Suspected fetal anomalies

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Abstract

Congenital anomalies are present in 2–3% of all fetuses. Suspicion or discovery of a fetal abnormality is therefore a frequent source of anxiety and upset for couples and their wider families. A proper understanding of the pathways of diagnosis and care is vitally important in facilitating informed choice and minimizing the stress experienced by couples. This review considers different scenarios for suspected fetal anomalies; from a low risk patient with a suspected fetal anomaly at the first trimester ultrasound scan (USS), to a high risk patient with a fetal malformation diagnosed at the anomaly USS. Here, we discuss the different pathways in these scenarios and the different management options available to families and doctors, including non-invasive prenatal testing, amniocentesis, treatment options and termination of pregnancy.

Keywords amniocentesis; chorionic villous sampling; fetal medicine; non-invasive prenatal testing; prenatal counselling; prenatal diagnosis; termination of pregnancy

Introduction

Congenital anomalies are present in 2–3% of all fetuses. This is a frequent source of stress to couples and their families. A proper understanding of the pathways of diagnosis and care is vitally important in facilitating informed choice and minimizing the stress experienced by couples.

New tools, tests and techniques have greatly increased our diagnostic capability and capacity to treat certain anomalies over the course of the past decade. The most important improvements have been made in molecular genetics, imaging and minimally invasive surgical treatment of the fetus. We discuss here the different pathways and the different management options available to families and doctors, including non-invasive prenatal testing, amniocentesis, treatment options and termination of pregnancy.

Case 1

A 32-year-old woman undergoes a first trimester ultrasound scan (USS). She has no past family or personal medical history and this is her first pregnancy. The first trimester USS does not show the normal image of the thalami (butterfly sign) but instead shows a single monoventricular cavity and fused thalami. The possible diagnosis of holoprosencephaly (HPE) is raised. The patient is referred to a Fetal Medicine Unit (FMU), where the diagnosis of alobar holoprosencephaly (AHPE) is confirmed. The parents are counselled and offered different options. The fetal medicine specialist (FMS) explains that AHPE is a structural abnormality of the brain and that most live born babies with this condition do not survive long after birth. She explains that HPE is a spectrum that can range from AHPE, the most severe form, to lobar HPE which can sometimes be found fortuitously in a clinically normal, or near normal, person. She explores further the possibility of milder forms of HPE in the family history.

Maternal diabetes, fetal alcohol and, drug exposure, and fetal infection are ruled out as possible aetiological causes. The FMS explains that a chromosomal abnormality may be the underlying cause and offers invasive prenatal testing with chorionic villous sampling (CVS). However, whatever the results of these investigations the prognosis will be poor and she also discusses with them the option of termination of pregnancy (TOP). The couple opts for a surgical termination of pregnancy (TOP) and karyotyping is performed on the trophoblastic tissue with consent. The karyotype is normal. The couple is referred to a genetic specialist in order to discuss the recurrence risk and the investigations necessary prior to the next pregnancy. Microdeletions or duplications, undetectable by a normal karyotyping procedure, may have been responsible, or indeed mutations within a number of single genes. Very close examination of both the woman and her partner will be needed to reassure against a partially penetrant familial autosomal dominant mutation. Because autosomal recessive single gene disorders can be responsible the recurrence risk could be as high as 25%, particularly if there is consanguinity.

If further genetic testing fails to find an underlying cause, in the next pregnancy the couple will be offered an early USS in a FMU to look for early signs of HPE, an early fetal anomaly USS at 16 weeks of gestation and a normal anomaly USS at 20 weeks. If all the USS are normal, the care will be normal after this point forward. If an underlying genetic anomaly is identified in the index pregnancy this will allow a very precise prediction of recurrence risk and the possibility of early molecular testing in a future pregnancy by CVS.

The fetal medicine consultation

In case of suspected fetal anomaly, the couple should be referred for a fetal medicine consultation.

This referral may occur preconceptually in case of a familial genetic or chromosomal anomaly or a family history of malformation. The couple may want to understand the risks to their future offspring, the ways to prevent such a problem, the future investigations available to assess if the fetus is affected and the options in such a case.

More often the referral occurs during the pregnancy. In this situation, the consultation has several purposes. The FMS must confirm, refute or refine the diagnosis, determine the severity of the anomaly, organize the aetiological investigations (infection, teratogenicity, genetic/chromosomal abnormality, etc.), refer the couple to the appropriate specialist (geneticist, neonatal surgeon, etc.), discuss and facilitate termination of pregnancy where appropriate, determine the most appropriate location and mode

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of delivery, and organize the immediate neonatal care. Pervading all these discussions must be an ethos of doctor–patient partnership. The FMS is there to provide high quality information, describe options and facilitate choice. The FMS must be supportive and non-directive.

After the delivery, a review consultation may occur where all the investigations done before and after the birth are reviewed, including the post mortem in the case of a TOP. The care prior to and during the next pregnancy can then be organized.

During this entire process, the FMS counsels the couple and reports to a multidisciplinary team composed of all the specialities relevant to the care of a fetus with an anomaly: geneticist, neonatal paediatrician, neonatal surgeon, perinatal mental health professional, social workers, etc. The different decisions are always taken according to the will of the parents and in agreement with the multidisciplinary team.

The parents should always be referred together to a Fetal Medicine Unit and it is ideal that both parents attend the consultation. The diagnosis and prognosis of the pathology can have life changing repercussions on the couple and they may not have talked together before of the possibility of being parents to a child with physical or developmental handicap. One or both of the parents may not understand part or the entire discussion. Support from the partner is important and he/she can help his/her partner recall parts of the discussion later. The FMS must recognise that this is happening to both partners, although in cases of disagreement between the couple, the wishes of the pregnant mother will govern subsequent management. In every case, the physician should advise the couple of sources of support open to them. There may be specialist midwives, trained counsellors, charitable support organisations or even perinatal mental health specialists who can help couples through the decision making process and the subsequent grief of a lost pregnancy, lost baby, or loss of the normal child they were expecting to have.

Case 2

A 38-year-old woman is referred following a high risk of trisomy 21 (T21) on her primary screening test. She has no past family or personal medical history and this is her fourth pregnancy. Her first pregnancy was without complication and resulted in the vaginal delivery of a boy three years ago. Since then, she had two first trimester miscarriages. The first trimester USS is normal with a crown-rump length of 62.1 mm and a nuchal translucency of 2.5 mm. The patient chooses to have the combined screening test, which measures the maternal blood level of pregnancy-associated plasma protein-A (PAPP-A) and human chorionic gonadotropin (hCG) and combined the results with the NT measurement and her age related risk. The risk for T21 is calculated as 1 in 80 (high) and for trisomies 13 and 18, 1 in 8000 (low). At the Fetal Medicine Unit (FMU), she discusses her options. The FMS explains to her the result and asks her if she would want to continue with the pregnancy if she knew with certainty that she was expecting a baby with a Down syndrome. The woman and her partner feel that they would opt for termination of pregnancy if T21 were confirmed. She is offered a chorionic villous sampling and the FMS explains the procedure with its risks and benefits (including a 1% risk of miscarriage). Because she had two miscarriages already, the patient does not want to have a CVS. The FMS raises the alternative option of non-invasive prenatal testing (NIPT), only currently available privately at a cost of approximately £400. The patient pursues this option and the NIPT result describes the fetus as low risk for T21 (<1/10,000). The couple is happy with the result and does not want to have an invasive procedure later in the pregnancy. The FMS organises the follow-up with an echocardiography, and an anomaly USS in the FMU for added reassurance. The follow-up is normal and the patient delivers a healthy baby at term.

Non-invasive prenatal testing

Non-invasive prenatal testing (NIPT) takes advantage of the fact that pregnant women have cell free DNA from trophoblast cells (placenta) circulating in their serum, alongside their own cell free DNA. The fetal contribution accounts for up to 10–15% of the total cell-free DNA. This blood test assesses the number of free DNA fragments arising from each chromosome using tertiary DNA sequencing strategies. Both maternal and fetal cell free DNA is assessed, but in a pregnancy trisomic for chromosome 21 there will be proportionally more DNA fragments arising from chromosome 21. This is a screening test, but it carries a much higher sensitivity (>99%), lower false positive rate (<0.1%) and higher positive predictive value (>90%) for Down syndrome than the combined test or the quadruple test. Non-invasive prenatal screening (NIPS) might be a better descriptor. Screening for other common chromosomal abnormalities can also be performed in this way. When the test is positive, the fetus is considered at very high risk for the aneuploidy in question. An invasive test (CVS or amniocentesis) is then necessary in order to confirm the diagnosis. At this stage, the risk of the pathology vastly outweighs the risk of miscarriage.

When the non-invasive screening test is negative, the fetus is considered to be at very low risk for the aneuploidy tested for. However NIPS is not diagnostic and cannot rule out totally the chromosomal abnormality screened for.

In a proportion of cases, the NIPS test is inconclusive. Most commonly this is because the fraction of fetal DNA in the total cell-free DNA is too low. Several factors can influence the fraction of fetal cell-free DNA, including gestation and maternal body mass index (lower levels in obese women) and the test should be repeated. After the test is repeated, it remains inconclusive in approximately 1%.

An ever increasing list of single gene disorders can be diagnosed using related non-invasive prenatal techniques employing mass sequencing. These might better be described as truly non-invasive prenatal tests.

Cytogenetics and molecular biology

Genetic and chromosomal abnormalities can lead to birth defects and developmental anomalies. Karyotyping is the most common investigation in case of suspected fetal anomaly but a large range of other cytogenetic and molecular biology tests are available.

A karyotype is the analysis of the structure and number of chromosomes after staining them with a dye. The staining process (banding) occurs once the cell cycle has been stopped in metaphase, when the chromosomes are at their most condensed. Banding produces the characteristic black-and-white pattern on each chromosome and the chromosomes are studied optically to look for anomalies. The main limitation of karyotyping remains

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