Advancing Fetal Therapy in the UK

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Abstract

Fetal therapy is a rapidly advancing sub-specialty, encompassing direct fetal treatment or the administration of substances to the mother to achieve fetal benefit. The goal of all fetal therapies is to improve the prognosis for a condition where there is evidence of pathology developing in utero. In this article we briefly examine all major types of fetal therapy and their current evidence.

Key words

Fetal therapy

Prenatal therapy

Fetal surgery

Fetoscopy

Introduction

In the last 30 years there have been rapid advancements in fetal diagnosis, due to both improvements in ultrasound technology and genetic analysis. In conditions which are lethal or progressive, prenatal diagnosis can lead to therapeutic options whilst still in-utero. Prenatal diagnosis can also facilitate patient choice as to whether to continue a pregnancy enabling postnatal preparedness, or to end the pregnancy if this is the parent's wishes. For many conditions, treatment options remain limited. This article will examine fetal therapies currently available, and some which are still experimental.

Medical Therapies

Many substances can be delivered to the fetus either directly or via the mother; we will explore some examples further below.

Vitamins and amino acids

It has been argued that several inborn errors of metabolism, which result in low levels of proteins or essential vitamins and/or accumulation of toxic waste products, already have an effect in-utero and may benefit from maternal supplementation.

- Maternal vitamin B12 has been given in cases of fetal methylmalonic acidaemia (MMA) and inherited cobalamin deficiency with reported success.
- Maternal vitamin B7 (biotin) has been given in cases of fetal multiple carboxylase synthetase deficiency.
- Maternal L-serine has been used to treat 3-Phosphoglycerate-dehydrogenase deficiency with reported success.

Antibodies

- Maternal Intravenous Immunoglobulin (IVIg) is used first line to prevent fetal alloimmune thrombocytopenia in women with platelet antibodies based on positive results from case series.
- Maternal Intravenous Immunoglobulin (IVIg) is used in cases of severe maternal red cell antibody isoimmunisation to delay the gestation at which in-utero transfusions become necessary.
- Maternal administration of IVIg in congenital fetal heart block has been tried with conflicting reports of success.

- A trial of an maternal IgG antibody, M281, for pregnancies at high risk for early-onset severe haemolytic disease of the fetus and newborn is currently underway.

Hormones

- Primary fetal hypothyroidism has been treated by administration of intra-amniotic cavity thyroxine in over 50 cases with reported success, although in one case report fetal death occurred.

Medications

- Anti-arrhythmic medications such as digoxin, verapamil and amiodarone have been used both by maternal oral and intravascular and fetal intramuscular administration in cases of sustained fetal tachycardia with cardiac failure with reported success.
- Maternal corticosteroids to treat conditions such as congenital heart block, fetal alloimmune thrombocytopenia and congenital adrenal hyperplasia have been administered with reports of success, although substantial doubt remains regarding their efficacy in these situations and treatment should probably be restricted to formal clinical trials.

Blood products

- Transfusion of red blood cells into the fetal vascular system is routine practice in cases of severe fetal anaemia, most commonly due to alloimmune haemolytic disease and secondary to fetal parvovirus infection. There are recent reports of fetal blood transfusion for alpha major thalassaemia, feto-

maternal haemorrhage and anaemia secondary to problems with monochorionic twin placentation.

- Fetal alloimmune thrombocytopenia has been treated by in-utero platelet transfusions. However, in most cases fetal transfusion can be avoided by maternal IVIg and/or corticosteroids.

Stem cells

The fetus is relatively immunologically immature and stem cell transplantation before birth may potentially avoid complications of postnatal transplantation such as rejection, and establish tolerance making postnatal treatment easier.

- Cases of haematopoietic stem cell (HSC) transplantation for severe combined immunodeficiency (SCID) have reportedly been successful.
- Cases of HSC transplantation for haemoglobinopathies via injection into the fetal peritoneum or vascular system have been reported. Safety has been shown but engraftment levels of transplanted cells have been low or negative.
- Combination of fetal blood transfusion with maternal bone marrow-derived HSCs for alpha-thalassaemia major is being performed for the first time in humans as part of a clinical trial.
- First trimester fetal liver-derived mesenchymal stem cells have been transplanted into the umbilical vein of fetuses with severe osteogenesis imperfecta (OI) with reported success in several cases. This is now undergoing evaluation in a multicentre European clinical trial (BOOSTB4).

Gene therapy

Gene medicines such as viral vectors or gene editing could be applied to the fetus to correct severe life-threatening congenital disease. The potential for fetal gene therapy has been demonstrated in animals models where conditions such as liver disorders, haemophilias and haemoglobinopathies have been ameliorated. Concerns using fetal gene medicine include the effects on the developing immune system, germ line transmission and oncogenesis.

Surgical Therapies

Procedures may be performed on the fetal environment or the fetus itself, by ultrasound guidance or in a fetoscopic or open manner. We will explore some examples further below.

Placenta

The Eurofoetus randomised trial of fetoscopic laser coagulation of chorionic vessels vs. amniodrainage in cases of twin-to-twin transfusion syndrome (TTTS) showed an increased survival and later gestational age at delivery in the laser group, which is now the recommended treatment for significant TTTS.

Umbilical cord

Fetal reduction is most commonly performed in cases of discordant anomalies; it may also be performed to reduce higher-order pregnancies to improve potential outcomes. In multiple pregnancies that share a placental circulation, fetal reduction cannot be performed using drugs such as intracardiac potassium chloride due to the risk of

transplacental passage. Destruction of the umbilical cord, via bipolar cord coagulation, radiofrequency ablation, laser photocoagulation or physical techniques such as cord ligation, must be performed instead. These techniques are now commonplace in tertiary fetal medicine units, with multiple case series showing success of the treatment with minimal morbidity to the remaining fetus(es) and mother.

Amniotic fluid

- Amnioreduction may be offered in polyhydramnios of any cause, including TTTS, for maternal improve maternal comfort and reduce the risk of preterm birth (PTB).
- Amnioinfusion for oligo or anhydramnios has not been shown to improve outcomes either with intact membranes or in cases of preterm rupture of membranes (PROM).
- Amnioexchange has recently been shown not to improve outcomes in cases of fetal gastroschisis.

Membranes

Therapies attempting to promote healing of the fetal membranes (e.g. in the scenario of PROM) have so far been unsuccessful. Recently a molecular mechanism for the failure of membrane healing has been identified involving the protein connexin 43, leading to a potential for future therapeutic intervention.

Ultrasound-guided fetal procedures

Balloon valvuloplasty in fetuses with severe aortic stenosis has been described in over 200 cases with reported benefits regarding left ventricular development.

Shunts

In the fetus a shunt may be inserted fetoscopically or under ultrasound-guidance.

- Bladder shunts: the PLUTO trial of vesicoamniotic shunting in cases of lower urinary tract obstruction was compromised by low recruitment, but suggested a higher survival in shunted cases.
- Thoracic shunts may be placed in cases of congenital cystic adenomatoid malformation, although maternal steroids are more commonly used in this scenario. Thoracic shunts have also been placed in cases of pleural effusion and chylothorax with mixed results.
- Ventricular shunts: a case series of ventriculoperitoneal shunts in cases of fetal hydrocephalus showed a high level of shunt migration with unclear benefits.
- Peritoneal shunts: case reports of shunts to drain ascites in selected cases of fetal hydrops appear to have good results although this treatment is not offered as standard of care.

Fetoscopic fetal surgery

- Congenital diaphragmatic hernia (CDH): fetoscopic endoluminal tracheal occlusion (FETO) involves the placement of an occlusive balloon into the fetal trachea under fetoscopic vision. Cohort studies have suggested an improvement in survival in cases of severe CDH; FETO for both moderate and severe CDH is currently being investigated in a randomised trial (TOTAL trial).
- Myelomeningocele (MMC, open spina bifida): fetoscopic repair of MMC is currently performed using a variety of techniques internationally. A systematic review found it to be comparable to open fetal repair in some respects but also

to have a higher rate of PROM and increased need for additional surgery. This procedure is still evolving and individual centres are reporting promising results.

Open fetal surgery

- MMC: the MOMS randomised trial published in 2011 showed that open repair of MMC in pregnancy, by maternal laparotomy and hysterotomy, improved ventriculoperitoneal shunt rate, hindbrain herniation and independent ambulation in the neonate and child. It was associated with risks to the fetus (the largest being prematurity) and mother.
- Sacrococcygeal teratomas (SCT), although predominantly benign, can grow exceptionally large and in severe cases lead to high-output cardiac failure. Prenatal open resection has been described in a small number of cases and seems to improve survival, although complication rates are high. Recent data suggests that when hydrops develops, early delivery may be more beneficial than fetal surgery.

Discussion

In this article we have briefly highlighted current and experimental fetal interventions. The list of therapies mentioned is by no means exhaustive and many others exist. A number of ethical and logistical issues are pertinent in the field of fetal therapy. One of the main concerns is the balance of maternal risks with potential fetal benefits. Maternal risks will vary with different therapies but particularly in surgical fetal therapies, they may be significant and impact her future reproductive life. Maternal long term follow up data after fetal interventions is often lacking, which limits patient counselling. Some ethical discussions have viewed the fetus as a patient in its own right, with concerns about the potential conflict which that view may have on maternal autonomy. Evidence from randomised trials may be challenging to obtain in fetal therapy due to the rarity of conditions and difficulties in standardizing interventions. In addition, experimental treatment is usually only considered when the fetus is in extremis, which may lead to bias when positive outcomes are reported. The support of the fetal surgery community was key to the success of the MOMS trial, in which a nation-wide moratorium was honoured during trial recruitment that limited fetal repair to randomization between prenatal surgery or expectant management with postnatal repair at three study centres. As prenatal diagnostic capabilities increase, we anticipate that interest in fetal therapies will escalate; practice should develop in a responsible way with careful follow up of maternal outcomes and sharing of standardized outcome data sets through registries.

Practice Points

- Common maternal medical therapies used to treat the fetus include IVIg in fetal alloimmune thrombocytopenia and corticosteroids in congenital heart block and congenital adrenal hyperplasia.
- Fetal blood transfusion is standard practice in severe fetal anaemia.
- Fetoscopic placental laser photocoagulation and cord occlusion is commonplace for the treatment of monochorionic twin pregnancy complications.
- Open repair of fetal MMC is available in many countries.
- Most other therapies are currently not widely available or are experimental, with several clinical trials ongoing.

Suggested reading

RCOG Green Top Guideline No. 65: The Management of Women With Red Cell Antibodies During Pregnancy 2014

RCOG Scientific Impact Paper No. 61: Prenatal Management of Pregnancies at Risk of Fetal Neonatal Alloimmune Thrombocytopenia 2019

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