Advances in fetal therapy

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Abstract
Fetal medicine is a rapidly evolving specialty with improving imaging, prenatal diagnosis and evolving technology. Advances in fetal therapy have enabled us to prevent and treat conditions and improve outcome. Although the most common forms of fetal therapy used currently are preventative non-invasive methods, invasive fetal therapies, both pharmacological and surgical are rapidly evolving. As interventions become more widely available, care must be taken in selecting patients, and consideration must be given to long-term outcomes and risks and benefits to mother and the fetus. This article discusses the established therapeutic strategies as well as those that are currently being evaluated.

Keywords fetal and neonatal alloimmune thrombocytopenia; fetal endoscopic tracheal occlusion; fetal therapy; free fetal DNA; genomics; meningo(myelo)cocoele; twin–twin transfusion syndrome

Introduction
Fetal therapy was first described in 1952, when Brevis performed an amniocentesis for management of rhesus isoimmunization. Fuchs and Riis used amniotic fluid for genetic diagnosis in 1956, looking at the Barr bodies to determine fetal gender, which was later used to manage patients with haemophilia A and Duchenne muscular dystrophy. Liley described the changing bilirubin levels in amniotic fluid with gestation and developed the ‘Liley’s graph’ to assess severity of rhesus disease. He then went on to perform the first intraperitoneal transfusion in 1963. Although ultrasound was being used in fetal medicine as early as 1960s, it was the development of real time ultrasound in 1975, which allowed the rapid expansion of fetal therapy.

Advances in fetal therapy have enabled us to prevent and treat conditions and improve outcome. Currently, the most common forms of fetal therapy are preventative, non-invasive methods such as antenatal corticosteroids for assisting fetal lung maturation, antenatal anti-D for prevention of Rhesus isoimmunization and folic acid to prevent neural tube defects. Invasive fetal therapies, both pharmacological and surgical, can have significant risks to both mother and fetus. In this article we aim to cover established therapeutic strategies as well as those which are currently being evaluated.

Pharmacotherapy
A variety of fetal conditions can be treated by maternal administration of drugs which cross the placenta to the fetus.

Fetal arrhythmias: 1–2% of fetuses of mothers with antiribonucleoprotein antibodies (for example anti-Ro and anti-La antibodies associated with conditions such as systemic lupus erythematosus) develop congenital heart block (CHB). These antibodies are thought to cross the placenta and bind with myocardial cells causing inflammation and scarring of atrioventricular node. Although some retrospective observational studies have shown improvements when treating CHB with maternal steroids, the PR Interval and Dexamethasone Evaluation (PRIDE) study showed no such benefit. In fetuses with third degree heart block there was no reversal in either the treated or untreated groups. Intravenous immunoglobulin has been tried as an alternative therapy in CHB. Two recent multicentre trials, Preventive Intravenous Immunoglobulin Therapy for Congenital Heart Block (PITCH) study, and a European multicenter study, both failed to show any benefit with a relatively low dose compared to that used in management of fetal alloimmune thrombocytopenia. Whether a higher dose is required for transplacental transfer to show any benefit remains to be answered.

A variety of fetal cardiac conduction defects can result in fetal tachyarrhythmias. Although maternal administration of antiarrhythmic drugs is an established practice, there is little consensus regarding the drug of choice for this purpose. Digoxin, sotalol, flecainide and amiodarone have all been used to treat fetal tachyarrhythmias. A recent non-randomized multicentre study showed that Digoxin and Flecainide are significantly better at converting arrhythmias to normal ventricular rhythms compared to other drugs, albeit associated with maternal side effects.

Congenital adrenal hyperplasia (CAH): CAH is an autosomal recessive condition affecting steroidogenesis, causing virilization of female fetuses. Maternal administration of corticosteroids has been shown to normalize androgen precursor levels reducing the virilizing effects on female genitalia. There are, however, concerns regarding maternal side effects such as hypertension, abnormal glucose tolerance and potential osteoporosis if used long term. Since the development of external genitalia takes place between 7 and 12 weeks, steroids have been used from early in the first trimester. Fetal exposure to steroids from such an early gestation raises concerns regarding possible disruption of the hypothalamic–pituitary–adrenal axis, with long-term behavioural and neurodevelopmental changes, as well as the risk of growth restriction.

Fetal gender can be ascertained as early as 7 weeks, using free fetal DNA. Diagnosis of male fetuses would negate the need for treatment. Although the use of free fetal DNA is relatively inaccurate before 7 weeks, it may be offered to women wishing to avoid steroids prior to commencing the treatment. This should be followed by retesting after 7 weeks gestation to confirm fetal gender. Currently a trial “Determining the Long-Term Effects of...
Prenatal Dexamethasone Treatment in Children with 21-Hydroxylase Deficiency and Their Mothers is underway to address the question of optimal therapy.

**Fetal and neonatal alloimmune thrombocytopenia**

Similar to rhesus alloimmunization, fetal and neonatal alloimmune thrombocytopenia (FNAIT) is caused by transplacental passage of platelet-specific antibodies in an antigen-negative mother. This leads to destruction of fetal platelets, which can cause significant thrombocytopenia. The most severe complication is intracranial haemorrhage (ICH) resulting in neurological complications in up to 26% of surviving infants and perinatal mortality in up to 7% of the cases (Figure 1). Unlike cases of rhesus alloimmunization, the fetus in the first pregnancy can be severely affected. Therefore in the absence of screening modalities, a history of an affected fetus or infant is the only means of identifying women at risk.

Traditional management was similar to that of red cell isoimmunization, with aggressive serial platelet transfusions. However, in a fetus with low platelet count, the cumulative risk of fetal demise from exsanguination following serial weekly transfusions was 12% per pregnancy in one series.

Modern treatment is now based on the weekly administration of maternal IVIG (1 g/kg). Although the exact mechanism of action of IVIG in management of FNAIT is unclear, it is thought to cause dilution of anti-platelet antibodies crossing the placenta, block the placental receptors, and block the receptors on macrophages in the fetal circulation, thus preventing platelet destruction. Although treatment with IVIG is very successful in preventing ICH, all the studies have documented a significant percentage (8–87%) of relative non-responders (platelet count of less than 50 × 10^9/L). In non-responders, increasing the dose of IVIG (to 2 g/kg weekly), with or without the addition of corticosteroids, has been used. Because high dose corticosteroids are associated with significant maternal and fetal complications, combining prednisolone with IVIG is preferred. Although there is a trend towards higher platelet counts with the use of 2.0 g/kg IVIG or the combination of IVIG and prednisone, in the cases with a previous prenatal ICH, none of these treatment options have proved to be significantly superior to each other. A recent Cochrane review stratified low and high risk based on pre-treatment platelet counts of more than or less than 20 × 10^9/L and the presence or absence of a history of ICH in a sibling. The authors suggest IVIG or prednisolone alone as first line for the low risk group and combination therapy for the high risk group.

There is variation regarding the gestational age at which IVIG is commenced in different centres, from 12 to 26 weeks. Because fetal platelet antigens are fully expressed by 16–18 weeks, it would seem reasonable to commence treatment around this time.

Fetal blood sampling (FBS) with platelet cover at around 32 weeks can be used to monitor response to the treatment and to plan mode and timing of delivery. Because this procedure is associated with significant risks, especially in non-responders, FBS is generally reserved for cases with a history of ICH.

Delivery should be conducted in a unit where the neonatologists and paediatric haematologists are used to managing this condition. There is no consensus regarding mode of delivery. A prospective study of 32 pregnancies with FNAIT without a history of ICH, concluded that vaginal delivery was safe in this group of cases. Vaginal delivery is generally considered safe if the platelet count is more than 50 × 10^9/L. In cases where the platelet count is unknown, caesarean section before term is commonly recommended, albeit with little evidence to support it.

**Twin–twin transfusion syndrome (TTTS)**

TTTS is a condition unique to monochorionic placentation, occurring in about 10–15% of these pregnancies. The incidence of monochorionic pregnancies is increasing, largely due to an increase in assisted reproductive techniques and a rising number of pregnancies in older women. Vascular anastomosis within the monochorionic placenta allows for blood flow between the fetuses. The interplacental unbalanced transfusion through these

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**Figure 1** Intracranial haemorrhage.

**Figure 2** Fetoscopic image of the donor twin in TTTS with the amnion “stuck” over the fetus’ shoulder.
anastomoses results in a volume depleted donor twin (Figure 2) and volume overloaded recipient twin, with potentially lethal consequences. Untreated, it is associated with poor prognosis and overall mortality rate of around 80%.

Quintero classified TTTS in five stages (Table 1) on the basis of sequence of ultrasound findings during the progression of the condition. Although initially the classification was meant to guide prognostication based on stage at presentation, this system appears to be more useful in monitoring disease progression. This classification, does however, broadly correlate with outcome, with stages I and II having better outcomes than stages III and IV. Prognostication can be refined further with the identification of arterial to arterial anastomosis (AAA), where detection of an AAA is associated with a higher likelihood of survival of at least one twin (at 28 days of age: \( P = 0.009 \) and at 6 months of age: \( P = 0.002 \)). The laser treatment group also had a lower incidence of cystic periventricular leukomalacia (\( P = 0.02 \)) and lesser incidence of neurologic complications at 6 months of age (\( P = 0.003 \)). A recent meta-analysis compared laser treatment and serial amnioreduction over a period of ten years (1997–2007) and yielded similar results, confirming that laser treatment is a superior first-line treatment for severe TTTS as compared to amnioreduction. The reduction of the risks of fetal or neonatal death or of long-term major neurological impairment at the time of diagnosis and treatment were shown to be stable through the long-term follow-up, up to the age of 6 years. Follow up of children born following laser treatment for TTTS in Germany also showed good long-term recovery for both the cardiovascular and renal system and also for the growth discordancy caused by the TTTS prior to laser treatment. 45% of recipient twins had tricuspid regurgitation and biventricular hypertrophy at birth. This had resolved in all cases by 6 months of age. Eighteen pairs of twins who were followed up for renal impairment showed normal renal function (blood and urine tests) by the median age of 31 months.

Residual anastomosis following laser surgery can cause complications such as persistent, recurrent or reversed TTTS, feto-fetal haemorrhage resulting in twin anaemia polycythaemia sequence (TAPS), intrauterine demise of both twins or one twin with neurological hypotensive sequelae in the surviving twin.

Uncertainty remains regarding the best treatment for stage I TTTS. Progression rates of 10–45% have been reported. However, a large number of TTTS stage I patients do not progress (28%) and some regress (41%), suggesting that expectant management is an option. However, stage I disease is associated with significant morbidity; up to half of the recipient fetuses have myocardial dysfunction and nearly 50% will have absent urine production. In order to identify the better mode of management, a randomized controlled trial is currently being undertaken comparing conservative management with laser surgery for stage I TTTS. (clinicaltrials.gov/ct2/show/NCT01220011).

### Radiofrequency ablation

Selective fetal reduction in monochorionic multiple pregnancies is complicated by the placental anastomoses. Fetal death or non-occlusive feticide of one fetus in a monochorionic pair will result in an acute transfusion into the circulation of the dying fetus, through the anastomoses, causing acute hypoxia and hypotension in the surviving fetus which may lead to death or neurological injury.

Various vaso-occlusive techniques such as bipolar cauterization, laser, injection of vascular sclerosants and fetoscopic ligation of the cord have been evaluated for selective fetal reduction in monochorionic multiple pregnancies, in an attempt to prevent this acute transfusion. Recently, success has been achieved with radiofrequency ablation (RFA). RFA uses high frequency alternating electric current creating heat and causing coagulation of the tissue, usually at the point of cord insertion. Paramasivam et al have described their experience in 35 cases using RFA for selective feticide at a median gestation age of 17\(^{+3}\) weeks (13–27\(^{+4}\)), with a liveborn rate of 88.6%. RFA can be used in early gestation under local anaesthetic, with a precise ablative area between the tynes of the needle. A recent review showed improved survival following RFA (86%), compared to bipolar cord ablation (82%), laser cord coagulation (72%) and cord ligation (70%).

### Diaphragmatic hernia

In isolated congenital diaphragmatic hernia (CDH), the main predictive factor of the outcome is lung volume on the contralateral side. The poor perinatal outcome is generally secondary to pulmonary hypoplasia and pulmonary hypertension. Therefore, attempts at promoting lung growth prenatally have been the hallmark of studies undertaken for management of antenatally diagnosed CDH. The initial attempts at prenatal surgical anatomical repair were performed in late 1980s. These were soon discontinued because of high perinatal morbidity and mortality rates.

The finding of increased lung volume in fetuses with congenital high airway obstruction syndrome (CHAOS) inspired the use of tracheal occlusion techniques in management of CDH. Tracheal occlusion aims at blocking the outlet of the lung-fluid, which accumulates within the lungs increasing the transpulmonary pressure, promoting lung growth.

Jani et al described their experience using percutaneous fetal endoscopic balloon tracheal occlusion (FETO) in 210 cases of severe CDH. 97% of these fetuses were born alive and 48% were

<table>
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<tr>
<th>Classification of twin–twin transfusion syndrome</th>
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<tr>
<td>Stage I</td>
<td>Polyhydramnios in one and oligohydramnios in the other (defined by deepest vertical pools of more than 8 cm and less than 2 cm, respectively)</td>
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<tr>
<td>Stage II</td>
<td>Non-visible donor bladder</td>
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<td>Stage III</td>
<td>Abnormal Doppler waveforms (AREDF in the donor umbilical artery, and/or in the recipient, ductus venous reverse flow or pulsatile umbilical venous flow)</td>
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<td>Stage IV</td>
<td>Recipient hydrops</td>
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<td>Stage V</td>
<td>Fetal death</td>
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Table 1
discharged home after corrective surgery. In the light of this outcome, randomized control trials are now underway comparing FETO during late pregnancy (30–32 weeks gestation) versus expectant management in fetuses with moderate left sided congenital diaphragmatic hernia (clinicaltrials.gov/ct2/show/NCT00763737) and FETO at 27–30 weeks for severe cases (clinicaltrials.gov/ct2/show/NCT01240057).

Meningomyelocoele

Although open neural tube defects are associated with significant morbidity, it is rarely associated with mortality. The pathology of injury to the nervous tissue is thought to be two fold. Firstly, the failure of closure of the neural tube leaves the spinal cord exposed, and secondly, the impact of direct trauma and exposure to the potential toxins within the amniotic fluid results in damage to the developing nervous tissue. Closure of the defect early in the pregnancy could therefore potentially prevent this injury.

Attempts have been made to close the neural tube defect through open and endoscopic surgery. In one series of 10 open repairs, nine fetuses survived with all of them showing reversal of hindbrain herniation (on MRI) within 3 weeks of surgery, with only one child needing shunting. Bruner compared outcomes in fetuses with isolated meningomyelocele with endoscopic repair ($n = 4$) with a maternal split-thickness skin graft in a CO$_2$ environment at 22–24 weeks’ gestation and standard open neurosurgical closure ($n = 4$) at 28–29 weeks’ gestation. There were two survivors in the endoscopy group, with both the infants requiring further repair after delivery, compared to 100% survival with well healed repairs in the open repair group. Following this, further attempts at endoscopic repair were abandoned.

A study of 50 selected patients showed reversal of hindbrain herniation, and improvement in fetal head growth and cortical index following open repair of meningomyelocele. The need for postnatal ventriculo-peritoneal shunting was halved and post-natal leg function was better in 57% of the cases compared to historical controls. A 2-year follow up of these children confirmed that the cognitive neurological outcome was no worse when compared to expected outcome in historical data. Children who did not need shunting scored higher on the cognitive assessment compared to those requiring shunting.

A randomized trial of prenatal versus postnatal repair of meningomyelocele (MOMS) has been recently published. The study aimed to recruit 200 patients but was stopped after recruiting 183, when the interim analysis demonstrated benefit in the prenatal treatment group. 158 babies were evaluated at 12 months of age (78 from the prenatal surgery group and 80 from the postnatal repair group). The first primary outcome was a composite of fetal or neonatal death or the need for placement of a cerebrospinal fluid shunt by the age of 12 months. This occurred in 68% in the prenatal surgery group compared to 98% in the postnatal repair group ($P < 0.001$). An improvement was also noted in the second primary outcome, which was a composite assessment of mental development and motor function at 30 months ($P = 0.007$), as well as several secondary outcomes such as ambulation at 30 months. The need for shunt placement was halved in the prenatal surgery group. Although the results were encouraging, there was significant associated morbidity. 13% of the infants in the prenatal surgery delivered before 30 weeks gestation compared to none in the postnatal repair group. One-third of the women who underwent prenatal surgery had an area of dehiscence or a very thin prenatal uterine surgery scar at the time of delivery. As well as very stringent selection criteria, the prenatal surgery was performed in three centres which had gained substantial experience and expertise in the technique. Therefore interpretation and generalization of these results requires great caution. Techniques to improve outcome without increasing morbidity need to be sought. Further evaluation of other techniques involving tissue engineering is currently being undertaken, such as attempts at prenatal closure of meningomyelocele with gelatin sponges incorporating fibroblast growth factor.

Lower urinary tract obstruction

Lower urinary tract obstruction (LUTO) can be partial or complete, due to conditions such as posterior urethral valves and urethral atresia and may be associated with various developmental abnormalities. Significant obstruction can cause severe oligohydramnios, which can lead to the development of potentially lethal pulmonary hypoplasia. The increasing fluid in the collecting system can cause increased pressure and renal impairment.

Vesico-amniotic shunting has been used in an attempt to improve outcome. It allows the urine to pass into amniotic cavity hence assisting pulmonary development and reducing the back-pressure on the renal system. The procedure is not without risks. Maternal trauma, infection, miscarriage, preterm labour, shunt blockage or displacement and fetal trauma have all been reported. A recent meta-analysis however, showed statistically significant improvement in perinatal survival ($P = 0.03$) and a trend towards improved postnatal survival, albeit not statistically significant ($P = 0.09$). The current evidence does not provide sufficient information on safety and efficacy of vesico-amniotic shunts for LUTO, however, a multi-centre randomized controlled trial of singleton pregnancies with ultrasound evidence of LUTO is currently evaluating the safety and effectiveness of in utero shunting compared to conservative management (PLUTO).

Genomics and free fetal DNA

All pregnancies carry a risk of fetal genetic abnormality. Factors such as maternal age, previous pregnancy and family history, all contribute to defining individual risk. Prenatal testing at present is performed by invasive techniques such as chorion villus sampling and amniocentesis in high risk pregnancies. The cells obtained can be analyzed using direct techniques such as fluorescent in-situ hybridization (FISH) and also by obtaining cell cultures and using traditional methods such as karyotyping.

Karyotyping is a relatively slow and labour intensive procedure, detecting only large imbalances, compared to the more recently developed DNA-array based techniques such as 24-chromosome single-nucleotide-polymorphism (SNP) arrays, and array comparative genomic hybridization (CGH). FISH methods are used to detect a limited number of different chromosome anomalies, while DNA-array based techniques can detect the
number of chromosome copies as well as copy-number varia-
tions. Such techniques are faster and can identify much smaller
imbalances, compared with conventional karyotyping. Although
these techniques are rapidly developing, their use in clinical
practice needs careful evaluation. The copy-number variations
identified can be useful when a specific variation is known to be
associated with a specific condition. However, the clinical
significance of many of these variations is unknown and not all
imbalances cause problems. Currently a multicentre study is
being undertaken (EACH study) to evaluate the efficacy of
prenatal array CGH and address the hypothesis that array CGH
detects more de novo pathogenic chromosomal imbalances than
standard karyotyping.

All the invasive techniques used to obtain fetal DNA are
associated with risk of fetal loss. The “holy-grail” of prenatal
diagnosis seeks to obtain sufficient fetal DNA for genetic diag-
noses by non-invasive means. The cell free fetal DNA (cffDNA)
and RNA released by apoptosis of placental trophoblasts can be
obtained from maternal plasma as early as first trimester,
allowing the opportunity for early non-invasive prenatal diag-
nosis. cffDNA has been used for sex determination to inform
management of X-linked diseases. Paternal genomic contribution
to the cffDNA has been used for some time to identify fetal
Rhesus status in Rhesus negative mothers. A study is currently
being undertaken to assess the feasibility of widespread cffDNA
testing of all Rhesus negative mothers to establish the fetal
Rhesus status. This technique can also be used in prenatal
diagnosis of paternally transmitted dominant conditions such as
Huntington’s disease, and determining carrier status for condi-
tions such as cystic fibrosis where the parents are carriers of
different mutations (compound heterozygotes).

Gene therapy and fetal stem cells

Gene therapy has progressed rapidly over the last two decades,
from laboratory experiments to clinical trials, for a variety of
diseases, including neurodegenerative diseases, pancreas and
prostate cancer and genetic disorders such as muscular dystrophy.
Gene therapy uses selected gene sequences to replace or alter the
defective gene, enabling expression of the proteins to produce the
desired therapeutic effect. The genes are transported in vectors,
usually viruses that have been treated to prevent replication.

Other than efficiently providing long-term regulated therapeu-
tic protein expression, an ideal vector must be safe for mother
and fetus. It should not initiate the fetal immune response, be
teratogenic or oncogenic and should be relatively easy to
administer. The NIH Recombinant DNA Advisory Committee
suggest that candidate diseases for prenatal gene therapy should
pose serious morbidity and mortality to the fetus or neonate and
not have any effective postnatal treatment.

Prenatal gene therapy can have distinct advantages over post-
natal therapy. Prenatal treatment can influence the condition
before long term damage has occurred, for example in mucopo-
lysacharidosis, where brain damage can occur before birth.
Applying vectors to rapidly dividing cells such as fetal stem cells,
can produce large numbers of transduced cells, reducing the need
for repeated administration and improving the therapeutic effect.
Additionally, there is higher tolerance to foreign cells during the
fetal life. Fetal skin appears to be more amenable to gene transfer
compared to postnatal keratinocytes and organs may be more
accessible during their developmental stage than postnatally.

Fetal stem cells (FSC) are an attractive alternative to adult and
embryonic stem cells. They are more rapidly proliferative, have
greater differentiation potential compared to adult stem cells, and
have less oncogenic potential than embryonic stem cells. Umbilical
cord blood is an accessible source of FSC, although these stem cells
are present in preterm cord blood samples in much greater quantity
than term cord blood. FSC can also be obtained from organs such as
liver, spleen, bone marrow, lungs as well as amniotic fluid and
placenta.

Persistent FSC have been found in wide range of maternal
organs for several decades following the pregnancy —
a phenomenon known as microchimerism. The FSC seem to have
immunomodulatory properties, due to which the maternal
immune system fails to illicit a reaction or cause rejection of
these cells. Therefore FSC are able to engraft and proliferate
within maternal tissue, and are a good candidate for micro-
chimerism and tissue repair.

Use of FSC as a target for vector application is a relatively new
concept and is currently being evaluated for prenatal therapy.
Transplantation of FSC in-utero may be an option for the treat-
ment of hereditary haematological, metabolic and immunological
diseases in the future. Further studies are needed to identify
‘safe’ regions on the human genome to reduce the ‘oncogenic’
risks and to evaluate long-term outcomes.

Summary

Fetal medicine is a rapidly evolving specialty with improving
imaging, prenatal diagnosis and advancing technologies fuelling
prenatal interventions and management. However, the new proce-
dures and technologies need to be thoroughly evaluated before being
brought into mainstream medical practice. Most of the studies so far
have been conducted in highly selected groups of patients. As
interventions become more widely available, care must be taken in
selecting patients and consideration must be given to long-term
outcomes and risks and benefits to mother and the fetus.

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**Practice points**

- Fetal therapy can be associated with significant maternal and fetal risks
- Careful patient selection is necessary when planning fetal treatment
- Free fetal DNA can be used as early as first trimester for fetal assessment
- In severe TTTS, laser treatment is the preferred method of management
- Vaso-occlusive techniques must be used for selective fetal reduction in monochorionic multiple pregnancies
- Maternal administration of IVIG is the standardized first-line treatment of FNAIT