Advances in fetal therapy

Gemma Ulivi [a]

Andrew CG Breeze [b]

Abstract

Fetal Medicine as a specialty has seen great advances over the past few decades. Advances in ultrasound and fetoscopy now allow access to the 'fetal patient' for both diagnostic and therapeutic procedures. While a number of fetal disorders may be amenable to fetal therapy – either direct or indirect – the evidence to support some treatment strategies is limited. Further developments in fetal therapy should aim to reduce maternal and child morbidity, wherever possible by less-invasive means, and with a firm evidence base to support their use.

Keywords congenital abnormality; fetal therapy; growth restriction; monochorionic gestation; multiple pregnancy; prenatal diagnosis; twin twin transfusion syndrome; ultrasound

The fetus as a patient

The idea of fetal therapy requires the fetus to become a patient, which can be ethically challenging and complex. The extent to which fetal therapy is possible is dependent on parental wishes and the interventions that can be offered, which may depend on the local healthcare system and expertise. Some fetal interventions have a limited evidence-base to support their use, and may be sometimes requested by parents (and/or offered by clinicians) despite an absence of evidence of benefit.

Fetal therapy may be considered as any type of therapeutic intervention with the purpose of treating (or preventing) a fetal anomaly or underlying condition. This can be split into non-invasive treatment, which is pharmacological/maternal–fetal therapy; or invasive, more direct (although inevitably involving the maternal patient herself) therapy such as surgical fetal therapy.

Indirect/maternal fetal therapy

Folic acid

The most widely used pharmacological fetal (or embryonic) therapy is the use of folic acid in a dose of 400 μg/day recommended to all pregnant women with the aim of preventing neural tube defects. Those with a previous child affected with a NTD should receive 5 mg/day for 3 months pre-conceptually, and this is expected to reduce the risk of recurrent neural tube defects by about 70%. Other women with significant risk factors (such as some anticonvulsant drugs, maternal diabetes or obesity) may also be advised to take a higher dose. More recently, there has been interest in the use of inositol as additional prophylaxis for women who have had a previous pregnancy complicated by a neural tube defect. The pilot PONTI (Prevention of Neural Tube defects with Inositol) study showed no recurrences in the women randomized to inositol 1 g daily as well as high dose folic acid; however, the study was underpowered to draw any conclusions about this. While a larger randomized trial should be ideally performed to clarify the value (or any unexpected harms) of inositol, women may be reluctant to be randomized (and potentially allocated to a placebo arm) in any future trials.

Corticosteroids

The use of maternal corticosteroids from 24 + 0 to 33 + 6 weeks' gestation in women with preterm or suspected preterm labour has been demonstrated to improve perinatal outcomes and also appears to improve longer term neurodevelopmental outcomes. Women are usually given 24 mg of betamethasone or dexamethasone in 2 divided doses over 24 hours by intra-muscular injection. While there are fewer data available, steroids administered before birth at gestational ages <24 weeks may confer some survival benefit.

Magnesium sulphate

Intravenous magnesium sulphate has been shown to confer neuroprotection to the newborn at risk of preterm delivery. NICE guidelines recommend that this is offered to women between 24 + 0 and 29 + 6 weeks of pregnancy and should be considered in those up to 33 + 6 weeks.

Sildenafil

There has been interest in the use of sildenafil citrate as maternal–fetal therapy for severe early onset growth restriction, with an anticipated poor prognosis. The results from the UK arm of the multinational STRIDER study (Sildenafil Therapy in Dismal Prognosis Early-onset intrauterine growth restriction) however showed no evidence of benefit for prolonging pregnancy, nor for improving birthweights nor for reducing the risk of perinatal death. At present, the only treatment to improve outcomes for severe growth restriction appears to be appropriate timing of delivery.

Fetal arrhythmias

Fetal arrhythmias are discovered in about 1% of fetuses and can be associated with significant morbidity and mortality. The aim of fetal therapy is to restore a normal fetal rhythm when possible (without unacceptable side effects) and/or to prolong the pregnancy until delivery and/or *ex utero* therapy has a realistic prospect of a good outcome.

Ectopic beats

The commonest form of fetal arrhythmia arises due to ectopic beats. Ectopic beats are normally atrial in origin and are most common in the second trimester until term, but if very frequent they can produce a slow heart rate that may mimic heart block. While most are usually benign, there may be a small chance (approximately 2%) of tachyarrhythmia, which may require

***Gemma Ulivi**, BSc MB ChB MRCOG is a Subspecialty Trainee in Maternal and Fetal Medicine at Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Leeds, UK. Conflicts of interest: none declared.*

***Andrew C.G. Breeze**, MA MD MRCOG is a Consultant in Obstetrics and Fetomaternal Medicine at Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Leeds, LS1 3EX, UK. Conflicts of interest: none declared.*

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treatment. Otherwise, no treatment is indicated but the heart should be assessed to check for other cardiac problems. Because of the small risk of associated tachyarrhythmia, weekly FH assessment is recommended. Very frequent ectopics may present difficulty performing adequate fetal monitoring in labour.

Tachyarrhythmia

Tachyarrhythmias are defined as sustained fetal heart rates more than 180 beats per minute (bpm). These are sinus tachycardia, SVT, atrial flutter and ventricular tachycardia.

Sinus tachycardia: may rarely present with fetal heart rates of 180–200 bpm. This may be in the setting of maternal pyrexia, certain medications, maternal thyrotoxicosis or fetal systemic disease such as anaemia, fetal compromise and occasionally infections.

Atrial flutter: accounts for approximately 20% of fetal tachycardia and may be associated with structural abnormalities and the development of fetal hydrops.

AF is defined as an atrial rate from 250 to 500 bpm with either fixed or variable atrioventricular (AV) block, with the atrial rate typically much faster than the ventricular rate. Medical management in cases without hydrops may consist simply of digoxin therapy, with second-line agents such as flecainide or sotalol sometimes being required.

SVT: accounts for almost half of all cases of fetal tachycardia and is uncommonly associated with structural abnormalities. The most common SVT is an AV re-entrant tachycardia (AVRT) with a re-entry circuit between the atrium and the ventricle. SVT may be continuous or paroxysmal and is often associated with fetal hydrops. Medical management varies from centre to centre, but typically involves maternal administration of digoxin, flecainide or sotalol. In the presence of fetal hydrops, digoxin is rarely effective. Rarely, direct fetal therapy may be considered, by intrafetal administration of adenosine to attempt cardioversion. This may be considered after unsuccessful maternal therapy, and/or when delivery is likely to result in a poor outcome.

Intrauterine transfusion

Alloimmunisation is an immune-mediated process that is caused by maternal antibodies that cross the placenta and target fetal red blood cell antigens. This causes haemolysis and fetal anaemia. Fetal anaemia in pregnancy is serious and can be associated with fetal demise.

Indications for fetal intrauterine transfusion are fetal anaemia and thrombocytopaenia, although the latter is rarely performed now due to the introduction of intravenous immunoglobulin therapy. The majority of fetal transfusions used to be performed for fetal anaemia caused by rhesus-D antibodies but this has shifted to a diversity of other antibodies, and anaemia due to parvovirus infection.

Hydropic fetuses, those at risk of fetal anaemia following parvovirus infection or secondary to the presence of maternal red blood cell antibodies, should be managed within a tertiary fetal medicine unit. Serial sonography, typically at 1–2 weekly intervals to monitor middle cerebral artery Doppler peak-systolic velocities, may be performed from 16 weeks, or when antibody levels reach a threshold at which the risk of fetal anaemia becomes significant. This determines when an intrauterine transfusion is likely to be required due to MCA PSV above the treatment line (1.5 Multiples of the Median). The procedure involves injecting packed red cells into the umbilical vein (either intrahepatic or at the placental cord insertion) via ultrasound guidance. Before around 20 weeks' gestation, this may be technically very challenging, and occasionally intraperitoneal or even intracardiac transfusion may be required to sustain the fetus before access to the fetal vasculature can more easily be achieved.

Thrombocytopaenia

Fetomaternal alloimmune thrombocytopaenia (FMAIT, or in the neonate 'NAIT') is relatively uncommon but can be associated with severe morbidity and mortality. It is the leading cause of severe thrombocytopaenia in the newborn. It results from the placental transfer of maternal immunoglobulin (IgG) antibodies against fetal platelet antigens inherited from the father. Over twenty human platelet-specific alloantigens (HPAs) have been described. In white populations, the most common antibody is anti-HPA-1a. The second most common antibody is anti-HPA-5b.

Most cases are mild with evidence of widespread petechiae and other skin lesions. However, severe cases can cause intracranial haemorrhage resulting in long term disability or even fetal death. It may develop during first pregnancies, with a high recurrence rate and often with progressively severe manifestations in subsequent pregnancies.

At present, there is no definite maternal marker that predicts the severity of NAIT. The history of a previously affected child, especially if that child developed intracranial haemorrhage, is the strongest predictor of recurrence and severity of NAIT in future pregnancies.

Using cell-free DNA for non-invasive fetal HPA-1a genotyping for those individuals at risk has been described in the literature but is not currently in widespread clinical use.

The antenatal management of NAIT remains controversial, and currently involves 3 treatment options: maternal intravenous immunoglobulins (IVIG), either alone or in combination with maternal steroid administration, or serial platelet transfusions (IUPT).

First line treatment is IVIG (~1 g/kg body weight) to the mother at weekly intervals starting at around 20 weeks' gestation, depending on the previous history. Delivery by caesarean section is often recommended due to the anticipated risk of haemorrhage however, normal vaginal delivery can be considered in parous woman with a favourable cervix.

Pleural effusions

Pleural effusions are collections of fluid within the pleural space; they may be unilateral or bilateral but the former is more common, with an incidence of approximately 1 in 10,000 pregnancies. The aetiology of pleural effusions is unknown in most cases. However possible causes include congenital chylothorax, goitre, lung tumours, chromosomal or genetic disorders, and infection. The risk of perinatal mortality is related to the development of hydrops, prematurity and pulmonary hypoplasia.

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