Advances in fetal therapy

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Abstract

The specialty of fetal medicine has benefited from advances in technology in recent years, improving maternal and fetal outcomes. This review considers four case studies to illustrate some of the challenging and complex pregnancies that present to this field of medicine. They demonstrate how evolving research has led to new therapies that are becoming more widely available. Appropriate case selection is a priority; risks and benefits to both mother and fetus require consideration and should be included in patient counselling.

Keywords fetal and neonatal alloimmune thrombocytopenia; fetal endoscopic tracheal occlusion; fetal therapy; intrauterine fetal transfusion; non-invasive prenatal testing; radiofrequency ablation

Introduction

Fetal therapy began over 50 years ago with the first intraperitoneal transfusion for rhesus disease by Liley in 1963. With the introduction of real time ultrasound in 1975, improved prenatal diagnosis has enabled significant progress with both preventative and in-utero treatment.

The development of endoscopic instruments has recently paved the way for direct surgical treatment of specific fetal conditions and the greater understanding of fetal disease processes has allowed the development of medical therapy for others. The following cases illustrate these recent advances in fetal therapy.

Case 1: non-invasive prenatal testing (NIPT)

A 39 year old woman presented for her dating scan in her third pregnancy. Her first pregnancy required an emergency caesarean section at term for fetal distress, delivering a healthy male infant weighing 2.3 KG. In her second pregnancy combined screening gave a low risk of 1/175. However, at the 20 week scan congenital heart disease was diagnosed and an amniocentesis confirmed Down's syndrome. She subsequently underwent a termination of pregnancy at 22 weeks gestation. In this pregnancy her dating ultrasound showed a viable intrauterine singleton pregnancy at 9 weeks gestation. Options were discussed including 1) conservative management 2) combined screening, 3) definitive testing by either chorionic villus sampling or amniocentesis and, 4) non-invasive prenatal testing. The woman opted for combined screening and NIPT. Combined screening gave a low risk for Down's Syndrome (1/860) with a βHCG 0.82 MoM PAPP-A 0.75 MoM and NT 2.2 mm. The results of NIPT are presented in Table 1. The anomaly ultrasound was normal.

NICE recommends that all women should be offered screening for Down's syndrome. In the first trimester, combined screening is the method of choice. This "combines" information from an ultrasound scan, particularly the nuchal translucency, with a blood test which measures beta human chorionic gonadotrophin (βHCG) and pregnancy-associated plasma protein-A (PAPP-A) between 11 and 13 + 6 weeks gestation. The test also takes into account maternal age, crown-rump length and previous history of trisomy to compute a risk of the pregnancy being affected with Down's syndrome. Current national guidance recommends offering all women with a risk of 1/150 or more invasive testing by either amniocentesis or CVS. This approach allows the identification of approximately 85% of pregnancies affected by Down's syndrome for a false positive rate of 3%. For women that book late or miss the opportunity for the combined test, the quadruple test can be offered. This simple blood test is performed between 14 and 20 weeks gestation and measures alpha-fetoprotein (AFP), βHCG, unconjugated estriol and Inhibin A. The quadruple test has a detection rate of approximately 75–80% for a false positive rate of 3%. The widespread adoption of Down's syndrome screening and sequential improvements in this screening have significantly reduced the numbers of invasive procedures over the last decade because women are no longer having invasive testing based purely on their age. This was demonstrated in Denmark where the number of chorionic villus samplings decreased from 3322 in the year 2000 to 2302 in 2006 and amniocentesis procedures were reduced from 4202 to 1208 in the same years. During the same time period, there has been a steady rise in the number of prenatally diagnosed cases of Down's syndrome.

The challenge however, is to continue to improve screening tests such that fewer women who are carrying normal fetuses are misclassified as "high-risk" i.e. screen false positives and offered invasive procedures which put their pregnancy at risk of iatrogenic miscarriage.

A significant step towards this goal has been realised with the development of non-invasive prenatal testing (NIPT). This technology utilises the discovery in 1997 by Lo et al. that significant quantities of cell-free fetal DNA exist in the maternal circulation. It is now possible to detect an over-expression of fetal DNA specific to chromosomes 13, 18 and 21 in the maternal circulation, allowing highly accurate screening for these common trisomies. A recent study in women undergoing routine first trimester screening showed that NIPT risk scores for trisomy

Results of NIPT

Chromosome	Result	Probability
Trisomy 21	Low risk	Less than 1/10,000
Trisomy 18	Low risk	Less than 1/10,000
Trisomy 13	Low risk	Less than 1/10,000
Fetal sex	Female fetus	Greater than 99/100

Table 1

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were able to be calculated in 95.1% of cases with a detection rate of >99% and a false positive rate of <0.1%. Free fetal DNA is cleared from the maternal circulation within a few hours of delivery so that interference from a previous pregnancy does not occur.

A dating scan is required before NIPT, which is generally undertaken from 10 weeks gestation. The failure rate of the test is 4%, and this is more likely to occur in obese women. It is recommended that a positive NIPT result be confirmed with chorionic villus sampling or amniocentesis. NIPT can be used effectively in a monochorionic twin pregnancy, where both fetuses are genetically identical. In dichorionic twin pregnancies the situation is more complex because the fetuses will be either monozygous (identical) or dizygous (non-identical). A negative result would mean both fetuses would be very low risk but a positive result would not allow determination of whether one or both fetuses are affected.

Which pregnancies should have NIPT? Whilst it is a useful tool for screening for the common trisomies, it does not negate some of the benefits of combined screening. A nuchal translucency (NT) of 3.5 mm or greater may be related to multiple fetal abnormalities, not only trisomies. These include major cardiac defects, diaphragmatic hernias, exomphalos and skeletal abnormalities. Major cardiac anomalies have been shown to have a prevalence that is six times higher in a fetus with a nuchal translucency on the 99th centile. A significantly increased NT in the presence of normal chromosomes identifies a sub-group of pregnancies where a detailed assessment of the fetal heart and anatomy should be offered at the mid-trimester anomaly scan. In this subgroup there is also an association with other chromosome and genetic problems such as congenital adrenal hyperplasia, Noonan syndrome and spinal muscular atrophy. Invasive testing by either amniocentesis or CVS may be more appropriate in this group allowing not only full karyotypic assessment but also the opportunity for array CGH analysis to look for more subtle genetic problems. In addition, PAPP-A has also been shown to be of significance in predicting those fetuses at risk of growth restriction. A low level of PAPP-A (<0.415 MoM) is now deemed a major risk factor for delivery of a small for gestational age (SGA) fetus.

NIPT has been of particular importance in managing pregnancies affected by Rhesus disease, the fetal Rhesus D genotype can be determined through maternal serum. This can now be performed routinely to avoid giving unnecessary anti-D to women who are carrying a Rhesus D negative fetus, although this policy has not yet been adopted in the UK The fetal status of other red cell antigens, such as Kell and Rhesus c, can also be determined non-invasively using free fetal DNA studies.

The technique of testing free fetal DNA has wider uses. It may be an opportunity for sex determination to inform management of X-linked disorders. It can also be used to diagnose paternally transmitted autosomal dominant conditions such as Huntington's disease.

The case study illustrates that a "low-risk" combined screening result does not mean "no risk". Despite a risk of 1 in 175 in her second pregnancy, the fetus was subsequently diagnosed with Down's syndrome. The development of non-invasive prenatal testing is likely to be adopted widely over the next few years to improve significantly the detection rate for the common trisomies with a parallel reduction in the number of invasive tests on euploid fetuses.

This will also provide the much needed early reassurance in women who have previously had an affected pregnancy.

Combined screening performed for the ongoing pregnancy was useful, however, because the ultrasound scan findings were normal and the PAPP-A was reassuring given her history of growth restriction in her first pregnancy. The negative NIPT test was reassuring giving a risk of trisomy 21 of <1 in 10,000.

Case 2: management of neonatal alloimmune thrombocytopenia (NAITP)

A 21 year old woman was referred to fetal medicine at 16 weeks into her second ongoing pregnancy. Her first baby was diagnosed postnatally with NAITP after a petechial rash was noted 4 hours after a spontaneous vaginal delivery. The neonatal platelet count was 15×10^9/Litre. Maternal anti-platelet antibodies were found. Cranial ultrasound showed bilateral intraventricular haemorrhages. Paternal testing confirmed homozygosity for HPA-1a, and she was advised that all future pregnancies with her partner would be affected.

IVIg (human immunoglobulin) was started at 16 weeks. The anomaly scan performed at 20 + 4 was normal. The patient was offered fetal blood sampling (FBS) at 28 weeks gestation to assess response to IVIg. She was scanned monthly particularly looking for features of intracranial haemorrhage. The patient underwent an uncomplicated elective caesarean section at 36 weeks gestation after a course of antenatal steroid treatment for fetal lung maturity. The postnatal fetal platelet count was 195×10^9/Litre.

Neonatal alloimmune thrombocytopenia is the most common cause of thrombocytopenia in neonates and is classified as severe if platelets are $<50 \times 10^9$/Litre. 10% of this group will develop intracranial haemorrhage (ICH). It is therefore possible that it is a condition that is under diagnosed.

NAITP is caused by maternal alloantibodies against an HPA antigen. 80% of cases are caused by antibodies against platelet antigen HPA-1a, 15% by HPA-5b and 5% by others. If the father is heterozygous for the particular HPA antigen, there is a 50% chance that the fetus will not be affected (in which case amniocentesis could be offered to determine fetal platelet type). The antibodies are of IgG type and can cross the placenta. Unlike red cell alloimmunisation the fetus can be severely affected in the first pregnancy.

There is no screening programme for the condition and it is most frequently diagnosed postnatally when a neonate presents with a petechial rash or signs of an intracranial haemorrhage (cerebral palsy, seizures and death in up to 1–7%). Identifying pregnancies at risk relies on the history of a previously affected child.

Antenatal treatment of the condition historically has been similar to that of red cell isoimmunisation with intrauterine platelet transfusions. However, puncturing the umbilical cord of a fetus with thrombocytopenia puts it at risk of exsanguination. Also, platelet transfusions are required at least weekly due to their short half-life. The risk of fetal loss per procedure is approximately 1.2% but cumulative risk of serial weekly transfusions is in the region of 6% per pregnancy.