Review Advances in fetal therapy

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Key content:

- Fetal medicine is a rapidly developing subspecialty.
- The mainstay of treatment for fetal alloimmune thrombocytopenia remains maternal immunoglobulin therapy.
- Stem cell transplantation and gene therapy have advanced over the last decade but must still be considered experimental.
- Laser coagulation is the best treatment for all stages of twin-to-twin transfusion syndrome presenting before 26 weeks of gestation.
- Fetoscopic endoluminal tracheal occlusion appears to improve prognosis in severe congenital diaphragmatic hernia.

Learning objectives:

- To gain an overview of the recent developments in fetal therapy.
- To understand the benefits and risks of different methods of fetal therapy.
- To appreciate the importance of high-quality research in fetal medicine.

Ethical issues:

- With the option of fetal therapy, the value and implications of prenatal diagnosis have to be reviewed.
- The acceptability of fetal therapy to parents and to society should be investigated.
- The consideration of the mother and fetus as individual people presents an inherent difficulty in implementing randomised controlled trials in fetal medicine.

Keywords congenital diaphragmatic hernia / fetal alloimmune thrombocytopenia / gene therapy / lower urinary tract obstruction / stem cell transplantation / twin-to-twin transfusion syndrome

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Background

There has been rapid development in the field of fetal medicine over the last three decades. This development has been driven by improvements in fetal imaging technologies. Better resolution of two-dimensional ultrasound, three-dimensional ultrasonography and magnetic resonance imaging (MRI) has allowed more accurate and earlier prenatal diagnosis. Advances in therapeutic techniques (ultrasound-guided needle therapy, fetal endoscopy and pharmacotherapy) and improved management of the possible complications of treatment *in utero* (e.g. preventing preterm labour, neonatal care) have allowed fetal therapy to be offered to parents or guardians of affected offspring in certain conditions.

Treatment of the unborn baby may be of immediate benefit or may reduce associated postnatal complications, but there may be risks to both mother and fetus. Animal models have provided clinicians with a better understanding of the aetiology and natural history of fetal disease. There has also been a move towards evidence-based medicine in our subspecialty in the last 5 years, with the efficacy and safety of interventions being investigated by randomised controlled trials and critical appraisal of the evidence in systematic reviews. Clinicians are thus better able to counsel parents about the benefits and risks of therapies and provide accurate prognosis. Despite these advances, there is still a need for research into diagnostic and prognostic indicators for disease and for robust, critical appraisal of the safety, efficacy and long-term outcome of the majority of interventions.

In this article we consider the recent advances in and controversies about fetal therapeutic interventions, including medical treatments and surgical interventions for placental disease and structural abnormalities.

Medical therapy

Fetal thrombocytopenia: alloimmune disease

Fetal thrombocytopenia is a major cause of severe platelet deficiency and intracranial haemorrhage among fetuses and the newborn.[1,2] The overall incidence of neonatal thrombocytopenia of $<150 \times 10^9$/l is 1–4%, with immunological thrombocytopenia specifically having a much lower incidence of 0.3%.[2] The most important types among these immune-mediated thrombocytopenias are fetal alloimmune thrombocytopenia (FAIT) and idiopathic thrombocytopenic purpura. The latter is often associated with a maternal history of autoimmune disorder, such as systemic lupus erythematosus, and usually results in a mild deficiency of fetal platelets and seldom requires treatment.[3] FAIT can lead to more serious consequences, mainly intracranial haemorrhage with associated neurological morbidity and 7% mortality.[4] FAIT is analogous to rhesus isoimmunisation with maternal immunoglobulin alloantibodies directed against human platelet antigens (HPAs) on fetal platelets. FAIT affects the first pregnancy in >50% of cases,[5] the condition being suspected following diagnosis of intracranial haemorrhage either antenatally or after delivery. The diagnosis is confirmed by thrombocytopenia in the fetal/neonatal circulation and parental genotyping of HPA antigens.

The prenatal management of FAIT is controversial; the goal is to identify any fetus at risk and prevent the sequelae of severe thrombocytopenia. Most countries do not have a screening programme for this as they do for rhesus disease. Studies have shown that the natural history of HPA-1a alloimmunisation among HPA-1a-negative women is for 1 in 350 pregnancies to be affected[6] and that implementation of a screening and intervention programme can reduce the number of cases with severe FAIT complications.[7] However, research in health economics has highlighted a lower frequency of serious bleeding complications than first suspected[8] and has shown that screening neonatally may be more cost effective.[9] Thus, at-risk women are usually identified after a previous affected pregnancy. The severity of risk is determined by the history of the previously affected child, platelet count and associated morbidity; monitoring anti-HPA antibodies has been shown to be an inaccurate prognostic measure.[10]

Traditionally, management of pregnancies affected by FAIT involved early elective caesarean section and platelet transfusion for the baby. However, with the development of fetal blood sampling and intrauterine transfusion of platelets, treatment can delay the need for delivery. The high complication rate of this invasive treatment (up to 6% fetal loss)[11] led to the development and introduction in the early 1980s of maternal therapy with corticosteroids (dexamethasone). Subsequent studies have demonstrated low effectiveness; potential long-term adverse effects for both mother and fetus limit the use of steroid treatment.[12] Maternal therapy was developed further with the repeated administration of intravenous immunoglobulin potentially to inhibit the immunologically mediated mechanism of fetal platelet destruction (although the exact mechanism has not been elucidated). The dosage of intravenous immunoglobulin at 1 g/kg/week has been commonly prescribed since the first publication of its use in 1988,[13] but the scientific rationale for

this dosage is weak. Reported response rates vary from 30–85%[11] and long-term effects on mother and child remain unclear. An international multicentre study is currently investigating the optimal dose of intravenous immunoglobulin treatment (see **Websites**). Despite concerns regarding efficacy and adverse effects, administration of maternal intravenous immunoglobulin will be the mainstay of management until there is high-quality evidence that fetal blood sampling and intrauterine transfusion of platelets improve outcome.

Decisions regarding mode of delivery should be based on previous pregnancy history and fetal platelet count if known. Where the history is of a sibling affected by intracranial haemorrhage due to FAIT, elective delivery at 36 weeks of gestation by caesarean section is advocated unless the fetal platelet count is known. Vaginal delivery has been advised in pregnancies where a sibling had a low platelet count but no complications or if the fetal platelet count in the current pregnancy is known to be $>50 \times 10^9$/l.[14]

The best management strategy for this condition is still undecided. In the future, screening for the HPA status of pregnant women may be advocated if shown to be cost effective. Developments in the analysis of free fetal DNA in maternal plasma are expected to allow reliable assessment of fetal HPA status. If a non-invasive method can be found to assess the fetal platelet count, or if a new laboratory measure can be developed to improve the predictive accuracy of antibody status, then the management of FAIT could be greatly improved.

Stem cell transplantation

Advances in prenatal diagnosis of single gene disorders have led to the possibility that many genetic diseases could be diagnosed in early pregnancy and treated before delivery. The human fetus early in gestation has a unique biology, affording it advantages as a donor recipient. It has a unique tolerance to foreign antigens and the ability to transport large cell volumes, leading to the assumption that it could be an ideal candidate for stem cell transplantation.[15] Mouse[16] and lamb[17] models have added support to this assumption. However, successful intrauterine haematopoietic stem cell transplants have only been achieved in the immunodeficient fetus, suggesting that there may still be an immunological barrier. Studies have shown an allogenic response from 9–12 weeks of gestation, the magnitude of response increasing with gestational age,[18] adding weight to the theory that failure in the non-immunodeficient fetus may be due to graft-versus-host reaction as reported in animal models.[19] Human leukocyte antigen compatibility may thus be important in the success of fetal stem cell transplantation. Fetal immunosuppression has been achieved in the non-human primate model and could possibly be accomplished in the human with the use of corticosteroids or antibody mediation.

Intrauterine human stem cell transplantation has been performed for haemoglobinopathies, immunodeficiencies, storage diseases and osteogenesis imperfecta, but experience is still limited (**Box 1**). Tiblad and Westgren[20] reviewed the reported cases and found that the timing of intervention, source of donor cells and target disease varied significantly. They reviewed 46 cases of transplantation; the only successes were among eight children with immunodeficiencies with engraftment, several of the children having a benign clinical course. However, the advantages of intrauterine transplantation are that this procedure is less expensive and the recipient does not require chemo- or radiotherapy.

It must be concluded that stem cell transplantation shows promise but is still experimental. To improve success rates, more research is needed into fetal immunological function and modification of the fetal recipient immune response.

Gene therapy

Many of the theoretical advantages of stem cell transplantation in the fetus can be applied to gene therapy, where genetic material is delivered directly into the cell by a vector (viral or non-viral). The immature response of the fetal immune system is an advantage when using viral vectors and smaller numbers are required to produce the same response; there is also a lack of immune reaction to the product of the gene introduced. The therapeutic effects of gene therapy are to correct an existing genetic abnormality and provide the cells with a new function. For example, among individuals with haemophilia the targeted cells are able to produce the previously deficient clotting factor. Thus the advantages of gene therapy are not only that it may offer a cure for certain diseases but

Box 1
Summary of diseases where fetal stem cell transplantation has been performed. (Adapted from Tiblad *et al.*[20] Copyright 2008, with permission from Elsevier)

Haemoglobinopathies	Immunodeficiencies	Storage diseases	Skeletal disorders
α-thalassemia	Bare lymphocyte syndrome	Globoid cell leukodystrophy	Osteogenesis imperfecta
β-thalassemia	Severe combined immunodeficiency	Hurler syndrome	
Sickle cell anaemia	X-linked severe combined immunodeficiency	Niemann–Pick disease	
Rhesus isoimmunisation	Chronic granulomatous disease	Metachromatic leukodystrophy	
	Chédiack-Higashi Omenn syndrome		

also that it may prevent the irreversible damage to organs that can occur before or shortly after birth in early-onset genetic diseases. This would be particularly helpful when the organs at risk are inaccessible after birth.

Fetal gene therapy has been advocated in those diseases that are life-threatening with no available satisfactory treatments (e.g. urea cycle defects) and in which prenatal therapy would offer a clear advantage over cell transplantation or postnatal gene therapy[21] (e.g. in cystic fibrosis where lung damage occurs before birth). Correction of the affecting condition has been demonstrated in mouse models for haemophilia A and B, congenital blindness, Crigler Najjar type I syndrome and glycogen storage disease type II. Animal models, such as the fetal lamb, have been used to develop methods of intrauterine delivery of vectors using minimally invasive ultrasound-guided techniques targeting the peritoneum, liver, diaphragm, muscle, trachea and cerebral ventricles. Maternal mortality rates for the pregnant sheep are reported as negligible, with rates for the fetal lamb between 3–15%.[22] The ideal stages of gestation at which therapy should be instituted for the different application routes are yet to be defined.

The risks of fetal gene therapy still require full clarification: in theory the gene product or vector could interfere with normal fetal development, or germ-line transmission could occur, so long-term studies are needed to determine these risks. Risk factors already shown to be associated with the use of viral vectors are: insertional mutagenesis (where the vector inserts the new gene adjacent to a potential oncogene, thus switching it on, with the possibility of tumour formation); vector toxicity; effects on the fetal immune response; and, as already discussed, maternal and fetal morbidity and mortality.

Again, as with stem cell transplantation, any fetal gene therapy would need to be safe, reliable and effective at treating the disease in question[23] before it could offer the parents a realistic alternative to either termination or acceptance of an affected child. Development of improved vectors and vector administration, and research into the optimal gestational ages for gene therapy, will help the progression of this experimental treatment into clinical practice. To determine the cases that might benefit from this type of therapy, an effective and comprehensive screening policy for genetic disease would need to be introduced.

Placental disease

Twin-to-twin transfusion syndrome

Twin-to-twin transfusion syndrome (TTTS) is a morbid condition complicating 10–15% of all (predominantly twin) monochorionic pregnancies and is associated with multiple placental vascular anastomoses between the fetal circulations. Twin-to-twin transfusion syndrome is defined by the combined presence of polyhydramnios in the sac of the donor twin and oligohydramnios in the sac of the recipient twin of a monochorionic diamniotic pregnancy.[24] The Quintero staging system[25] has been used (**Table 1**) over the last 10 years, but the natural clinical course remains variable. Different pathophysiological mechanisms have been suggested for different stages of the condition, including fetal myocardial dysfunction in the recipient and co-existent placental insufficiency in the donor, in addition to unilateral net blood flow from donor to recipient twin.[26] Without treatment, TTTS is associated with an 80–100% mortality rate and a 15–50% risk of disability among survivors.[27]

Early stages of TTTS (I and II) have previously been managed conservatively with close monitoring by ultrasound, but even monitored cases can be associated with early cardiac dysfunction and can progress unpredictably to end-stage disease.[26] In view of the rarity of TTTS among monoamniotic twins, septostomy over the intervening fetal membranes was advocated as a treatment option in the past, but the efficacy of this has been described as poor.[28] For severe TTTS, fetoscopic laser ablation of vascular anastomoses has been shown to be a more effective option than amnioreduction.[29] A recent Cochrane systematic review[28] of the literature indicated a trend towards improved survival in stage I/II disease, although the majority of fetuses randomised in the reported controlled trial had Quintero stage II–III disease. The overall survival after laser therapy is 60–70%, with at least one fetus surviving among 75–80% of cases presenting before 26 weeks of gestation, but this depends on the stage of the disease at the time of therapy. The risk of severe handicap among survivors of laser therapy is <5%[30] and there is an increased chance of the babies still being alive

Stage	Liquor volume abnormal[a]	Bladder absent in donor	Abnormal Doppler[b]	Hydrops	Demise of either twin
I	+	–	–	–	–
II	+	+	–	–	–
III	+	+	+	–	–
IV	+	+	+	+	–
V	+	+	+	+	+

[a] Polyhydramnios: maximum vertical pool >8 cm; oligohydramnios: maximum vertical pool <2 cm
[b] Presence of at least one of the following: umbilical artery absent or reversed end-diastolic flow; reverse flow in ductus venosus; pulsatile umbilical venous flow

Table 1
Quintero staging of twin-to-twin transfusion syndrome based on ultrasound and Doppler findings.[25] Reprinted by permission from Macmillan Publishers Ltd

with no neurological abnormality at the age of 6 months, as compared with the results of amnioreduction (RR 1.66, 95% CI 1.17–2.35).[28] However, this effect was not seen to persist beyond 6 months of age. Laser therapy carries small risks of preterm prelabour ruptured membranes (5%) and intra-amniotic haemorrhage (<1%). Patching of membranes with platelets and cryoprecipitate[31] has been used following fetoscopy and, more recently, patching with platelet-rich plasma *in vitro*;[32] these techniques may reduce the morbidity and mortality associated with preterm prelabour rupture of the membranes in the future.

For amnioreduction, the overall long-term survival rate is similar but the handicap rate among survivors is significantly higher, at up to 25%. A recent study[33] showed a less satisfactory survival rate for laser therapy following one amnioreduction compared with serial amnioreduction. This may reflect the difficulty of performing laser ablation following amnioreduction, due to membrane complications and bleeding into the amniotic cavity, and the disadvantage of amnioreduction in allowing progression of myocardial dysfunction in the recipient twin.[26]

Selective feticide has been used in severe TTTS (stage IV disease), in an attempt to save one twin when the outcome for the other has appeared hopeless and delivery was not an option. Techniques to achieve feticide must be adapted to the presence of a communicating circulation between the twins and thus fetoscopic laser coagulation[34] and, at later gestational ages, ultrasound-guided bipolar cord coagulation,[35] are preferred. The maximum survival rate for the pregnancy is, obviously, 50%, with a 70–80% rate of intact survival for the co-twin; preterm prelabour rupture of the membranes and its associated complications remain a significant risk.[36]

The last decade has seen rapid developments in the management of TTTS, with sufficient evidence to recommend laser therapy as the treatment of choice for severe disease. Further randomised controlled trials are needed to assess fully the role of fetoscopic laser ablation in stage I disease and in relatively late onset disease. Long-term morbidity remains a concern for babies treated by laser ablation and follow-up of survivors of all disease stages is mandatory. In the future, advances in the knowledge of the pathophysiology of the disease, developments in first-trimester markers and mapping of the vascular tree of the placenta with newer imaging techniques and contrast agents will help improve the management and survival rates still further.

Placental chorioangioma

This is a benign vascular tumour of the placenta arising from the primitive chorionic mesenchyme. Aetiology of these tumours is unknown and incidence varies from 1 in 3500–9000 pregnancies.[37] Diagnosis may be made antenatally when a large hyperechoic mass is seen within the placenta, with colour Doppler helping to differentiate the tumour.[38] Risks to the fetus include fetal anaemia and resultant hydrops; maternal risks include polyhydramnios and preterm delivery. Complications do not usually occur when the diameter of the tumour is <6 cm.

A number of interventions have been tried in the past to treat the tumour, with varying success. These include: laser therapy;[39] intrauterine endoscopic devascularisation with suture ligation and bipolar cautery;[37] microcoil embolisation;[40] and alcohol injection.[41] Management involves monitoring of the pregnancy, surveillance of the fetus for anaemia with middle cerebral artery Doppler ultrasound and treatment with intrauterine transfusion if necessary.

Structural abnormalities

Congenital diaphragmatic hernia

This potentially lethal condition has an incidence of 1 in 2500–5000 and is usually a sporadic phenomenon: <2% of cases are familial. There is an association with certain chromosomal abnormalities and genetic disorders, such as Pallister Killian syndrome (tetrasomy 12p, mosaic). Diagnosis is made with ultrasound, the diaphragm being easily visualised with high-resolution equipment during the first trimester; if it is absent, abdominal organs will be seen in the thorax. It is important to exclude other associated anomalies, which occur in approximately 40% of cases: in this group <15% will survive. For isolated congenital diaphragmatic hernia the prognosis depends on the canalicular development of fetal lung and may be made by, for example, the position of fetal liver (supra- or infradiaphragmatic) or the lung:head dimension ratio. The best predictive method is still to be defined, although a combination of these indices shows promise in predicting severe pulmonary hypoplasia.[42] Left-sided diaphragmatic hernias are more common than right-sided lesions (84% versus 13%) and classically are associated with better postnatal outcome. For pregnancies with good prognostic features (including infradiaphragmatic liver position and lung:head ratio >1.0), expectant management and regular monitoring by ultrasound is recommended. Transferral to a centre with appropriate neonatal and paediatric surgical support for delivery can optimise the immediate postnatal management.

For pregnancies complicated by congenital diaphragmatic hernia with poor prognosis (liver in the fetal chest and lung:head dimension ratio <1), there is some 'case-cohort' evidence that intervention to reverse the development of pulmonary hypoplasia before delivery can be considered. Intrauterine anatomical repair was the option first advocated, but it was abandoned because of poor results. Fetal tracheal occlusion has been demonstrated to trigger lung growth in animal models.[43] Following occlusion, the accumulated lung fluid creates a positive pressure and is levelled by fetal breathing movements. The cyclic nature of the pressure change and tissue stretching is essential for lung tissue growth and differentiation.[44] The current approach to fetal tracheal occlusion is endoscopic placement of a balloon in the upper part of the trachea under fetoscopic guidance. The balloon can accommodate an increase in tracheal diameter as the fetus grows and does not cause tracheal damage,[45] although laryngomalacia has been described. The procedure is performed at between 26–28 weeks of gestation; effects depend on pre-existing lung size, but reported survival rates are 50% until discharge.[46]

Traditionally, occlusion reversal was achieved by removing the balloon at the time of caesarean delivery using an extrauterine intrapartum treatment (EXIT) strategy. However, a recent animal study[47] has shown that intrauterine reversal of occlusion could lead to morphologically better lung maturation. This provides the rationale for reversing the occlusion at 34 weeks of gestation, either by ultrasound-guided puncture or fetoscopy. Associated complications are those of an invasive prenatal procedure (preterm premature rupture of the membranes and preterm delivery).

There are currently two randomised controlled trials recruiting in Europe; participants will undergo randomisation to either fetal tracheal occlusion or no intervention. The first trial will be co-ordinated from Belgium and the primary outcome will be the occurrence of bronchopulmonary dysplasia (see **Websites**). The second trial, co-ordinated from Germany, will look at whether the same intervention can reduce the need for postnatal intensive care (see **Websites**). The outcomes of such trials are essential before availability of this form of fetal therapy can be widespread.

As to the prediction of survival, we can look forward to advances based on MRI of fetal lung volumetry and intrauterine assessment of lung vasculature to assess for pulmonary arterial hypertension. This is a complication in the neonatal period believed to be related to structural changes in the vessels of lungs in cases of congenital diaphragmatic hernia. Three-dimensional ultrasound and fetal MRI have been used to measure lung volume and work is ongoing to validate the reliability and predictive accuracy of these measurements.[48,49] Three-dimensional ultrasound has been performed to measure vessel diameter, flow velocimetry and flow volume in the lung vasculature and nomograms have been published.[50]

Lower urinary tract obstruction

Lower urinary tract obstruction (LUTO) is caused by pathology such as the presence of a posterior urethral valve, urethral atresia in the male fetus or cloacal anomaly (hypoperistalsis microcolon syndrome) in the female fetus. Diagnosis is made on ultrasound, with an obstructed distended bladder and 'keyhole' sign (dilated posterior urethra) at the bladder neck. In severe cases, the upper urinary tract is distended bilaterally and renal tissue appears thin and hyperechogenic, showing cystic change due to scarring secondary to compression and ischaemia. Oligohydramnios is another very common ultrasound feature associated with decreased renal function and thus urine output. If this occurs in the canalicular phase of fetal lung development (18–24 weeks of gestation) there will be associated pulmonary hypoplasia. Ultrasound can confirm the diagnosis and define the level of obstruction. The exact pathology, however, is usually difficult to delineate and other complementary imaging techniques, such as MRI, may be required.

Prenatal intervention can be considered with the aim of preventing permanent renal damage associated with bilateral LUTO. Single needle tapping of the urinary bladder (vesicocentesis) under ultrasound guidance can relieve the pressure within the urinary tract. In the past, fetal urinalysis was performed to determine the degree of renal damage by urinary biochemistry including sodium, calcium and β2-microglobulin levels. However, our recent systematic review of the literature[51] indicated that such analysis had poor positive predictive value.

Vesicoamniotic shunting may be considered with the aim of minimising compression damage to the renal tissue and reducing the risks of pulmonary hypoplasia. In one overview, the survival rate was reported as 47%; however, among the survivors there was a high proportion of end-stage renal disease (40%).[52] In our recent systematic review of the literature of the effectiveness of this intervention, management with vesicoamniotic shunting demonstrated a trend towards improved outcome, particularly in the 'poor prognostic group' (according to

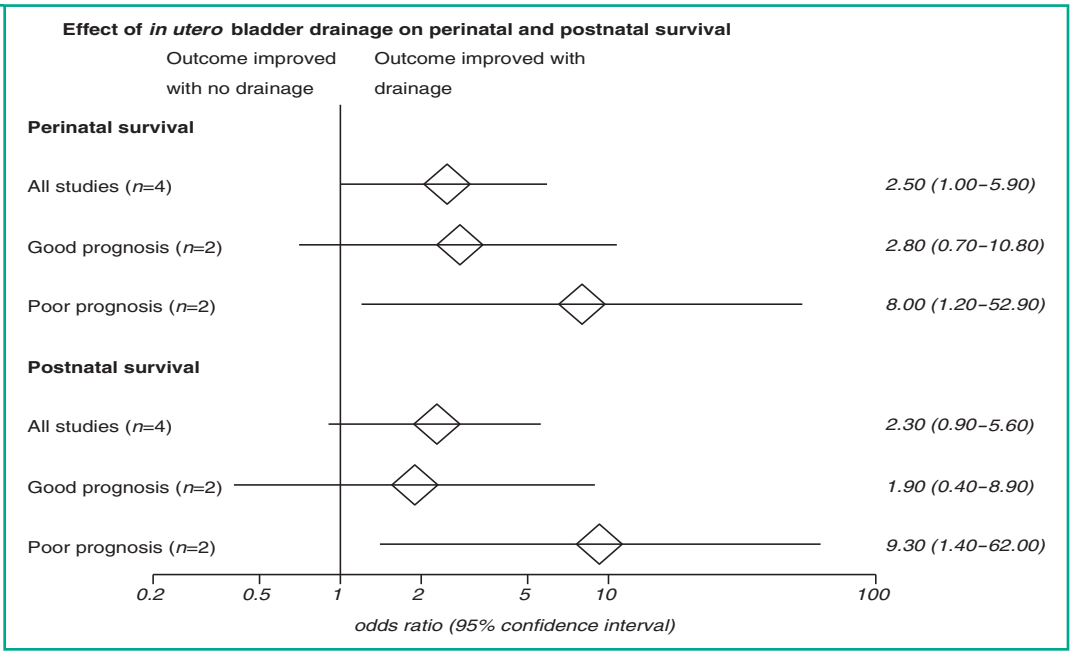

Figure 1
Forest plot showing summary of effects of prenatal bladder drainage, using summary odds ratio, on perinatal and postnatal survival in fetuses with ultrasound evidence of lower urinary tract obstruction (analysis corrected for voluntary pregnancy terminations).[59] Copyright 2009, with permission from Elsevier

ultrasound features and fetal urinalysis) (see **Figure 1**). However, the indication and optimal timing for intervention remained unclear.[53] The review also indicated a relative lack of high-quality evidence to inform clinical practice reliably, i.e. evidence relating to prenatal bladder drainage in fetuses with ultrasound evidence of LUTO. An international multicentre randomised trial (PLUTO) (see **Websites**) is addressing this issue, assessing in particular the role of vesicoamniotic shunting in a severely affected cohort with associated oligohydramnios, in classic LUTO cases and in those cases where oligohydramnios is yet to develop but there is evidence of obstruction with a normal or borderline liquor volume. This will help to answer questions about the management of these varying presentations, such as: once there is severe oligohydramnios, is it too late to shunt to prevent further renal and pulmonary damage? In the less severely affected cohort with obstructive features but no oligohydramnios, does shunting help prevent renal damage? Post hoc analysis will also assess the influence of gestation in affecting the success (or not) of this therapy. Primary outcomes will be perinatal mortality and renal function among survivors at 6 weeks of age. Follow-up will be until 5 years of age and will look at renal function, bladder function, cognitive development and quality of life among survivors.

Specific assessment and treatment for urethral obstruction using fetal cystoscopy has also been described. When compared with vesicoamniotic shunting, this technique has the advantage of restoring normal bladder dynamics as opposed to chronic bladder decompression, but has only been assessed in small cohorts.[54] Complications include bleeding, preterm labour, chorioamniotic membrane separation and preterm prelabour rupture of membranes; these limit its use.

Future research, such as the PLUTO trial and further animal work to determine the exact pathophysiology of renal damage in LUTO, will allow accurate identification and thus appropriate antenatal intervention in cases where the fetus is at risk of renal impairment and its consequences.

Intrauterine valvotomy

Congenital heart defects represent the most common congenital malformation among the newborn and they may be caused by genetic and environmental factors. It is increasingly recognised that normal blood flow is crucial for normal cardiac development. Fetal valvular stenosis or atresia cause ventricular dysfunction which may initially produce ventricular dilatation. However, as myocardial damage arrests ventricular growth, this can lead to pulmonary atresia and hypoplastic right ventricle or hypoplastic left heart syndrome. It has been shown that intervention when the fetus is at a certain gestational age may change the natural history of the disease,[55] improve postnatal surgical outcome, preserve pulmonary and cerebral function *in utero* and prevent intrauterine death.

At present, fetal interventions are performed for obstruction or atresia of the right or left semilunar valves. Pulmonary valvuloplasty in the case of severe obstruction and an intact septum results in decreasing signs of heart failure, delivery at term and favourable anatomy for a biventricular circulation after birth.[56] Aortic stenosis is relieved, with reversal of heart failure and hydrops, reducing premature delivery and allowing the possibility of biventricular corrective surgery after birth.[57] The procedure is usually performed at 21–32 weeks of gestation under

local maternal anaesthesia and sedation, with intramuscular fentanyl, pancuronium or atropine for the fetus. Under ultrasound guidance, a needle is passed percutaneously through the maternal abdomen into the fetal chest and the atretic valve and balloon dilatation is then performed. Fetal positioning is critical to enhance success and reduce complications. Better long-term outcomes have been seen with pulmonary than with aortic valve atresia because of the lower pressure system of the right ventricle. It has also been suggested that earlier timing of the intervention may be associated with a better prognosis.

Maternal complications are related to the anaesthesia, uterine manipulation and infection. Fetal complications include haemopericardium, bradycardia, pericardial effusion and intracardiac thrombus formation. Contraindications to treatment include evidence that the disease has progressed to the point where there is severe cardiomyopathy, so that recovery of myocardial function would not be possible. Criteria to select cases for intervention in aortic stenosis are a left ventricle with a length of at least 80% of the right ventricle, patency of the aortic valve and an apparently normal mitral valve. The cardiovascular profile score has also been used to estimate the severity of compromise.

The decision about whether to perform fetal intervention is a challenge in itself. As techniques have improved so have outcomes, and the availability of smaller needles and balloon catheters may allow operation at earlier gestations with better prognosis. Postnatal operations have also advanced, with increased survival rates. Improved methods of case selection for fetal intervention and for cardiovascular monitoring post-procedure will help determine the exact place of fetal interventions in the future. The National Institute for Health and Clinical Excellence (NICE) has produced interventional procedure guidance (IPG175) for fetal balloon valvuloplasty for aortic stenosis,[58] concluding that there is insufficient evidence on safety and efficacy at present and that all cases should be entered onto the intention-to-treat registry developed by the Association for European Paediatric Cardiology (see **Websites**).

Conclusion

In this article we provide an overview of the recent advances in fetal therapy. As imaging and interventional techniques improve, so the number and complexity of fetal diseases that can be treated *in utero* increases. These rapid developments, while exciting and in certain situations the only option for cure, must be viewed as experimental treatments until good quality evidence informs us of their true effectiveness. Their implementation in clinical practice must then always be considered within an ethical framework, balancing benefits with risks and harm to both mother and fetus.

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Websites

NOICH study (a multicentre trial on alloimmune thrombocytopenia) [www.medscinet.com/noich/]

EuroCDH and TOTALtrials (for congenital diaphragmatic hernia) [www.totaltrial.eu]

Trial on fetoscopic tracheal balloon occlusion in left diaphragmatic hernia [www.clinicaltrials.gov/ct2/show/NCT00373438]

Association for European Paediatric Cardiology [www.aepc.org]

PLUTO [www.pluto.bham.ac.uk]

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