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Introduction

The mid-pregnancy screening examination using ultrasonography (USS) is offered to all women in the UK and is taken up by more than 95%.[1] If a structural abnormality of the fetus is recognized, the woman is offered a more detailed 'anomaly scan' performed by a senior doctor with specialist training in ante-natal USS. Structural abnormalities may be picked up for the first time later in pregnancy if a woman has another USS examination because of, for example, reduced fetal movements or poor growth. The fetal brain is a common location for such problems and there is a wide range of potential abnormalities which vary massively in terms of post-natal clinical significance. A woman may consider termination of pregnancy if the fetus has severe abnormalities and in such cases the woman needs to be provided with the best quality information possible in order to make an informed decision. The diagnostic accuracy of USS is approximately70% as reported in several publications[2-8] and confirmed by a recent large prospective study.[9] That study (MERIDIAN) was designed to assess the improvement in diagnostic accuracy brought about by adding in utero MR (iuMR) to the diagnostic pathway and it demonstrated a statistically significant improvement from under 70% to over 92%. Similar levels of improvement has also be shown in systematic reviews and meta-analyses[10-13] providing compelling evidence to support the use of iuMR imaging if a fetal brain abnormality is shown or suspected on USS.

Radiologists performing iuMR imaging in the UK are beginning to recognise use of iuMR imaging of the brain in situations not covered by the scope of the MERIDIAN study suggesting a 'technology creep' and this is also our experience. Specifically, iuMR is being increasingly offered to pregnant women when the fetal brain is normal on USS but the pregnancy is judged to be at 'increased risk' of a brain abnormality. There are several clinical scenarios that may lead to that position, which we outline in this paper and discuss the existing literature that either supports or contradicts

the use of iuMR imaging in that situation. We will also outline the future research required to guide clinical management in these pregnancies.

Why a fetus may be classified as at increased risk of a brain abnormality

a) Problems concerning a sibling from an earlier pregnancy.

Increased risk may be based on a brain abnormality in an earlier pregnancy and may have been recognised either on imaging during the pregnancy or on post-natal imaging. If the brain abnormality is thought to be developmental in origin a clinical geneticist may be asked to quantify the recurrence risk in future pregnancies. This can be done with some accuracy if a specific genetic abnormality is known or strongly suspected (e.g. in many cases of lissencephaly), alternatively if a specific genetic abnormality is not found (e.g. most cases of agenesis of the corpus callosum) the risk will be based on empirical observation from the published literature. We are aware of only one publication (from our group) that specifically looked at the discrepancy between USS and iuMR results in this caseload.[14] 100 non-selected cases were described and brain or spine abnormalities were shown in 22% of fetuses of which 9% were shown only on iuMR imaging. In addition to developmental brain abnormalities, there are an increasing number of acquired brain lesions found in children on post-natal studies that are due to inheritable/genetic disorders (e.g. many metabolic disorders) which have an increased risk of recurrence in future pregnancies.

Agenesis of the corpus callosum

It is difficult to be certain about the prevalence of agenesis of the corpus callosum in the general population but most estimates are in the range of 0.3% to 0.7%, although it is seen in 2% to 3% of people with a developmental disability.[15] As more MR imaging examinations are performed on normal people as part of research studies it will be possible to refine the prevalence estimates of agenesis of the corpus callosum. We have performed many MR studies on adult volunteers from the

staff of our local hospital and university, including 900 brain examinations. Those adults did not know which part of their body they would have scanned before volunteering (which reduces self-selection bias) and we have not seen any cases of agenesis of the corpus callosum in the 900 studies (unpublished but see reference[16]). Using the 3/n rule,[17] the estimated prevalence of agenesis of the corpus callosum in the general population has an upper 95% confidence interval of 0.33%. Most cases of agenesis (and dysgenesis) of the corpus callosum are sporadic but it can be part of conditions that inherit with autosomal dominant (e.g. Rubenstein-Taybi syndrome), autosomal recessive (e.g. Andermann syndrome) or X-linked (e.g. Aicardi syndrome) patterns.[15] If other definable genetic abnormalities can be excluded the recurrence rate in siblings is thought to be approximately 5% .[18] Our empirical experience shows that although the recurrence rate of isolated agenesis of the corpus callosum is low, pregnant women with this family history usually ask for iuMR imaging in a subsequent pregnancy. This is often supported by the fetal maternal consultant because of the emerging problems of detection with USS and the high association with other brain abnormalities.[9,19]

Cortical formation abnormalities

The term 'cortical formation abnormality' covers a wide range of pathologies that result from failure of neuronal/glial proliferation, migration and/or organisation of the cerebral cortex .[20] Classic (type 1) lissencephaly is characterised by under-migration of neurons and mutations of LIS1 or DCX genes account for 77% of such cases (65% and 12% respectively).[21,22] The inheritance pattern is autosomal dominant for LIS1 (chromosome 17) and X-linked for (DCX) but the majority of cases are de novo mutations. In a small number of cases there may be an identifiable parental genetic defect, for example, if a woman with a mild phenotype carries a defective copy of the DCX gene the recurrence risk may be as high as 50%. Alternatively, when one parent has a balanced translocation involving the LIS1 gene the recurrence risk for isolated lissencephaly sequence is thought to be

10 to 15%. “Cobblestone” or type 2 lissencephaly results from over-migration of neurons past the basement membrane and is common in Walker-Warburg syndrome, Muscle Eye Brain disease and Fukuyama muscular dystrophy.[20] The recurrence risk for cobblestone lissencephaly is 25% (autosomal recessive inheritance), as is the cases of lissencephaly with cerebellar hypoplasia.

A recent report from our group studied the use of iuMR in pregnancies at increased risk of lissencephaly based on a previously affected sibling[23] and highlights a number of difficulties of studying such abnormalities in the fetus, the first relating to the scarcity of the disorder. The 23 fetuses reported in that study took 8 years to recruit despite a wide geographical coverage and in only three cases did the lissencephaly recur. Secondly, when can lissencephaly be diagnosed reliably? All three of the fetuses with lissencephaly were successfully recognised on iuMR with varying degrees of certainty but four other fetuses were considered to be ‘possible lissencephaly’ on the 22-24 week iuMR studies based on mild sulcation delay. The follow up studies performed at 28 weeks in those four cases were normal and were considered to be normal after birth, which indicates a tendency to report false positives in the late second trimester. We should expect similar pre-natal diagnostic problems on iuMR for other cortical formation abnormalities such as polymicrogyria, which is being increasingly recognised as inheritable, particularly if it is bilateral and symmetrical.[21-24] It may be difficult to diagnose polymicrogyria even if anatomically extensive and focal polymicrogyria or focal cortical dysplasia is likely to be exceptionally challenging or impossible. The ability to confirm (figure 1) or exclude (figure 2) cortical formation abnormalities confidently is equally important to the families.

Metabolic disorders

We have discussed the problems of diagnosing some developmental brain abnormalities antenatally with iuMR because of lack of conspicuity at some stages of pregnancy and the purpose of

this section is to add further caution if attempting to diagnose brain abnormalities in a fetus at risk of an inherited metabolic disorder. Di Mauro and Garone[25] describe the wide range of inheritable metabolic disorders concentrating on glycogenosis and mitochondrial defects in the fetus and their general observations are highly pertinent to ante-natal detection. Mendelian and maternally inherited disease must be present in the fetus but it does not mean that the fetus is 'clinically' affected. Many of these metabolic disorders do not produce brain injury until infancy, childhood or even adulthood and there are a number of reasons why the individual may not be affected in utero. For example, a genetic defect may produce a mutated mature enzyme which has a fetal counterpart that is not involved. In some situations, the mother is able to metabolise an abnormal gene product, or the build-up of a toxic intermediate compound made by the fetus. Defects of the mitochondrial respiratory chain are amongst the most important inheritable metabolic disorders in terms of brain involvement and impaired oxidative metabolism in the child or adult metabolically active areas. In contrast, fetal tissues rely more on anaerobic glycolysis for ATP production rather than oxidative mechanisms, hence providing a measure of protection.[26] A normal iuMR study in these situations should not be used to exclude a metabolic disorder in a fetus although there are sometimes non-specific finding on iuMR that may be useful (figure 3).

b) Abnormalities of the current fetus that increase the risk of a brain abnormality.

Other findings in the current pregnancy may indicate increased risk of brain abnormality in the fetus such as the association between spine and brain malformations. Alternatively, there may be serological findings that indicate a maternal infection has passed to the fetus (e.g. the 'TORCH' infections) or chromosomal/genetic abnormalities have been recognised that may raise concern for brain involvement. The intra-uterine environment can also adversely affect the fetal brain, particularly in multi-fetal pregnancies.

Structural abnormalities outside the brain associated with increased risk of brain abnormalities

The association between 'open' spinal dysraphism (myelomeningocoele or myelocoele) and brain malformations and if that type of spinal problem is shown on ante-natal USS there is an approximately 90% chance that a Chiari 2 malformation will be present as well. Conversely, finding a Chiari 2 malformation on USS instigates close scrutiny of the fetal spine because the vast majority of Chiari 2 malformations are found in conjunction with open spinal dysraphism. There is no consistent association between closed spinal dysraphism (skin covered abnormalities) and brain malformations but careful assessment of the brain in such cases is still warranted on USS. There is a paucity of research data about the value of iuMR imaging in the assessment of fetuses with spinal abnormalities demonstrated on USS. Our group reported the results of 50 such fetuses and showed disagreements between USS and iuMR imaging in 10/50 (20%) but all of those were in the description of the spinal abnormalities, not in intra-cranial findings.[27] Similarly, there were 21 fetuses with Chiari 2 malformations in the MERIDIAN study and again extra brain abnormalities were not seen on iuMR imaging in any fetus.[28] In spite of this low diagnostic return iuMR imaging is frequently requested in a fetus with a spinal abnormality on USS and in such cases we always image the fetal brain as well as the spine.

One area of interest in the recent obstetric literature is the association between congenital heart disease (CHD) and fetal brain abnormalities. CHD occurs in 6-8/1000 live births[29] and is a common cause of childhood morbidity. A recent systematic review found pre-natal detection of structural brain abnormalities in fetuses with CHD gave a prevalence of 28% (95% CI, 18-40%) but those figures are based on three publications from only 221 cases.[30] Some of the reported brain abnormalities were obvious focal abnormalities, both developmental and acquired, but the most frequently reported 'brain' abnormality in the systematic review was ventriculomegaly (found in 8.6% of fetuses with CHD in total). It is open to debate if ventriculomegaly should be considered as a 'devel-

opmental' or 'acquired' abnormality or indeed as an anatomical variant in some cases. Other included brain abnormalities were more non-specific such as reduced brain growth and maturation, MR spectroscopic changes consistent with metabolic 'stress' or reduced blood flow to the brain on Doppler USS. Much more detailed, prospective research is required in order to define the association rate of CHD with developmental brain malformations (figure 4) and acquired brain pathology and to explore the possible significance of those findings vis-à-vis the known CDH.

Cytomegalovirus as an example of a trans-placental infection that may affect the fetal brain

The acronym 'TORCH' is often used to describe the commonest infective agents that cause transplacental infection (TOxoplasmosis, Rubella, Cytomegalovirus (CMV) and Herpes), although an increasing number of other viruses have been implicated. CMV infection is numerically the most important in the UK but fetal infection although HIV and, more recently, Zika virus present major challenges on the global scale. Leruez-Ville and Ville[31] state that the birth prevalence of congenital CMV infection in European countries with low maternal seroprevalence is around 0.4% and there is a roughly equal ratio of primary CMV infections during pregnancy and reactivation of a previous maternal CMV infection.[32,33] CMV specific symptoms are found in 12.7% of new-borns with congenital CMV and approximately half of those will have permanent sequelae, many of which are brain-related. Unfortunately 13.5% of infected but asymptomatic new born babies will develop permanent problems relating to CMV infection.[34] Transplacental infection of the fetus with CMV can lead to spontaneous abortion/stillbirth or result in termination of pregnancy if recognised. If the infection is acquired in the early second trimester CMV seems to have a predilection for the cells in the germinal matrix (ventricular zone), which interferes with normal neuro-glial proliferation, migration and/or organisation of the cerebral cortex. A recent article[35] has tried to explain the range of imaging findings in relation to the timing of the infection e.g. second trimester infections at the time of neuronal/glia proliferation and may produce microcephaly and/or micrencephaly, whereas agyr-

ia/lissencephaly is more likely to result from a failure of migration and polymicrogyria results from abnormal cortical organisation (figure 5). Fetuses infected in the third trimester tend to have white matter injury with calcifications.

The diagnosis of maternal CMV infection during pregnancy can be difficult. The most convincing data comes from documented seroconversion in pregnancy by showing increased specific IgG but this is rarely feasible because screening and prospective monitoring is not performed.[31] In most cases in which a fetal infection with CMV is confirmed ante-natally there was a reason to look for it and this often comes from USS imaging. Leruez-Ville and Ville describe USS findings that may provide clues to CMV infection under the headings of 'severe USS brain abnormalities' 'mild USS brain abnormalities' and 'extra-cerebral USS abnormalities'.[31] Most of those are non-specific and in our experience the referral information for USS usually involves some combination of 'microcephaly', 'ventriculomegaly', 'enlarged extra-axial spaces' or 'germinal cysts' (figure 6). The literature comparing USS and iuMR findings in congenital CMV infection is sparse. Picone et al.[36] studied 38 fetuses (24-37 weeks gestational age) with proven congenital CMV infection and retrospectively assessed the value of iuMR imaging over USS. They concluded that iuMR should be performed in any situation that the USS examination is not completely normal and the major value was in cases in which USS had recognised extra-cerebral manifestations of the infection but reported a normal brain. Doneda and colleagues[37] also studied 38 fetuses with confirmed CMV infection, iuMR being performed at 24-30 weeks gestational age. They reported added diagnostic value for iuMR in 18/38 (47%) cases and an increase in sensitivity for pathology from 38% for USS to 92% for iuMR imaging. The sensitivity of general USS in ante-natal care should be considered as low as 35%[38] whilst the addition of iuMR is thought to produce negative predictive values close to 90%.[36,39]

Brain injury in the co-twin survivor after fetal demise in monochorionic pregnancies

Multiple pregnancies are generally a high risk group for both mother and fetus. This has increasing importance as the rate of multiple pregnancies increase with the widespread use of assisted conception methods. Twins occur in about 1 in 60 pregnancies and one factor for increased risk is chorionicity.[40] Monochorionic twins make up approximately 30% of all twin pregnancies and have a single placenta with shared vascular anastomotic channels between the two fetuses. In the event of demise of one twin, the surviving co-twin is at increased risk of injury because of adverse effects on perfusion or thromboembolism arising in the dead fetus or placenta. There is a 15% risk of death of the co-twin in a monochorionic pregnancy and the risk of abnormal neurological development in survivors is 26%.[41] Death of one twin in a monochorionic twin pregnancy can occur spontaneously or after an intervention such as laser ablation of placental vessels for twin-twin transfusion syndrome (TTTS). TTTS complicates 8 to10% of twin pregnancies and is responsible for approximately half of all perinatal deaths in monochorionic twins.[42] Again, the relative rarity of this clinical situation makes properly powered, prospective studies about possible benefits of iuMR imaging over USS exceptionally difficult, if not impossible without multi-centred, international trials. Our previous work in the field showed brain abnormalities in 9/68 (13.2%) of co-twin survivors after demise of one twin in monochorionic pregnancies and three of those abnormalities were shown correctly on USS.[43] Examples are shown in figures 7 and 8. The small number of other publications in this area support the use of iuMR imaging after single fetus demise in monochorionic twin pregnancies or suggest the value of larger studies to confirm the perceived benefits of iuMR.[44,45]

Microcephaly

Microcephaly (small skull size) is frequently found in fetuses with developmental and acquired brain pathology including many of the conditions described in previous sections. Here we will discuss some of the issues that arise if microcephaly is the only abnormal finding on USS or if there are only non-specific abnormalities such as enlarged CSF spaces or germinolytic cysts. Assessment

of the skull size on USS is made by measuring biparietal diameter, occipito-frontal diameter and/or head circumference and compared with normative charts. This is done routinely because a small head size in a fetus is considered to be an independent risk for poor neurodevelopmental outcome.[46-48] Important issues for research that can be answered by performing iuMR imaging alongside USS include:

a) What is the accuracy of skull measurements on USS? The MERIDIAN study did not recruit fetuses with microcephaly only but when it was found in conjunction with another brain abnormality there was the opportunity to compare the head sizes made on USS with those on iuMR imaging. Thirty fetuses were referred with a diagnosis of microcephaly and the diagnosis was refuted on iuMR in 8/30 (false positives on USS - 27%) of cases. In addition, a further 13 fetuses had microcephaly diagnosed on iuMR that was not recognised on USS (false negative rate on USS 13/35 =37%). This data indicates a substantial problem in correctly identifying microcephaly on USS.

b) What degree of microcephaly warrants further investigation by iuMR imaging? There is little agreement in the literature about what measurement constitutes microcephaly, some authorities using $<10^{th}$ centile and others $<3^{rd}$ centile and there is little scientific justification for either position. A prospective, formally powered study that recruits fetuses with varying degrees of small head size diagnosed on USS followed by iuMR imaging will be able to measure the proportion of cases iuMR had diagnostic and clinical impact. By this means it will be possible to set a level of microcephaly which will benefit from iuMR imaging.

c) A more fundamental issue is the mismatch between head size and brain size. It is a common feature of many of our iuMR studies that microcephaly was overlooked on USS but equally important are the cases where the <u>head</u> size is not a cause for concern on either USS or iuMR but the <u>brain</u> size is disproportionately small on iuMR imaging (micrencephaly). This

is coming into sharp focus now it is possible to make accurate and reproducible measurements of fetal brain volume (figures 1 and 5 and reference[49]).

Conclusions

USS will remain the mainstay of the national programme for fetal screening and anomaly scanning, however, we are beginning to learn more about its limitations and that iuMR improves diagnostic accuracy at a clinically significant level. Most comparative studies have concentrated on fetuses with brain abnormalities visible on USS but we believe it is appropriate to perform research studies on fetuses that are at increased risk of a brain abnormality but USS finding are either normal or non-specific. Heightened parental and clinician anxiety is to be expected in these pregnancies and we have spoken of 'technology creep' based on the unproven assumption that iuMR imaging will provide more information and certainty but it is important for the clinical research community to provide the evidence for or against this expensive resource.

References

1. Ward P, Soothill P. Review Fetal anomaly ultrasound scanning: the development of a national programme for England. The Obstetrician and Gynaecologist. 2011;13:(4). Last accessed 11/01/2017 at: http://onlinelibrary.wiley.com/doi/10.1576/toag.13.4.211.27685/pdf
2. Antonsson P, Sundberg A, Kublickas M, et al. Correlation between ultrasound and autopsy findings after 2nd trimester terminations of pregnancy. J Perinat Med 2008;36:59–69.
3. Carroll SG, Porter H, Abdel-Fattah S, Kyle PM, Soothill PW. Correlation of prenatal ultrasound diagnosis and pathologic findings in fetal brain abnormalities. Ultrasound Obstet Gynecol 2000;16:149–53.
4. Akgun H, Basbug M, Ozgun MT, et al. Correlation between prenatal ultrasound and fetal autopsy findings in fetal anomalies terminated in the second trimester. Prenat Diagn 2007;27:457–62.
5. Amini H, Antonsson P, Papadogiannakis N, et al. Comparison of ultrasound and autopsy findings in pregnancies terminated due to fetal anomalies. Acta Obstet Gynecol Scand 2006;85:1208–16.
6. Fadda GM, Capobianco G, Balata A, et al. Routine second trimester ultrasound screening for prenatal detection of fetal malformations in Sassari University Hospital, Italy: 23 years of experience in 42,256 pregnancies. Eur J Obstet Gynecol Reprod Biol 2009;144:110–14.
7. Grandjean H, Larroque D, Levi S. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus Study. Am J Obstet Gynecol 1999;181:446–54.
8. Richmond S, Atkins J. A population-based study of the prenatal diagnosis of congenital malformation over 16 years. BJOG 2005;112:1349–57.
9. Griffiths PD, Bradburn,M, Campbell MJ, et al. Use of MRI in the diagnosis of fetal brain abnormalities in utero (MERIDIAN): a multicentre, prospective cohort study. The Lancet 2017;389:538-46.

10. Mundy L, Hiller J, Braunack-Mayer A, Merlin T. MRI for the detection of foetal abnormalities. Adelaide: Adelaide Health Technology Assessment (AHTA). 2007.
11. Rossi AC, and Prefumo F. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system anomalies: a systematic review of the literature. Ultrasound Obstet Gynecol 2014;44:388–93.
12. Van Doorn M, Oude Rengerink K, Newsum EA, Reneman L, Majoie CB, Pajkrt E. Added value of fetal MRI in foetuses with suspected brain abnormalities on neurosonography: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2015;23:1–13.
13. Jarvis D, Mooney C, Cohen J, et al. A Systematic Review and Meta-Analysis to Determine the Contribution of MR Imaging to the Diagnosis of Fetal Brain Abnormalities in utero. Eur Radiol. 2016;27(6)2367-80.
14. Griffiths PD, Porteous M, Mason G, et al. The use of in utero MRI to supplement ultrasound in the foetus at high risk of developmental brain or spine abnormality. Br J Radiol. 2012;85(1019):1038–45.
15. Chen H. Atlas of genetic diagnosis and counselling. Humana press, Totowa, NJ, 2006.
16. Hoggard N, G Darwent, D Capener, Wilkinson ID, Griffiths PD. The high incidence and bioethics of abnormal findings on MR brain imaging of normal volunteers for neuroscience research. Journal of Medical Ethics 2009;35:194-199.
17. Jovanovic BD, Levy PS. A Look at the Rule of Three. The American Statistician 1997;51(2):137-39.
18. Young ID, Trounce JQ, Levene MI, Fitzsimmons JS, Moore JR. Agenesis of the corpus callosum and macrocephaly in siblings. Clin Genet. 1985;28(3):225-30.
19. Griffiths PD, Brackley K, Bradburn M, et al. Anatomical subgroup analysis of the MERIDIAN cohort: Failed commissuration. Ultrasound Obstet Gynecol 2017; DOI: 10.1002/uog.17502. [Epub ahead of print]

20. Barkovich AJ, Raybaud C. Congenital malformations of the brain and skull (Chapter 5). In: Pediatric Neuroimaging (fifth edition).Lippincott Williams & Wilkins, Philadelphia 2012.
21. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R and Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology 2005; 65(12):1873-87.
22. Guerrini R, Dobyns WB and Barkovich AJ. Abnormal development of the human cerebral cortex: genetics, functional consequences and treatment options. Trends Neurosci 2008; 31(3):154-62.
23. Williams F, Griffiths PD. In utero MR imaging in foetuses at high risk of lissencephaly. British Journal of Radiology 2017:20160902. doi: 10.1259/bjr.20160902.
24. Dobyns WB, Mirzaa G, Christian SL et al. Consistent chromosomal abnormalities identify novel polymicrigyria loci in 1p36.3, 2p16.1, p23.1, 4q21.21-q22.1, 6q26-q27 and 21q2. Am J Med Genet 2008;146A:1637-54.
25. DiMauro S, Garone C. Metabolic disorders of fetal life: Glycogenoses and mitochondrial defects of the mitochondrial respiratory chain. Sem Fetal Neonatal Med 2011;16:181-89.
26. Papa S. Mitochondrial oxidative phosphorylation changes in the life span. Molecular aspects and physiopathological implications. Biochem Biophys Acta 1996;1276:87-105
27. Griffiths PD, Widjaja E, Paley MNJ, Whitby EH. Imaging the fetal spine using in utero MR: Diagnostic accuracy and impact on management. Pediatric Radiology 2006 36(9):927-933.
28. Griffiths PD, Brackley K, Bradburn M, et al. Anatomical subgroup analysis of the MERID-IAN cohort: Posterior fossa abnormalities. Ultrasound Obstet Gynecol. 2017. doi: 10.1002/uog.17485. [Epub ahead of print]
29. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39:1890–1900.

30. Khalil A, Bennet S, Thilaganathan B, Paladini D, Griffiths P, Carvalho JS. Prevalence of prenatal brain abnormalities in fetuses with congenital heart disease: a systematic review. Ultrasound Obstet Gynecol. 2016;48(3):296-307.
31. Leruez-Ville M, Ville Y. Fetal cytomegalovirus infection. Best Practice & Research Clinical Obstetrics and Gynaecology 2017;38:97-107
32. Foulon I, Naessens A, Foulon W, et al. 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. J Pediatr 2008;153(1):84-88.
33. de Vries JJC, van Zwet EW, Dekker FW, et al. The apparent paradox of maternal seropositivity as a risk factor for congenital cytomegalovirus infection: a population-based prediction model. Rev Med Virol 2013;23(4):241-49.
34. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol 2007;17(5):355-63.
35. Fink KR, Thapa, MM, Ishak, GE, Pruthi S. Neuroimaging of Pediatric Central Nervous-System Cytomegalovirus Infection. RadioGraphics 2010;30:1779–96
36. Picone O1, Simon I, Benachi A, Brunelle F, Sonigo P. Comparison between ultrasound and magnetic resonance imaging in assessment of fetal cytomegalovirus infection. Prenat Diagn. 2008;28(8):753-8.
37. Doneda C, Parazzini C, Righini A, et al. Early Cerebral Lesions in Cytomegalovirus Infection: Prenatal MR Imaging. Radiology 2010;255(2):613-621.
38. Guerra B, Simonazzi G, Puccetti C, et al. Ultrasound prediction of symptomatic congenital cytomegalovirus infection. Am J Obstet Gynecol 2008;198(4):380.e1-7.
39. Benoist G, Salomon LJ, Mohlo M, Suarez B, Jacquemard F, Ville Y. Cytomegalovirus-related fetal brain lesions: comparison between targeted ultrasound examination and magnetic resonance imaging. Ultrasound Obstet Gynecol 2008;32:900–05.

40. Visintin C, Mugglestone MA, James D, et al. Guideline Development Group. Antenatal care for twin and triplet pregnancies: summary of NICE guidance. Br Med J 2011;343:d5714.
41. Hillman SC, Morris RK, Kilby MD. Co-twin prognosis after single fetal death: a systematic review and meta-analysis. Obstet Gynecol 2011;118(4):928–40.
42. Fieni S, Gramellini D, Piantelli G, et al. Twin–twin transfusion syndrome: a review of treatment option. Acta Biomed 2004;75 (Suppl. 1):34–9.
43. Griffiths PD, Sharrack S, Williams F, Kilby M. The risk of brain injury acquired in utero in survivors of twin pregnancies complicated by the demise of one fetus. Prenatal Diagnosis 2015;35(6):583-591.
44. Simonazzi G, Segata M, Ghi T, et al. Accurate neurosonographic prediction of brain injury in the surviving fetus after the death of a monochorionic cotwin. Ultrasound Obstet Gynecol 2006;27:517–21.
45. Glenn OA, Norton ME, Goldstein RB, et al. Prenatal diagnosis of polymicrogyria by fetal magnetic resonance imaging in monochorionic cotwin death. J Ultrasound Med 2005;24:711.
46. Gilmore EC, Walsh CA. Genetic causes of microcephaly and lessons for neuronal develop-ment. Wiley Interdisciplinary Reviews: Developmental Biology. 2013;2(4):461-78.
47. Deloison B, Chalouhi GE, Bernard JP, Ville Y, Salomon LJ. Outcomes of fetuses with small head circumference on second-trimester ultrasonography. Prenat diagn. 2012;32(9):869-74.
48. Stoler-Poria S, Lev D, Schweiger A, Lerman-Sagie T, Malinger G. Developmental outcome of isolated fetal microcephaly. Ultrasound Obstet Gynecol 2010; 36(2):154-58.
49. Jarvis D, Akram R, Paddock M, Mandefield L, Armitage P, Griffiths PD. Quantification of total fetal brain volume using 3D MR imaging data acquired in utero. Prenat Diagn. 2016;36(13):1225-1232.

Figure legends.

Figure 1. A case in which recurrence of a brain malformation was confirmed on iuMR imaging. The older sibling of the current fetus had a post-natal MR diagnosis of agenesis of the corpus callosum (1a) and a cortical formation abnormality (lissencephaly with a posterior hemispheric predilection - b). In utero MR imaging was performed at 33 weeks' gestation in the next pregnancy and agenesis of the corpus callosum was confirmed (1c) along with a bilateral, symmetrical cortical formation abnormality (1c and 1d), most likely to be lissencephaly although polymicrogyria could not be excluded on the basis of the imaging alone. The total brain volume was reduced in comparison with the published reference range as described in the text (1e and reference[49]).

Figure 2. A case in which recurrence of a brain malformation was excluded on iuMR imaging. The older sibling of the current fetus had a diagnosis of bilateral perisylvian polymicrogyria made on post-natal MR imaging (2a-2c). USS imaging in the next pregnancy showed mild ventriculomegaly and iuMR was performed at 24 weeks, which confirmed mild ventriculomegaly but showed no evidence of polymicrogyria (2d-2f). A repeat iuMR study at 31 weeks' gestational age showed resolution of the ventriculomegaly and cortical sulcation/gyration that was appropriate for gestational age.

Figure 3. A case in which recurrence of a metabolic disease was strongly suspected on iuMR imaging in spite of relatively non-specific findings. Mild ventriculomegaly was detected on ante-natal USS in a fetus at 20 weeks gestational age and the only history of note was an early neonatal death in the previous pregnancy. iuMR imaging was performed at 21 weeks gestation and axial ssFSE T2-weighted (3a) and FLAIR (3b) images confirm mild ventriculomegaly (trigones 11 and 12mm) and show bilateral cysts in the germinal matrix close to the frontal horns. Cytomegalovirus infection was looked for and excluded and a repeat iuMR at 30 weeks (3c axial and 3d sagittal ssFSE) showed progressive ventriculomegaly (trigones 12 and 13 mm) and more extensive germinolytic

cysts. Pyruvate carboxylase deficiency was confirmed post-natally and similar appearances were shown in the next pregnancy (3e and 3f) with the same outcome.

Figure 4. A case with associated cardiac and brain malformations confirmed on iuMR imaging. Double outlet right ventricle with transposition of the great vessels and VSD had been diagnosed on USS and iuMR imaging of a fetal brain was performed at 33 weeks. Hypogenesis of the cerebellar vermis was demonstrated on the sagittal (4a) and coronal (4b) iuMR images. Bilateral cleft lip/palate was demonstrated (4c) and had also been diagnosed on USS.

Figure 5. Post-natal MR imaging of a child with microcephaly, severe epilepsy and global developmental delay (6a-6d). There is an extensive bilateral cortical formation abnormality consisting of polymicrogyria and bilateral schizencephaly. A subsequent diagnosis of congenital infection by cytomegalovirus was made.

Figure 6. A case in which congenital CMV infection was made on iuMR imaging, with subsequent serological/histological confirmation. A fetus referred for iuMR imaging at 31 weeks gestation because of ventriculomegaly on USS. The iuMR imaging (5a-5c) confirmed ventriculomegaly but also showed microcephaly, ventricular stranding and extensive bilateral polymicrogyria. The cortical formation abnormality is well shown on the model of the left lateral surface created from 3D volume data (5d) in comparison with an aged matched normal (5e). The brain volume was substantially reduced (5f).[49]

Figure 7. Three cases of demise of a fetus in monochorionic pregnancies. 7a and 7b is a case of spontaneous twin demise at 20 weeks and the iuMR study performed at 23 weeks. The demised twin is on the right in both images. The surviving co-twin is micrencephaly from generalised en-

cephalomalacia. 7c and 7d show the surviving co-twin after spontaneous twin demise at 17weeks and the iuMR study performed at 26 weeks. There is micrencephaly and bilateral brain injury involving the territory supplied by middle cerebral artery on both sides. 7e and 7f are images of the surviving co-twin in a monochorionic pregnancy complicated by twin-twin transfusion syndrome. Laser ablation of the placental vessels was performed at 18 weeks and one twin died shortly afterwards. The surviving co-twin had iuMR imaging at 25 weeks which evidence of a unilateral stroke with haemosiderin staining indicating previous haemorrhage.

Figure 8. Post-natal imaging (12 weeks) of a co-twin survivor of a monochorionic pregnancy complicated by twin-twin transfusion syndrome. There is loss of volume and abnormal cortex at the posterior part of the right sylvian fissure (8a and arrowed on 8b). 8c and 8d are non-orthogonal reformations of the sylvian fissures from T1 volume data showing the normal sylvian fissure on the left (8c) and the abnormal posterior extension of the sylvian fissure on the right lined by abnormal cortex (arrowed 8d). It is likely there was a focal infarction during the second trimester that has healed by reparative polymicrogyria.[43,45]