Received: 17 August 2024 | Accepted: 11 February 2025

DOI: 10.1111/dmcn.16301

INVITED REVIEW

The fetal neurologist: Strategies to improve training, practice, and clinical care

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Abstract

Fetal neurology addresses counselling parents on the clinical significance of brain anomalies encountered in their fetus, including disruptive lesions (i.e. stroke, periventricular haemorrhagic infarction, and infection), and genetically based cortical (i.e. hemimegalencephaly, lissencephaly, cobblestone malformation, polymicrogyria, heterotopia) or posterior fossa anomalies (i.e. cerebellar agenesis and hypoplasia, rhombencephalosynapsis, Dandy–Walker syndrome, mega cisterna magna, Blake's pouch cyst). Unlike paediatric neurologists, fetal neurologists cannot examine the infant directly so they diagnose and prognosticate using imaging and other diagnostic studies. The integration of fetal neurologists into fetal multidisciplinary teams is essential for providing expert counselling and cohesive care. This review emphasizes the need for specialized training, multidisciplinary collaboration, and the development of comprehensive service designs to ensure consistent and effective care for families. Additionally, it emphasizes the critical role of fetal neurologists in identifying brain anomalies early and providing thorough counselling to parents, helping them to understand the prognosis, potential interventions, and long-term outcomes for their unborn child.

Perturbations in brain development can be caused by specific genetic disorders or acquired processes, such as ischaemia, haemorrhage, infection, or exposure to teratogens.[1] The diagnostic stage has advanced dramatically in the last few decades owing to developments in fetal neuroimaging (neurosonography and magnetic resonance imaging [MRI]) and genetics. In utero MRI (iuMRI) has greater diagnostic accuracy than transabdominal ultrasound;[2] however, other studies have shown that dedicated neurosonography, transabdominal and intravaginal, also performs better than standard ultrasound.[3–5] iuMRI has an important role in the elucidation of malformations of cortical development, where it is available. Similarly, whole-exome and genome sequencing has improved the rates of diagnosis of genetic disorders compared to karyotype and microarray systems.[6,7]

Once diagnosed, it is essential to give families the best parental counselling about the outcomes of fetal brain abnormalities as soon as possible. We would normally expect the aforementioned diagnostic developments to improve the accuracy of parental counselling, but is that the case? In the MERIDIAN study, iuMRI did not improve prognostication significantly when interpreted by obstetricians.[8] This is not the obstetrician's fault because they receive limited, if any, training in paediatric neurology and developmental medicine; they do not routinely see children and families to understand the impact of brain abnormalities on development in the longer term. They may also not have access to paediatric neurologists who are willing to work with them, and the scientific data on outcomes are limited. For example, the outcomes measured during the MERIDIAN study were at a relatively young age and a proportion of participants only received a screening tool rather than developmental assessment. Therefore, while the iuMRI can be an important tool where resources are available, it should not be seen as a 'crystal ball' for prognostication. Significant experience is needed when interpreting its findings and nuances.

Abbreviations: CMA, chromosomal microarray analysis; iuMRI, in utero magnetic resonance imaging; TOP, termination of pregnancy.

This leads us to the inevitable conclusions that working together in multidisciplinary teams and clinics is increasingly important to share the knowledge of different specialists, including experts in fetal neuroimaging, paediatric (fetal) neurology, and genetics. These teams should be aware of the range of aetiologies and outcomes for the fetal brain abnormalities, and the ethical challenges that fetal neurology teams and families are likely to face. These have recently been summarized in another article from an American perspective.[9] Some of the ethical issues the fetal neurology team should be aware of include: females, families, and society's views on when life begins, such as at conception or the threshold of viability; ensuring consent for further testing is truly informed and outlines the chances of useful information being found, false negative and positives, and how results may influence their choices; the risk of uncertain results that do not give clear answers; the local laws on maternal and fetal rights; the likelihood of potential treatments and their effectiveness in utero or postnatally; the practicalities and effects of therapeutic termination of pregnancy (TOP) on the mother and infant, including perceived suffering of the fetus; the family's religious beliefs and an understanding there is a range of beliefs about these issues between people who share the faith, as outlined recently by a rabbi;[10] the female's view of personal risk; the financial and emotional ability of the family to look after a child; the chance of coercion from a partner to make a decision the female does not want to; the effects of pressure from society and extended family members; the laws on termination in their country or state, particularly where they are changing quickly, such as in the USA.[9–12]

Naturally, it is not the fetal neurology team's role to have dry, theoretical, and complicated discussions about ethics with females and their families, but these factors should be weaved through the discussions the fetal neurology team have with families. A particularly interesting point that Rabbi Brody makes is that abortion should not be seen as the primary motivation for screening and testing, but the focus for society and families should be that investigations allow for access to fetal treatments, help with planning mode of delivery, and help preparing for neonatal and subsequent developmental care.[10]

The recommendation to work in multidisciplinary teams is hampered by the fact that fetal neurology is not recognized as a subspeciality of paediatric neurology across the world. There may also be limited training in fetal neurology for paediatric neurology trainees, in the same way as for obstetricians. As noted previously in this journal, paediatric neurologists may feel overwhelmed and underprepared for fetal consults.[13] We believe that fetal neurology curricula should be developed, and they should include topics like how to sensitively communicate imaging findings and test results to females; their significance; how to encourage informed decision-making regarding pregnancy management without judgement; the psychological impact of the diagnosis for parents; ethical issues raised around diagnosis and sanctity of fetal life; uncertainty of outcome and decision-making; the ethics and legality of TOP in their country and those neighbouring their borders where females may seek medical care that is not available locally; and developmental neurology.[11,14–17] In the USA, a fetal and neonatal neurology programme called 'The First Thousand Days' recognizes the importance of the early years and intervention for long-term neurodevelopment;[18] alternative schemes should be developed and tailored across the world. This will depend on the structure of health care services and the resources available, as well as local laws and ethics, because it is unlikely that 'one size fits all' populations.

What this paper adds

- Fetal neurology teams/clinics and multidisciplinary teamwork can improve the diagnosis and prognostic information given to families whose fetus has brain abnormalities.
- There is no formal training scheme for neurologists, though curricula and fellowships are needed.
- Fetal neurology should be a distinct subspecialty within paediatric neurology.

There are many different models for how multidisciplinary collaborations can work. In Israel, the world's first fetal neurology clinic was established at the Wolfson Medical Center over 25 years ago. After gaining experience in the diagnosis of relatively common and isolated anomalies (e.g. ventriculomegaly, prenatal infections, and agenesis of the corpus callosum), it became evident that the encountered missions were far more complex and sensitive, and extended to diverse individuals.[19] These challenges still exist today and include: (1) difficulties in early diagnosis of a brain that is rapidly evolving and changing; (2) diagnosis of the full extent of cerebral abnormalities because of limitations in imaging technology; (3) training and experience of the person interpreting the images; (4) limitations in the diagnostic ability of genetic testing and difficulties in interpreting results; (5) application of knowledge acquired from postnatal studies to prenatal life; (6) limited and insufficient existing literature on developmental outcomes of fetal neurological anomalies. Common issues include retrospective study designs, small sample sizes, the lack of standardized developmental assessment, and varying definitions of atypical development;[11] (7) keeping up with the rapid advances and conceptual changes in the diagnosis and definition of brain anomalies[20] and their genetic or disruptive background; (8) genuine inability to accurately prognosticate in equivocal cases or rare anomalies; (9) counselling and treating patients from diverse backgrounds who have varying ethical views and beliefs mean that it is essential

to approach each individual with cultural sensitivity, understanding, and respect; (10) psychological and ethical issues in counselling parents after a prenatal diagnosis, especially in the third trimester;[11,15] and (11) difficulties in engagement between fetal medicine and paediatric neurology and neurodevelopmental teams who care for infants postnatally. These may include funding, time constraints, lack of expertise among paediatric neurologists, a lack of interest in the field or discomfort because of the ethical issues raised, or geographical distance between maternity and children's hospitals.

This paper discusses personal insights on how to establish fetal neurology teams and clinics and provide training for the fetal neurologists of tomorrow. We believe fetal neurology should be recognized as a new subspecialty of paediatric neurology.

THE FIELD OF FETAL NEUROLOGY

Paediatric neurology is a vast area of medicine, encompassing many complicated disorders. Paediatric neurologists see the child, take histories, examine them (and the family, if necessary), and may request an MRI in their quest to find an aetiology, prognosis, and potential treatment. Because the speciality is so large, it is typical for paediatric neurologists to subspecialize, for example, in complex epilepsy, movement disorders, inflammatory disease, or neuromuscular disorders. It is impossible to be an expert in all these areas. In many countries, paediatric neurologists are not part of the fetal medicine multidisciplinary teams or attend dedicated clinics, and the parents are only referred for consultations in the most difficult cases, not necessarily the most severe. Where this is the case, the paediatric neurologist infrequently or never sees the neurosonography images, and only occasionally sees the iuMRI. Relationships with other members of the fetal medicine team may be patchy or non-existent and each team may counsel the family independently without prior discussion, so may offer different advice. Alternatively, if they provide similar information while counselling separately, they still may appear to disagree because of different communication styles.

Fetal neurology is a similarly vast area of medicine, incorporating disruptive (acquired) lesions, such as stroke, periventricular haemorrhagic infarction, and infection, as well as genetically based cortical or cerebellar malformations. Unlike paediatric neurologists, fetal neurologists cannot examine the infant, so they must diagnose and prognosticate using imaging or other studies on their own. A 'fetal neurologist' should be an integral part of the fetal medicine multidisciplinary team and routinely attend consultations and clinics to give the counselling since they have the following.

- Expertise in the normal embryological processes and the gestational age when these processes occur.
- The ability to correlate brain imaging with eventual outcome and to give the most accurate prognostication.
- The ability to accurately describe the likely care, treatments, and adjustments necessary to manage the child's difficulties postnatally.
- Proficiency in describing the life of a family with a child with developmental disabilities and an ability to link parents with other families whose child has similar conditions.
- The capability to be the care providers of these children postnatally and the ability to evaluate their developmental progress and trajectory by using standardized testing (necessary for conducting postnatal outcome studies).
- Knowledge of local laws and processes for TOP.
- Close relationships with neonatologists, geneticists, paediatric neurosurgeons, and other paediatric specialities.
- Experience in supporting families during times of difficult decision-making, balancing what is 'right for them' while being the unborn child's advocate.
- The ability to ensure that high-quality updated information is given to reduce the risk, which can prevent legal cases of 'wrongful death' (where the infant who would be neurodevelopmentally typical is terminated based on inaccurate information) or 'wrongful birth' (a legal term for when families are incorrectly warned their child would have a typical outcome, and the child subsequently developed severe disabilities, when they would have chosen a TOP if the information provided had been accurate and the procedure offered).

Thus, we believe there should be a dedicated training pathway for fetal neurology, encompassing areas that are not included on the standard paediatric neurology syllabus or are only superficially covered.

There are very few fetal neurologists across the world, so access to training may be difficult and dedicated fellowships should be established. Similarly, many fetal conditions are rare and there may be little high-quality data published on their developmental consequences, so international collaboration is necessary to share experiences, outcomes, and develop research programmes.

Developmental Medicine & Child Neurology recently published an overview of how, when, and where fetal counselling should be performed and discussed the most frequently encountered fetal brain anomalies and their outcomes.[11,15] This included ventriculomegaly, hydrocephalus, complete and partial agenesis of the corpus callosum, macrocephaly and microcephaly, holoprosencephaly, malformations of cortical development (hemimegalencephaly, lissencephaly, cobblestone malformation, polymicrogyria, heterotopia), and posterior fossa anomalies (cerebellar agenesis and hypoplasia, rhombencephalosynapsis, Dandy-Walker syndrome, mega cisterna magna, Blake's pouch cyst). However, this is no replacement for seeing fetal neurology cases in your own unit, working with the fetal medicine team, and gaining personal experience of outcomes.

WHO SHOULD BE PART OF THE FETAL NEUROLOGY TEAM OR CLINIC?

The core members of the fetal neurology team will depend on service design and resources across the world, but would typically include midwives, fetal medicine obstetricians, neurosonographers, fetal neurologists, geneticists, and neuroradiologists with expertise in iuMRI. In specific cases, the fetal neurology clinic team will consult other paediatric specialists in the following disciplines: infectious diseases (with experience in congenital infections); pharmacy (with expertise in teratogenicity); endocrinology; nephrology; gastroenterology; cardiology; surgery; and neurosurgery. Psychologists and social workers should be in involved in cases where the parents have to cope with a possible unfavourable outcome and make difficult decisions regarding pregnancy management. An appointment in the fetal neurology clinic does not need everyone to attend. A careful balance needs to be made between having the right expertise in the room with having too many people, which makes the assessment intrusive and scary.

WHAT HAPPENS DURING THE FETAL NEUROLOGY ASSESSMENT?

The clinic starts with the introduction of the participants and their roles. It continues with the collection of the medical history, which includes the cause and source of the referral; gestational age; review of the current pregnancy, evaluations, medications, and complications; a family history of developmental abnormalities or pregnancy complications; genetic screening or genetic evaluation in the current pregnancy; TORCH (toxoplasmosis, rubella cytomegalovirus, herpes simplex, and human immunodeficiency virus) evaluation; and results of previous imaging (ultrasound and MRI). When a dominant disorder is suspected, it may be necessary to examine the prospective parents. Examples include: when the circumference of the fetal head is more than 2SD below or above the average for gestational age (plotting the parental head circumferences may give useful information); when there are concerns about neuromuscular disorders, such as myotonic dystrophy or neuropathy, examining parental muscle strength may be required; when the fetus has a corpus callosum disorder, checking mirror movements in the parents can enable giving a good prognosis (because of a possible *DCC* mutation). In some cases, it may even be necessary to obtain parental MRI.[21]

The next action is assessment of the fetal brain using dedicated neurosonography according to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology.[22] The transvaginal multiplanar approach is the preferred method to perform an adequate high-resolution targeted neurosonographic examination. The use of a 3D ultrasound approach is recommended particularly when good 2D imaging is difficult to obtain. The neurosonogram should be accompanied by a systemic scan at the first visit. Structural abnormalities should be established.

After imaging, the team reviews the findings and discusses the differential diagnosis and prognosis. When necessary, a review of the up-to-date literature is conducted. The group then formulates a possible diagnosis, whether further investigations are necessary, the prognosis, and who are the best professionals to talk to the parents. Further investigations may include amniocentesis for genetic studies (microarray, or whole-exome and genome studies, preferably a trio sample), and in utero infections. When ischaemic or haemorrhagic lesions are seen, evaluation for thrombophilia is recommended.

WHAT SHOULD THE DISCUSSION ABOUT THE FETAL ABNORMALITY BE LIKE?

When a fetal anomaly is discovered using ultrasound, the females should be told immediately. Females know something is wrong by the body language, lack of communication, and the phrases or noises health care professionals make like tutting or sighing because the health care professional focuses on one part of the infant for a long time, they turn the screen away from the family, or they ask for help. Females particularly mourn the loss of the more positive aspects of having an ultrasound, like someone pointing out the anatomy, such as the nose, eyes, hands, feet, and so forth. We recommend this is still done, where appropriate, even where an anomaly is found.

The identification of a possible anomaly should be immediately followed by a brief explanation that the scan may be abnormal and a promise that right after the ultrasound is completed, when everyone is seated, the couple will receive a full explanation about the findings and their clinical implications. Families should be given the opportunity to see the images and have the abnormalities shown on a 3D model or via an app, such as the free 3D Brain app. Families report that descriptions of abnormalities are often overly technical, with the focus on the biological aspects of the abnormality. This should be avoided and medical terminology should be explained.[15,23–25] Sometimes the diagnosis and outcome are obvious, in which case the second part of the counselling should occur seamlessly, assuming the family are ready to hear it. Sometimes, families will be shocked, particularly if they were hoping the scan would prove that a previously suspected abnormality was wrong. They may need time to process the information or to cry and compose themselves in a quiet room where they will not be distracted.

For more complicated or rare conditions, a pause might be needed while the fetal neurology team discuss what the findings are, the likely cause(s), what investigations are required, and the likely outcomes. These discussions should be held away from the family, particularly where there could

be a potential disagreement in views. Sometimes, a literature search or even consultation with experts from other centres needs to be performed for rare or unusual abnormalities. Once a plan is made, the family should be invited back into the room for a discussion with the most appropriate professional(s). When the assessed neurodevelopmental outcome is grave, a referral to a dedicated supporting midwife, social worker, or psychologist should be offered, if these resources are available.

During the following consultation, the family should be asked to explain what they had understood and what they want to know next. The clinician should follow the family's agenda, wherever possible. If further investigations are warranted, these can be discussed. The team should explain the balance between the likelihood the investigations will provide further useful information with the risk of harm, such as miscarriage after amniocentesis. Advice on prognosis should be offered; families should be told the best, worst, and most likely outcomes for their infant using understandable language. Functional outcomes should be used because families are more concerned about whether their child will walk, talk, go to mainstream school, play sports, and have a relationship as an adult, then they are about diagnostic labels. Thus, there should be a focus on the likely level of the child's functional ability, their ability to participate in life and activities of daily living, and their likelihood of independence. A discussion should be held on what care and support would be available after birth, and how these issues are likely to impact the family, such as the parents' ability to work, their need for respite care, and the likely effect on siblings. The health care professional should listen carefully to the family's views and situation because no two environments are the same. Where risk is discussed, it is probably better to use numerical data, where available, than descriptive terms like 'high or low'. The denominator should be the same for risks, positive and negative framing should be used, and visual aids should be available to help families understand risk, as we reviewed previously.[11] Where it is legally appropriate, the issue of termination should be discussed in a neutral manner.

After the discussion, all the information should be provided to the family and the referring physician in a detailed summary letter. The parents can be directed towards lay material on relevant conditions, ongoing support for families, and contact details of appropriate staff (trained midwives, counsellors, psychologists, or social workers, depending on the country and service design). The family should have contact details for the most appropriate person in the team in case they have further questions. Follow-up should be arranged, particularly when additional investigation results are awaited.

WHEN SHOULD FETAL MRI BE OBTAINED?

According to the International Society of Ultrasound in Obstetrics and Gynecology guidelines, fetal brain MRI is considered complementary to neurosonography and can add significant clinical information to answer specific questions posed by the neurosonographer. MRI has the advantage of not being limited by fetal position, obesity, or oligohydramnios, and visualization of the brain is not restricted by the ossified skull. With its higher resolution, contrast abilities, and a large field of view, MRI facilitates the examination of fetuses with large or complex anomalies, as well as visualization of lesions in the context of the entire fetal body.[26] Multiple studies demonstrated that MRI can add important knowledge, especially in malformations of cortical development and parenchymal lesions (ischaemic or haemorrhagic).[26,27] However, we acknowledge that the results are affected by the training and experience of the radiologists, so networks should exist for difficult cases for second opinions and to aid training. Similarly, iuMRI may not be available in all settings across the world currently.

The European Society of Paediatric Radiology Fetal Task Force recommends that fetal brain MRI should be offered for the following indications: a family history of severe brain abnormality in a previous pregnancy (in the absence of possible early genetic testing) to look for subtle similar signs; in high-risk cases for the development of disruptive brain lesions, such as fetal infections and ischaemic events in a stressful maternal environment (twin-to-twin transfusion syndrome, death of a monochorionic twin, maternal use of toxic agents); abnormal head circumference or other biometric sonographic measurements of brain structures (i.e. length of the corpus callosum, transverse cerebellar diameter); after identification of one or several brain abnormalities using ultrasound to clarify whether or not they are isolated.[28]

Where neurosonography or iuMRI has been performed early in pregnancy, the fetal neurology team should consider whether repeating the imaging around 32 weeks or later is warranted. This is because the fetal brain grows significantly during the third trimester and, other than the Sylvian fissures, there is little in the way of a sulcal-gyral pattern at 22 weeks or thereabouts. As an infant approaches term, the sulcal-gyral pattern is more established and migration disorders may be seen more easily. Similarly, microcephaly and macrocephaly may only be more prominent later in pregnancy. Therefore, while fetal neurology teams should aim to find abnormalities as early as possible in pregnancy, this is not always possible. The decision about whether to repeat iuMRI later in pregnancy should be specific to families and the setting in which care is provided. For example, where a family does not wish or is not legally allowed to have a late termination, later iuMRI may increase anxiety without leading to alternative treatment options. In other settings, families may value knowing the extent of the fetal brain abnormalities and allow them to mentally prepare for the birth. Where additional findings or abnormalities may lead the family to choose a legal TOP, the late iuMRI may be a key part of the decision-making process.

WHEN IS GENETIC TESTING INDICATED?

In a recent study on 114 females who underwent TOP after the detection of a major central nervous system anomaly, chromosomal microarray analysis (CMA) detected causative copy number variants in 10% of fetuses. Among 86 CMA-negative cases, exome sequencing detected causative sequence variants in 44%.[29] Where whole-exome sequencing reveals an aetiology, it had a clinical impact in 63% of cases, including aiding decision-making and perinatal management, and helping to approve late TOP.[30] Based on multiple studies reviewed by Chou and Choy,[31] the International Society for Prenatal Diagnosis issued an updated position statement on the use of genome-wide sequencing for prenatal diagnosis.[32] They support prenatal sequencing for the following indications: (1) a current pregnancy with a fetus having a major single anomaly or multiple organ system anomalies for which no genetic diagnosis was found after CMA and the phenotype is suggestive of a possible genetic aetiology; (2) or the multiple anomaly 'pattern' strongly suggests a single gene disorder with no prior genetic testing (as prenatal exome and genome sequencing are not currently validated to detect all copy number variants, CMA should be run before or in parallel with more complicated genetic testing); (3) a personal (maternal or paternal) history of a prior undiagnosed fetus (or child) affected with a major single or multiple anomalies; and (4) with a recurrence of similar anomalies in the current pregnancy without a genetic diagnosis after karyotype or CMA for the current or prior undiagnosed pregnancy.[32]

The results of genetic testing can take several weeks to return, depending on the country where they are performed. In countries with restrictive laws on TOP, the results may arrive too late to allow females to choose to end their pregnancy. Fetal medicine teams will need to explain this limitation to females and their families, and work with genetic teams to discuss the risk of genetic disease.

WHEN SHOULD THERE BE AN EVALUATION FOR INFECTIOUS DISEASES IN AMNIOTIC FLUID?

The evaluation of in utero infection is often offered for the following sonographic findings: fetal hyperechogenic bowel, hydrops, cerebral ventriculomegaly, echogenic foci, oligohydramnios, polyhydramnios, intrauterine growth restriction,[33] microcephaly, and fetal anaemia. The recommended studies include the STORCH (syphilis, *Toxoplasma gondii*, rubella, cytomegalovirus, herpes simplex) infections, human immunodeficiency virus, hepatitis B and C, parvovirus B19, enterovirus, varicella zoster virus, and *Leptospira interrogans*,[34] Zika virus and severe acute respiratory syndrome coronavirus 2, depending on the clinical situation and environment females are seen in.[35] A study on 392 maternal STORCH tests performed for fetal ultrasound abnormalities found that the most common ultrasound findings triggering viral testing were: intrauterine growth restriction (30.4%); microcephaly (1.5%); polyhydramnios (14.8%); and intrauterine fetal demise (13.3%). The yield of the tests was low: maternal infections were found in 3.4% of growth-restricted fetuses, 5.2% of polyhydramnios, and 1.9% of intrauterine fetal demise. The leading aetiologies were cytomegalovirus and parvovirus B19. The authors concluded that testing for STORCH infections should consider exposure history, clinical signs and symptoms, obstetric history, and fetal ultrasound findings, but with special attention paid to cytomegalovirus and parvovirus B19.[34]

Cytomegalovirus is the most frequent prenatal infection that can affect the brain. Typical imaging findings that warrant investigation are white matter lesions, subependymal cysts, temporal cysts, ventriculomegaly, ventricular adhesions, gyral abnormalities (polymicrogyria, schizencephaly), calcifications, and cerebellar hypoplasia.[35,36] The main radiological features of the other common neurotropic infections (toxoplasmosis, herpes simplex virus, rubella, parvovirus, coronavirus disease 2019, and Zika virus) are described in a table in the pictorial review by Lucignani et al.[36]

SUGGESTING THE OPTION OF TERMINATION OF PREGNANCY

When the neurosonographic finding are severe and extensive, or a genetic variant associated with poor neurodevelopmental outcome is discovered, TOP can be offered in countries where the law allows. In Israel, TOP is allowed at any stage of pregnancy when the chance of a severe neurodevelopmental disorder is over 30%. In the UK, late TOP is allowed when there is a 'substantial risk' that the infant would not survive or would have a 'significant handicap'. The wording is vague to allow clinicians and pregnant females latitude to make decisions in complicated situations where there is little published data on the outcome. In other countries, such as Poland, Nigeria, and the USA, there are far more restrictive laws on when or if TOP can be offered, and any fetal medicine team should be aware of this, as well as whether travelling to a neighbouring country for treatment is a legal and logistical possibility for the family who wish to explore this.[12]

Any discussion about TOP should be directed to informing the family if it is an option available to them, but the team would support their decision either way. If the family has previously indicated they would never consider a TOP, this discussion should be done sensitively so the family does not perceive that the health care professional is 'pushing them to reconsider' or thinks they have made the 'wrong decision'. Appropriate support should be available to pregnant females and their families to help them navigate these difficult decisions. This may be an experienced, dedicated midwife, a social worker, or a psychologist. If the parents elect to terminate the pregnancy, support should not stop, which is the reported experience of many females who feel cast adrift by

health care services.[24,37] Some families may value the offer of autopsy and infection screens; genetic studies are suggested, depending on the situation, if they have unanswered questions about why the abnormality occurred, whether it was their fault, or if recurrence in future pregnancies was likely or in other family members.

After all the results are obtained, the parents are called back for a concluding conversation to discuss the implications and to get precise recommendations for future pregnancies.

FOLLOW-UP AT THE FETAL NEUROLOGY CLINIC

When the parents do not elect TOP, in most cases, they are scheduled to return for follow-up, repeated neurosonography, review of investigations, and revised consultation. Parents may have had time to process the shock and complicated emotions they experienced at diagnosis, and may have performed internet searches, contacted charities and support groups, or discussed with their own or other families. They may have directed questions about further investigations, delivery, their infant's outcome, or what services would be available to them and the infant after birth. When necessary, additional specialists in applicable fields may need to be invited, such as paediatric neurosurgery, neonatology, or palliative care.

At present, we can convey good news increasingly more frequently after normal test results return and positive consultations with colleagues are received. For example, in a case with isolated agenesis of the corpus callosum, normal genetic testing decreases the risk of an adverse neurodevelopmental outcome below the threshold allowing TOP.

When the couple decides to continue the pregnancy, a careful and sensitive balance needs to be trod between ensuring they remain comfortable with their decision to knowing they can change their mind, if appropriate within the law. Clear communication needs to be made with the postnatal team on what investigations or follow-up after birth, which is a challenge if delivery is due to occur in a distant hospital from the one providing fetal neurology care.

POSTNATAL FOLLOW-UP FOR FAMILIES WHO CONTINUE THEIR PREGNANCY

The final summary letter should include clear instructions to the hospital in which the infant will be delivered, on any management required after birth, including postnatal MRI, genetic testing, infection screen, or metabolic testing and an invitation for a neurodevelopmental evaluation by the same paediatric neurologist who participated in the counselling.

The postnatal follow-up should be tailored to the details of the abnormality found, and the wishes of the family. If postnatal MRI is required, this should be performed in the first few weeks of life to avoid the need for sedation. Developmental review at 4 to 6 months can be useful to identify early concerns or to provide reassurance. After this, repeated appointments to review developmental progress by the fetal neurologist, preferably with a paediatric physical therapist, where available, should assess the developmental milestones and trajectory, and provide education and guidance on how to support their child's development at home. Appropriate developmental tools should be used for the child's age, ethnicity, and language. There should be close cooperation with community and disability services for children whose outcomes are atypical. It is wise to keep a database of cases that have been seen to review outcomes and the accuracy of advice given during prognostication, or for research publications.

In the next section, we provide fetal neurology vignettes that show how multidisciplinary working and postnatal follow-up can help with clinical care for families and improve knowledge of conditions to direct future care.

CLINICAL VIGNETTES

Clinical vignette 1

A 31-year-old healthy primigravida was referred to the multidisciplinary fetal neurology centre at 34.6 weeks gestational age for evaluation because of incomplete hippocampal inversion and dilatation of temporal horns. The parents were non-consanguineous. Family history was significant for adult-onset seizures in the father with a normal MRI.

Nuchal translucency and early ultrasound scan were normal. Since the second scan at 21.4 weeks gestational age, mild ventricular enlargement (10.8 mm) was documented. Fetal echocardiography was normal. At 25 weeks gestational age, neurosonography depicted mild ventriculomegaly, mild thinning of the corpus callosum, and slight flattening of the parieto-occipital and calcarine sulci. The mother was referred to ultrasound follow-up, fetal MRI at 32 weeks gestational age, and amniocentesis. Microarray and trio exome were normal. Neurosonography at 33 weeks gestational age revealed normal ventricular width; echogenicity of the right temporal horn ependyma with mesial parenchymal thinning; bilateral enlargement of both temporal horns; and thinning of the posterior body of the corpus callosum. MRI at 33 weeks gestational age demonstrated asymmetric triangular appearance of the temporal horns, normal atrial ventricular width (9 mm), pathological perpendicular position of the hippocampi with architectonic distortion of the mesial cortex, and mild thinning of the corpus callosum (Figure 1). The option of a TOP was discussed with the family.

The fetal neurology team repeated the neurosonography at 34.6 weeks gestational age and confirmed the findings, that is, suspected focal cortical dysplasia of the temporal lobes, incomplete hippocampal inversion, and temporal horn enlargement. As we had never encountered such a situation before, we could not formulate an accurate

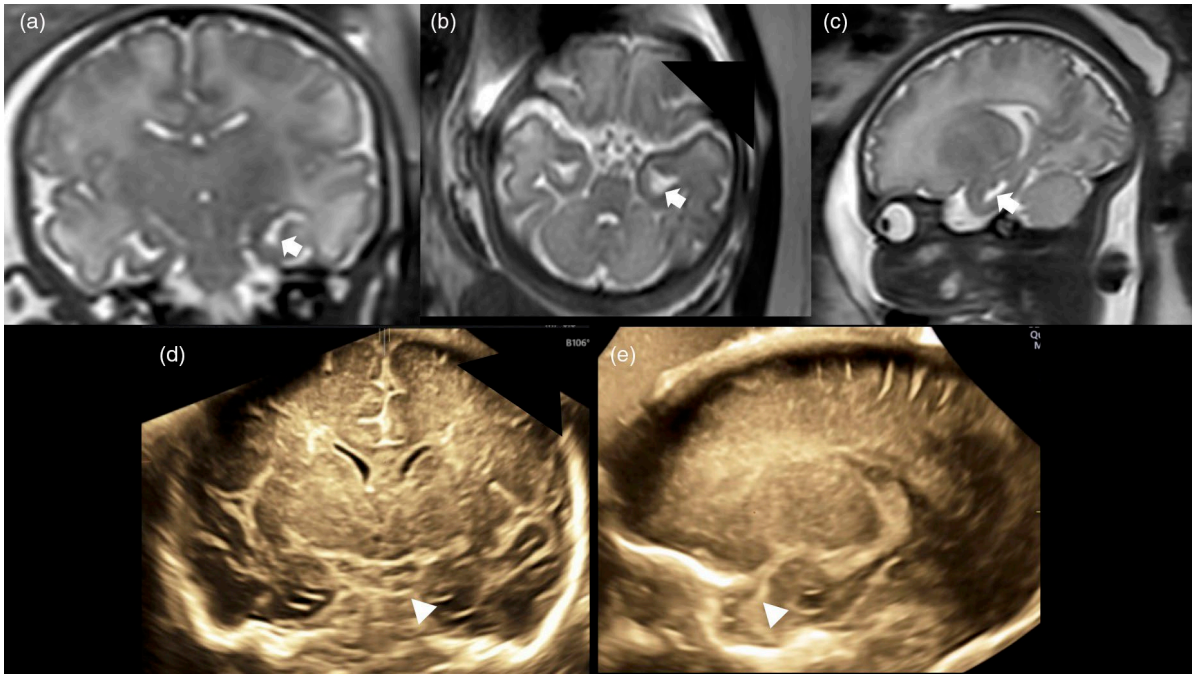

FIGURE 1 In utero magnetic resonance imaging at 34 weeks show bilateral atypical dilatation of the temporal horns (arrows), parenchymal thinning, and incomplete hippocampal rotation (T2-weighted images: [a] coronal view; [b] axial view; [c] sagittal view). Vaginal ultrasound at 35 weeks shows cystic temporal horn dilatation (arrowheads): (d) coronal view; (e) sagittal view. The lateral ventricles have otherwise normal shape and width.

prognostication. We searched the literature and consulted prominent paediatric neurologists and neuroradiologists with expertise in brain malformations. The full results of the literature search and expert opinions can be obtained from the corresponding author. Our conclusion, based on the literature review, was that incomplete inversion of the hippocampi could be frequently seen in children with cortical and callosal malformations and genetic syndromes; however, when such malformations are isolated the neurodevelopmental prognosis could be good. At 35.6 weeks gestational age, we gave the parents the final consultation after receiving the opinions of five international experts. They had never encountered an exact similar case; however, they all agreed that the pathology was in the temporal horns. Most of them believed that the risks for an adverse neurodevelopmental outcome and epilepsy were low.

The parents were relieved and decided to continue the pregnancy. An infant was born at full-term. He is currently 6 months old, and his development and neurological evaluation are typical.

Clinical vignette 2

A 33-year-old mother of a son was referred at 33.2 weeks gestational age for neurosonography and counselling due to an abnormal contour of the right lateral ventricle that was first demonstrated using ultrasound at 32.5 weeks gestational age. The couple are not consanguineous and there was no family history of neurological diseases. Nuchal translucency and early screening were normal. Ultrasound screening at 22 weeks revealed ventricular asymmetry without enlargement. TORCH serology and coagulation studies were normal. Fetal MRI at 32.5 weeks gestational age revealed asymmetric lateral ventricles (right 12 mm, left 9 mm). There were blood breakdown products in the right ventricle associated with irregularities of the ventricular border.

Neurosonography depicted normal fetal growth. The right ventricular body was irregular in the lateral periatrial aspect, with a width in this area up to 11.6 mm and increased echogenicity. The left ventricle had a normal shape and width. The intraventricular environment had no unusual echoes. Based on the ultrasound and MRI, we counselled that the fetus had a small parenchymal lesion in the wall of the lateral ventricle underlying the parietal lobe, with mild atrophy of the right thalamus. The findings were consistent with periventricular venous haemorrhagic infarction after intraventricular haemorrhage. We explained that because of the location of the damage, the risk of significant neurodevelopmental involvement was probably low, but the risk could be better assessed using tractography. We recommended amniocentesis for trio exome.

The patient was sent to Prof. Gregor Kasprian in Vienna to perform an MRI with tractography to assess possible involvement of the sensorimotor tracts. The fetal MRI findings were consistent with the chronic, subacute stage of an intraventricular haemorrhage on the right with associated post perihaemorrhagic and perihaemorrhagic infarction with parenchymal defect locally at the

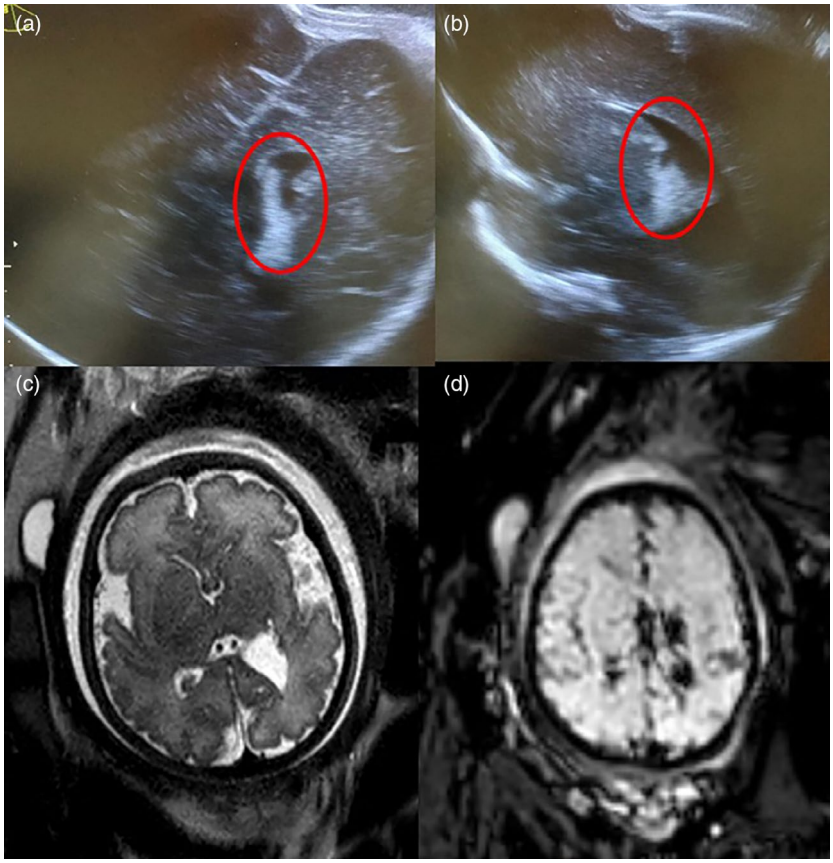

FIGURE 2 Late IVH sequelae / Presumed PVHI (a-d) 33 GW fetus referred due to lateral ventricle asymmetry diagnosed at third trimester. Cranial US (a) oblique coronal, (b) left parasagittal) demonstrate unilateral parietal left ventricular border irregularity and echogenicity. T2 weighted IUMRI at 34 GW (c) shows left parietal periventricular focal defect, blood remnants in both lateral ventricles and a smaller left thalamus. (d) Axial T2* gradient-echo IUMR image shows increased susceptibility effect due to blood remnants at the atrium of the ventricles bilaterally and on the caudothalamic groove on the left side.

posterior caudothalamic groove, slight asymmetry of the cerebral crus, and underdevelopment of the right thalamus (Figure 2). There was tractographic evidence of incomplete structural involvement of the right sensorimotor pathways.

The parents were counselled that there was damage to the thalamocortical and sensorimotor pathways, so there was a high risk for neurological involvement, but most likely mild (weakness and neglect mainly of the left hand with slighter involvement of the leg). No cognitive involvement was expected. We explained about the available treatments, such as physiotherapy including constraint and occupational therapy. The parents decided to accept this possible outcome and continue the pregnancy.

Just as they were leaving the room the result of the trio exome arrived: a de novo, most likely pathogenic mutation was found in *COL4A1* c.4231G > A, which is a known cause for a tendency to intracerebral haemorrhage and other diseases. After the result of the trio exome, they were counselled that there would be an increased risk of vascular events in young adulthood and there would be a very low risk of brain haemorrhage around birth. At this point the parents changed their mind and decided to have a TOP.

OBSTACLES FACED IN LOW- AND MIDDLE-INCOME COUNTRIES

We are aware that the perspective of this article is from privileged high-income countries, and the experience, resources, and investigations we recommend may not be available in low- and middle-income countries. Health care professionals from these settings face even more challenges, and teamwork is perhaps needed to an even greater extent to deliver and develop services for females and their families. One perspective from Nigeria highlighted the important role that introducing ultrasound has had on pregnancy care, and the lack of availability of iuMRI.[38] Even though Nigeria has restrictive laws on TOP, ultrasound programmes have allowed females to have a choice about their pregnancy and the option of TOP. From a wider global viewpoint, fetal medicine and neurology teams have a responsibility to partner with colleagues in lower- and middle-income services to provide support, training, evidence on aetiology and outcomes of fetal neurology conditions, and perhaps to help exert political pressure through our professional organizations. This will require collaborations with networks of teams and organizing crossing

international borders to improve access to care for females and families across the world.

FUTURE CHALLENGES IN FETAL NEUROLOGY AND THE EXISTING GAPS IN OUR KNOWLEDGE

Having argued the case for fetal neurologists and their specialized training, proving our value to fetal medicine teams around the world may be a challenge, and evidence is needed on how we improve counselling and care. Training courses and greater access to training are needed when so few currently work in this area of medicine. In health systems where funding streams are important, money for the fetal neurologist's time needs to flow from the fetal medicine service into paediatric teams, otherwise they may not be allocated dedicated time for their work. Fetal neurology is heavily dependent on resources and time, and it should not be additional work performed on top of a full-time paediatric neurology role, otherwise access to and quality of the fetal neurology service will be suboptimal. Fetal neurologists need to engage in large-scale, prospective follow-up studies that follow young people into adolescence and use appropriate assessment tools to show the rates of atypical outcome and whether variants can be predicted antenatally based on imaging and genetic tests.

Some examples of future frontiers in fetal neurology research include the following: (1) the risk for adverse neurodevelopmental outcome in fetuses with multiple minor abnormalities (mild ventriculomegaly, asymmetric ventricles, mega cisterna magna, Blake's pouch cyst, periventricular pseudocysts, obliterated or wide cavum septum pellucidum, cavum vergae, and cavum veli interpositi); (2) the effect of normal genetic studies on prognosis and parental decision-making (collaboration is needed with genetics research teams to look at how diagnostic rates of testing can be improved); (3) the effect of additional central nervous system or systemic anomalies on prognosis; (4) development of a fetal classification of disorders of the corpus callosum and evaluation of the correlation with prognosis; (5) development of a dedicated classification of fetal intraventricular haemorrhage and periventricular haemorrhagic infarction; and (6) understanding the full range of brain anomalies in disruptive injury and their influence on outcome.

SUGGESTED AREAS FOR A SYLLABUS

Suggested areas include the following: typical fetal brain development, as demonstrated by ultrasound and MRI at different gestational ages;[39–41] brain malformations, both supratentorial and infratentorial, and their neuroimaging findings at different gestational ages;[42–46] disruptive vascular brain lesions (aetiology, diagnosis, progression, and outcome);[47–49] the antenatal onset of neurological dysfunction in fetuses with congenital heart disease and primary genetic and dysgenetic conditions, and secondary disruptions of brain development and acquired encephaloclastic lesions;[50,51] brain disruption in prenatal infections (neuroimaging features and correlation with outcome);[52,53] the effect of genetic and acquired inflammatory disorders on the developing brain and clinical outcomes;[54,55] the association of atypical cerebral development with different inborn errors of metabolism, the potential mechanisms of the aberrant in utero metabolic environment, and the fetal neuroimaging presentation;[56,57] genetic disorders and their typical antenatal neuroimaging features;[58] advanced fetal genetic testing (indications, methods, diagnostic yield, clinical utility, variant interpretation, practical considerations, before and after test counselling);[59] fetal growth restriction and the effect on the developing brain;[60] placental disorders and brain disruption;[61] prediction of outcome in fetuses with a neurological anomaly;[15] the availability of maternal and fetal interventions and their value and limitations;[62] psychological and ethical issues in counselling;[11] communication skills, including how to discuss medical risks; and the range of developmental assessment tools that can be used at different ages postnatally.

CONCLUSIONS

Fetal neurology is a highly specialized area of paediatric neurology, and the skills required to deliver this service are either omitted or only covered briefly in paediatric neurology training. The fetal neurology team and clinic is a collaboration between fetal medicine, imaging experts, geneticists, and fetal neurologists, among others, with the aim to give high-quality information to pregnant females and their families on the significance of fetal neurological problems, aetiology, and prognosis. Such information can guide decisions on how a pregnancy can be managed, ensure females make the right decision for them, and hopefully avoid medical litigation for poor care or advice. Fetal neurologists also provide postnatal care, both surveillance for developmental problems and management of neurological outcomes and referral for appropriate support. Because the fetal neurologist follows children and families in the long term, they are best placed to discuss the relevance of fetal neurological abnormalities. However, there are many challenges to gaining acceptance of this specialty and expanding the service internationally. Dedicated training schemes or courses, and fellowships, are needed; outcome studies are needed to improve the data informing prognostication; resources are needed to ensure the time needed to deliver and develop the service are provided to paediatric teams; and collaboration with other specialties on service development and research into the significance of imaging and genetic findings are required. We argue that this should be a priority for health services

across the world. Females and their families are faced with complicated and traumatic news, after which they must make difficult decisions that affect their whole life, both termination and continuing the pregnancy. As such, they deserve the most accurate information possible to make truly informed decisions; we feel that the fetal neurologist, in conjunction with the wider team, has a critical role in this process.

ACKNOWLEDGEMENTS

We thank Prof. Lieven Legae for encouraging us to write this paper and suggesting the definition of the fetal neurologist as the unborn child's advocate.

We thank Dr. Leila Haddad, from Wolfson Medical Center, for providing the US images, and Dr Efrat Hadi and Prof Chen Hoffman from Sheba Medical Center and Prof. Gregor Kasprian from Medical University of Vienna, for providing the MR images. [Correction added on 08 May 2025 after first online publication: The second paragraph of the Acknowledgements section has been updated.]

We thank Stephanie Libzon for technical assistance.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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How to cite this article: Lerman-Sagie T, Hart AR. The fetal neurologist: Strategies to improve training, practice, and clinical care. Dev Med Child Neurol. 2025;00:1–12. https://doi.org/10.1111/dmcn.16301