrophobia and size may be presented. New wide-bore magnets with a diameter of 70 cm may be better tolerated by these women and metallic implants as for any MRI examination. Image acquisition is by single-shot techniques, minimising the effects of fetal and, to a lesser extent, maternal, motion on image quality. The image acquisition may take from 20–60 minutes depending on the number of sequences used and the availability of motion correction techniques. Without the latter, in a very mobile fetus sequence acquisitions may have to be repeated several times to acquire interpretable scans. T2-weighted images are the mainstay sequence providing excellent contrast between brain structures. T1-weighted techniques are useful for confirming the presence of haemorrhage, but are more challenging to obtain at sufficient quality. In a clinical setting diffusion-weighted imaging can be used to identify areas of acute ischaemia. More sophisticated techniques, such as volumetry and segmentation to assess cortical development, DTI to assess tissue microstructure and brain connectivity, MRI spectroscopy to assess cerebral metabolites, and phase contrast and T2 mapping techniques to assess fetal cerebral blood flow and oxygen extraction, remain in the research environment. Larger, long-term studies are needed to appreciate the importance of obtaining antenatal information about deviations in brain development with respect to counselling, delivery management and longer term neurodevelopmental outcomes.

3. Opinion

Cardiac disease remains the most prevalent congenital fetal anomaly. Improvements in antenatal screening have led to an increase in prenatal diagnosis, which is recognised to be associated with improved neonatal outcomes. Furthermore, advances in neonatal, infant and paediatric surgical interventions have contributed to the decline in mortality associated with CHDs. The longer term follow-up of these patients has recognised the neurological morbidity associated with CHDs. At present, the focus of antenatal and perinatal counselling has been centred on the risk of mortality and cardiovascular morbidity associated with specific cardiac anomalies. However, antenatal diagnosis using ultrasound and fetal MRI, alongside improvements in technologies and image acquisition, provide the opportunity to improve characterisation of the associated neurological morbidity antenatally. This has the potential of informing clinicians of the risk of neurological morbidity in relation to the perinatal period and surgical interventions, ultimately leading to improved counselling to expectant parents in the antenatal period.

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