Fetal Therapy

Fetal therapy offers an intervention before birth for the purpose of correcting, treating, or diminishing the deleterious effects of a fetal condition.

From: Noninvasive Prenatal Testing (NIPT), 2018

Related terms:

Neoplasm, Combination Therapy, Lesion, Ganciclovir

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Anesthesia for Fetal Surgery

Kha Tran, David E. Cohen, in Smith's Anesthesia for Infants and Children (Eighth Edition), 2011

Neurologic

Fetal therapies for prenatally diagnosed hydrocephalus and myelomeningocele (MMC) have been described. Results for in utero treatment of hydrocephalus with ventriculoamniotic shunts have not been encouraging, and this therapy is no longer actively studied or offered (Manning et al., 1986; Bruner et al., 2006). However, in utero closure of MMC defects is more promising. This closure involves accessing the midgestation fetus via maternal laparotomy and hysterotomy (Fig. 19-2). The MMC is repaired, and uterine and abdominal incisions are closed. Pregnancy is continued with the goal of delivering as close to term as possible.

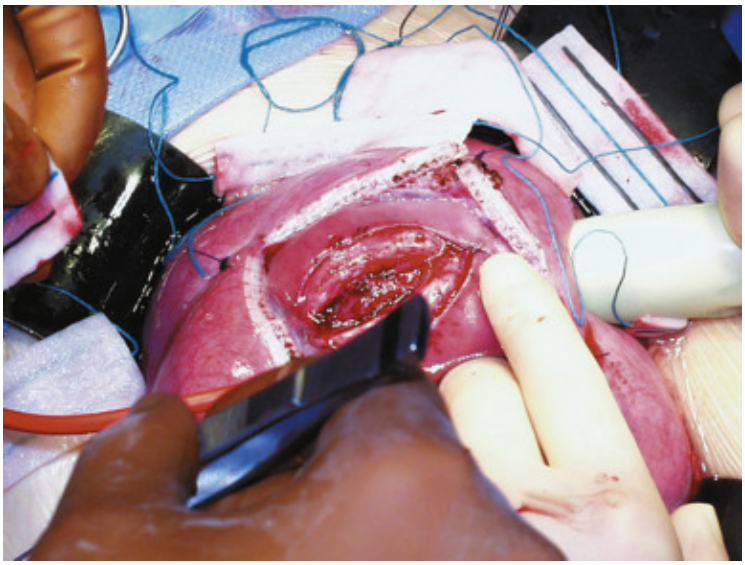

FIGURE 19-2. A fetus with myelomeningocele (MMC) exposed for in utero midgestation repair. The fetus is turned so that the MMC defect is exposed. Special uterine staples can be seen framing the hysterotomy. The red rubber catheter coming from the left side of the image is used to instill warmed crystalloid to maintain amniotic fluid volume.

(From Myers LB, Cohen D, Galinkin J, et al: Anaesthesia for fetal surgery, *Paediatr Anaesth* 12:569, 2002, with permission from Wiley-Blackwell.)

The rationale for in utero closure of MMC is based on animal models of fetuses with these lesions, where it appears that prolonged bathing of neurologic elements in the amniotic fluid worsens the neurologic outcome (Meuli et al., 1995; Meuli et al., 1996). In human studies, closure of fetal MMC decreases the need for postnatal ventriculoperitoneal shunting and the incidence of hindbrain herniation and Chiari malformation. Motor function may be somewhat improved, and cognitive behavioral testing does not appear to be adversely affected (Bruner et al., 1999; Tulipan et al., 1999; Johnson et al., 2003; Johnson et al., 2006). A randomized trial sponsored by the National Institutes of Health (NIH) is currently enrolling patients who are randomized either to standard postnatal closure of MMC or to in utero closure of MMC. Enrollment in the trial is, at this time, the only avenue for this surgery.

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CONGENITAL DIAPHRAGMATIC HERNIA AND EVENTRATION

KuoJen Tsao MD, Kevin P. Lally MD, in Ashcraft's Pediatric Surgery (Fifth Edition), 2010

Fetal Intervention

The impetus for fetal therapy for CDH coincided with the advances in prenatal diagnosis. Improvements in fetal ultrasonography revealed the true natural history of CDH and the hidden mortality during gestation and soon after birth. These poor outcomes prompted the researchers at the University of California, San Francisco, to explore fetal surgery for CDH. Subsequently, fetal CDH intervention evolved from open fetal surgery to the current state of endoscopic endoluminal tracheal occlusion.

The prerequisite for any fetal intervention is the ability to accurately diagnose CDH and predict severity of disease and survival. The most widely accepted prenatal sonographic prognosticators have been liver herniation and LHR, which have been discussed previously. Liver herniation and an LHR less than 1.0 are recognized as fetal characteristics that portend the poorest outcomes.[241]

After years of unfavorable outcomes with open fetal repair of CDH, prenatal intervention evolved to tracheal occlusion. Based on clinical observations that tracheal atresia causes pulmonary hyperplasia, novel animal experiments of lung distention, and an improved understanding of fetal lung growth, therapeutic tracheal occlusion was introduced as a treatment for pulmonary hypoplasia secondary to CDH.[99,242-244] Current techniques involve endoscopic placement of an occlusive balloon without maternal laparotomy or general anesthesia.[245] Tracheal balloons are placed between 24 and 28 weeks' gestation and deflated at 34 weeks. This strategy of temporary tracheal occlusion is based on avoiding the need for an ex-utero intrapartum treatment (EXIT) procedure at delivery. In addition, prolonged tracheal occlusion has been demonstrated to differentiate type II pneumocytes into type I pneumocytes, resulting in surfactant deficiency and necessitating the need for balloon removal.[246-248]

An NIH-sponsored randomized trial comparing fetal tracheal occlusion versus standard postnatal care was reported in 2003.[101] After 24 cases (11 by tracheal occlusion), the study was terminated early due to comparable survival outcomes (77% by postnatal care, 73% by tracheal occlusion) during interim analysis. The hazard ratio for mortality associated with tracheal occlusion, as compared with conventional therapy, was 1.2 (95% confidence interval [CI]: 0.29 to 4.67). However, when stratified based on LHR, survival was significantly better for LHR greater than 0.9. In fact, the hazard ratio for death with tracheal occlusion was 0.13 (95% CI: 0.03 to 0.64). This study recognized the wide spectrum of disease based on LHR and speculated that the patients with the most severe disease may still benefit from tracheal occlusion. Despite these results from the randomized trial, tracheal occlusion continues to be investigated owing to the significant mortality of infants with LHR less than 1.0 and liver herniation.

The FETO (Fetoscopic Tracheal Occlusion) task group, a European perinatology organization, created a multicenter prospective observational study.[100] In an attempt to select a more severe subset based on data from the NIH trial, the study included fetuses with liver herniation and LHR less than 1.0. In the initial 21 patients (15 left-sided CDH and 6 right-sided CDH), the investigators reported a survival of 48% for tracheal occlusion compared with 8% in the nonocclusion group. In addition to the survival advantage, the study also demonstrated an improvement in perinatal complications such as prematurity and premature rupture of membranes. The latest series reported overall survival of 57% for tracheal occlusion with survival greater than 62% for LHR between 0.6 and 1.0.[241] Although impressive, these results warrant further investigation in that the survival for LHR of 0.8 to 0.9 (78%) was higher than survival for LHR greater than 1.0 treated postnatally (65%). Furthermore, study limitations have prevented the widespread adoption of tracheal occlusion based on the European data. Control cases were taken from multiple centers that could not provide a standardized postnatal approach or reflect recent advances in postnatal care.

Long-term outcome with morbidity has yet to be reported for tracheal occlusion. However, one study examined pulmonary function in 20 patients (9 with conventional therapy and 11 with tracheal occlusions) from the NIH-sponsored randomized trial.[249] Infants were evaluated during the first 24 hours of life, before and after operative repair, and before elective extubation. The study demonstrated slight improvements in respiratory compliance and alveolar-arterial oxygenation gradients in patients who had undergone tracheal occlusion. However, other long-term outcomes remain to be seen. Based on the only randomized clinical trial, there appears to be no significant benefit from tracheal occlusion for the treatment of CDH. Although proponents of fetal intervention suggest that a subgroup of the most severe patients (liver herniation and LHR < 0.9) may still benefit from fetal intervention, the true efficacy of fetal tracheal occlusion for these severely affected infants will require a prospective randomized trial before its universal acceptance.

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Congenital Malformations of the Lungs and Airways

Jean-Martin Laberge, Pramod Puligandla, in Pediatric Respiratory Medicine (Second Edition), 2008

Fetal Surgery

Intuitively, CDH should be amenable to fetal therapy. By reducing the hernia contents, repairing the defect, and allowing the lung to grow while the fetus still derives oxygen and nutrients from the placental circulation, the pulmonary hypoplasia should reverse, allowing for normal postnatal lung function. An enormous body of experimental work, mainly in animals, has allowed the evolution of fetal therapy for CDH to progress to clinical trials.[410–413]

Early experimental work in animal models of CDH revealed that the creation of a diaphragmatic hernia in fetal sheep led to pulmonary hypoplasia, vascular maldevelopment, and clinical symptoms of respiratory distress that were similar to that observed in newborns with CDH.[414] From a clinical standpoint, the survival of infants with a prenatal diagnosis of CDH during this time period was dismal despite optimal neonatal care.[398] When the in utero correction of the hernia defect in animal models led to postnatal survival and normal lung function,[415] there was much optimism that these same results could be reproduced in human fetuses. The first successful fetal surgical procedure in humans for CDH was reported in 1990.[416] Although this first patient had an excellent outcome, subsequent patients fared less well. Indeed, only 5 of 21 fetuses undergoing surgery survived despite improvements in tocolysis and perioperative fetal care.[417] The main obstacle to successful repair occurred in those patients who had "liver up" in the chest, where replacement of the liver back within the abdominal cavity led to kinking of the sinus venosus, subsequent obstruction to umbilical vein flow, and fetal death.[418] A clinical trial evaluating the efficacy of open surgical repair for fetuses with "liver down" demonstrated that the outcome of these infants was no better than infants cared for by conventional means.[419] Thus, the optimism for open fetal surgical repair for CDH diminished, and other modalities were investigated.

> Read full chapter

Fetal Drug Therapy

Erik Rytting, Mahmoud S. Ahmed, in Clinical Pharmacology During Pregnancy, 2013

5.2 Indications for fetal therapy

Table 5.1 lists some common indications for fetal therapy and details regarding these conditions are provided below (see also Table 5.2). Nevertheless, as this table is not an exhaustive list, this section will identify a number of additional settings where fetal drug therapy may be beneficial.

Table 5.1. Examples of indications for fetal drug therapy and medications used

Indication for fetal drug therapy	Medications
Cardiac arrhythmias	Digoxin, flecainide, sotalol
Endocrinological disorders	
Congenital adrenal hyperplasia Fetal thyroid disorders	DexamethasoneLevothyroxine
Hematological disorders	
Alloimmune thrombocytopenia Erythrocyte alloimmunization	Gamma globulinAnti-D immunoglobulin
Lung maturation	Dexamethasone, betamethasone

Table 5.2. Pharmacokinetic considerations for some medications used in fetal drug therapy (see Table 5.1)

Drug	Typical dosing	Notes	References
Digoxin	0.5 mg bid for two days, then 0.25–0.75 mg/day	Therapeutic concentration 1.0–2.5 ng/mL; fetal/maternal ratio: 0.3–1.3; hydrops reduces placental transfer; substrate for P-glycoprotein	[66–74]
Flecainide	100 mg, tid or qid	Therapeutic concentration 0.2–1.0 mcg/mL; fetal/maternal ratio: 0.5–1.0; crosses placenta even in the presence of hydrops	[66, 73, 75–79]
Sotalol	80–160 mg, bid or tid	Therapeutic concentration 2–7 mcg/mL (atrial flutter); fetal/maternal ratio 1.0 ± 0.5	[66, 78, 80–87]
Dexamethasone (for lung maturation)	6 mg, four intramuscular doses, 12 hours apart	Fetal/maternal ratio ranged from 0.20 (50 min after dose) to 0.44 (after 265 min); a fraction is metabolized in the placenta to the inactive 11-ketosteroid	[88–92]
Betamethasone	12 mg, two intramuscular doses, 24 hours apart	Fetal/maternal ratio: 0.28 ± 0.04; a fraction is metabolized in the placenta to the inactive 11-ketosteroid	[93–97]
Levothyroxine	Case studies report intraamniotic doses ranging from 50–800 mcg (median dose 250 mcg), every 1–4 weeks	Concurrent dose reduction of maternal antithyroid drugs may be necessary; it may be advisable to start with a low dose (150 mcg), then increase if necessary; cordocentesis should be limited	[15, 98–101]
Gamma globulin	1–2 g/kg/week IV, depending on risk	Prednisone is often used in combination	[102]
Anti-D immunoglobulin	1500 IU as a single intramuscular injection at 28 weeks of gestation	A two-dose regimen consisting of either 500 or 1250 IU each at 28 weeks and 34 weeks may be more effective in maintaining suf-	[103–105]

		ficient anti-D levels at term	
Dexamethasone (for congenital adrenal hyperplasia)	20 mcg/kg/day based on pre-pregnancy body weight, divided in three doses	See notes on dexamethasone above	[11]

Among the most common pharmacological interventions for fetal therapy is the administration of antenatal corticosteroids to promote *fetal lung maturation* in anticipation of preterm delivery. Dexamethasone and betamethasone are the most common drugs prescribed for this purpose, which has demonstrated clinically significant reductions in respiratory distress syndrome, neonatal mortality, cerebroventricular hemorrhage, necrotizing enterocolitis, intensive care admission, and systemic infections in the first 48 hours of life [4, 5].

Fetal cardiac arrhythmias affect 1% of pregnancies [6]. Although intermittent extrasystoles can be common and may not require treatment, sustained fetal arrhythmias demand vigorous attention because this can lead to hydrops within 48 hours, a condition with poor prognosis [6–9]. Hydrops can impair transplacental transport, thereby necessitating fetal injection of medication [9]. The most common fetal arrhythmias are supraventricular tachycardia, atrial flutter, and severe bradyarrhythmia associated with complete heart block. Drugs used to treat fetal tachycardia include digoxin, flecainide, sotalol, procainimide, propranolol, amiodarone, and adenosine; questions remain regarding the use of steroids and sympathomimetics for bradycardia caused by heart block [7]. Attentive monitoring of response to most antiarrhythmic drugs is needed due to narrow therapeutic margins, and coadministration of digoxin and verapamil may cause fetal death [10]. Maternal side effects to fetal antiarrhythmic therapy include palpitations, second degree atrioventricular block, Wenckebach phenomenon, and hypotension [10].

Congenital adrenal hyperplasia is most often due to a 21-hydroxylase deficiency (CYP21A2) [8]. Decreased cortisol production results in excess androgen synthesis, which causes virilization of female genitalia. A survey of 13 countries demonstrated an overall incidence of 1 in 15,000 births, but the rate is as high as 1 in 282 births among Yupik Eskimos [11]. *In utero* treatment with dexamethasone reduces the abnormal levels of androgens, and this therapy prevents the devastating consequences of wrong sex assignment in affected females. Differentiation of external genitalia occurs between 7 and 12 weeks of gestation, so therapy in at-risk pregnancies must begin earlier, preferably by the 5th week [11]. Cell-free DNA testing provides non-invasive determination of fetal sex at 7 weeks of gestation, thereby enabling rapid discontinuation of dexamethasone for male fetuses [12, 13]. Chorionic villus sampling (CVS) can be performed at 10–12 weeks, at which point therapy can be halted for unaffected females [11]. Dexamethasone treatment (three times daily) will continue throughout pregnancy for an affected female fetus. Maternal side effects of fetal dexamethasone therapy include edema, striae, excess weight gain, Cushin-

goid facial features, facial hair, glucose intolerance, hypertension, gastrointestinal problems, and emotional irritability [8, 11, 14].

Congenital hypothyroidism, which affects approximately 1 out of every 4500 pregnancies, is usually a secondary condition caused by treatment of maternal hyperthyroidism, such as Graves' disease [8]. Fetal goiter can interfere with fetal swallowing and lead to polyhydramnios and premature rupture of membranes. Furthermore, fetal goiter can cause tracheal compression and asphyxia at birth [8, 15]. Fetal hypothyroidism can be successfully treated with levothyroxine. Levothyroxine is administered via intraamniotic injection due to its low transplacental transfer [8, 15].

Fetal hematological disorders that can be treated include alloimmune thrombocytopenia and erythrocyte alloimmunization. Fetal and neonatal alloimmune thrombocytopenia (FNAIT) has an incidence rate of 1 in 1500 and is caused by a maternal antibody-mediated response against a fetal platelet-specific antigen; this may lead to intracranial hemorrhage *in utero* [16]. Women at risk for a pregnancy with FNAIT are usually only identified after having a previous child with the disorder, but maternal administration of intravenous gamma globulin can successfully increase fetal platelet counts [8, 16]. *Erythrocyte alloimmunization* – the reaction of maternal antibodies with fetal erythrocyte antigens – can lead to hemolysis, fetal anemia, and hydrops fetalis [8]. The use of prophylactic anti-D immunoglobulin in Rh-negative women carrying an Rh-positive fetus can reduce the need for intrauterine blood transfusions to treat alloimmune hemolytic disease [17]. It should be noted that there are other types of red-cell alloimmunization besides anti-RhD without prophylactic immune globulins yet available [18].

In addition to the aforementioned indications, there are a number of fetal conditions for which experimental therapeutics are in various stages of testing. *Polyhydramnios* (excess amniotic fluid) affects approximately 1% of pregnancies, of which 55% are idiopathic and 25% are related to fetal diabetes [6, 19]. Amnioreduction and indomethacin administration have been investigated for polyhydramnios therapy, but not as randomized controlled trials [19]. Indomethacin likely decreases fetal urine production, with minor maternal side effects [6]. While some therapeutic options for intrauterine growth restriction currently under investigation require further study and randomized controlled trials to establish efficacy [20], it is clear that smoking cessation lowers rates of low birth weight and preterm birth [21]. Injection of picibanil into the pleural cavity for pleurodesis appears promising for the treatment of early second trimester, non-hydropic fetal chylothorax [22, 23]. Digoxin and furosemide have been injected into fetal intravascular space to treat idiopathic *non-immune hydrops fetalis* [24], and infection-induced non-immune hydrops fetalis has been treated with transplacental antiviral or antibiotic therapy [25]. *Fetal malignancies* are rarely diagnosed *in utero* [26], but this may represent a future area of potential fetal chemotherapy. There are also several examples of

maternal prescriptions with direct or indirect fetal benefit, including tocolytics preventing preterm birth, penicillin to treat syphilis [6], spiramycin for toxoplasmosis [6], antibiotics before delivery to reduce neonatal sepsis [27], and the reduction of maternal–fetal HIV transmission rates by the use of highly active antiretroviral therapy [28].

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REPRODUCTION AND DEVELOPMENT

Ronald J Trent PhD, BSc(Med), MB BS (Sydney), DPhil (Oxon), FRACP, FRCPA, in Molecular Medicine (Third Edition), 2005

FETAL THERAPY

A disappointment in molecular medicine has been the slow advances that have been made in fetal therapy. Although the availability and scope for prenatal diagnosis have improved considerably because of molecular diagnostics, the choices following prenatal diagnosis remain very limited if the baby is affected. It would be hoped that this is only an interim measure so that, in future, an adverse prenatal test is only the start of a fetal therapy option.

In utero fetal therapy is available in a very limited number of situations. Haemolytic disease of the newborn, usually secondary to rhesus immunisation (Rh disease), can be successfully treated by intrauterine blood transfusions (cordocentesis) until the fetus is considered to have reached an age where the risk of further transfusion is greater than the complications associated with prematurity. The ability to obtain pure fetal blood samples by cordocentesis means that the clinical progress of an affected fetus can be monitored more accurately through serial haemoglobin estimations rather than the less precise bilirubin levels in amniotic fluid.

In utero cellular therapies (allogeneic transplants, gene therapy, stem cell therapy and xenotransplantation) are potentially of benefit because the intrauterine fetal environment is ideal (i.e., highly proliferative, immunologically more tolerant and the number of cells required is relatively small). Prenatal correction might be used to minimise end-organ damage that would develop once the fetus was born. Fetal tissues for transplantation might also provide a better source of stem cells into which could be inserted normal genes. The underdeveloped immunological system in the fetus would be useful in situations in which transplantation from a genetically dissimilar donor will induce both graft rejection and graft versus host disease.

Implicit in the scenarios described above is an early detection system (i.e., DNA analysis) for the underlying genetic defect. Despite the obvious advantages of *in utero* fetal cellular therapy, the risks of manipulating the fetus remain major limitations.

In utero surgery to correct abnormalities such as lung lesions, obstructive uropathy, abdominal wall defects, sacrococcygeal teratoma, congenital hydrocephalus and diaphragmatic hernia, neural tube defects and a number of other conditions is available in very few centres. Fetal surgery is still in its early days, so it remains an experimental form of treatment. One of the important problems to overcome before fetal surgery becomes a realistic option is the control of premature labour.

Treating the Neonate

The placenta, which would normally be discarded following childbirth, is now proving to be an important source of haematopoietic stem cells. Cord blood is rich in $CD34_+$ cells (see Chapter 6) and so provides an alternative to bone marrow for transplantation. There is also some preliminary evidence that cord blood is (1) less immunogenic, thereby reducing the risk of transplant rejection, and (2) immunologically less active, and so the frequency of the second problem related to transplantation (graft versus host disease) is also reduced.

Cord blood cell transplantations in the neonate have proven to be effective in the treatment of some genetic disorders, e.g., β thalassaemia. Therefore, the next step from this was to take cord blood at birth from a newborn with the genetic immunodeficiency disorder ADA (adenosine deaminase deficiency) and transduce it *in vitro* with a normal gene. The cord blood was then returned to the newborn within a few days. Early results suggest that there has been long-term expression from the transduced cells; i.e., DNA has been transferred into stem cells.

An HLA-identical match for bone marrow transplantation is difficult to find even with a number of potential siblings as donors. An alternative in this situation is cord blood, which is easy to obtain and store. It also provides a broad ethnic representation, which can be a problem with conventional sources for bone marrow or organ donation. The potential advantage of cord blood for transplantation has led to cord blood banks being established. A disadvantage of cord blood as a source of marrow for transplantation is the small volume obtainable, so that this form of treatment is predominantly used in children. However, the volume problem might be overcome by using recombinant DNA–derived growth factors to increase the number of stem cells circulating in the cord blood.

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Invasive procedures in obstetrics

Yves Ville, in Ultrasound in Obstetrics and Gynaecology, 2009

INTRODUCTION

The introduction of a needle through the maternal abdomen under ultrasound guidance is the basis for invasive prenatal diagnosis and fetal therapy to treat a critically ill fetus. All intrauterine invasive procedures in obstetrics should be carried out under continuous real-time ultrasound control. These procedures carry a risk of fetal loss and/or preterm delivery or intrauterine death.

The most common reason for fetal invasive testing is karyotyping and there are three main techniques used to obtain fetal tissue: chorion villus sampling (CVS), amniocentesis (AC) and fetal blood sampling (FBS). All three have been credited with various risks and it is important to critically appraise the indications for each of these procedures. It is vital to understand that the risk of spontaneous miscarriage is present throughout the pregnancy, even though it decreases with increased gestation: from 15% at 5 weeks down to 1% at 16 weeks of gestation (Fig. 12.1).

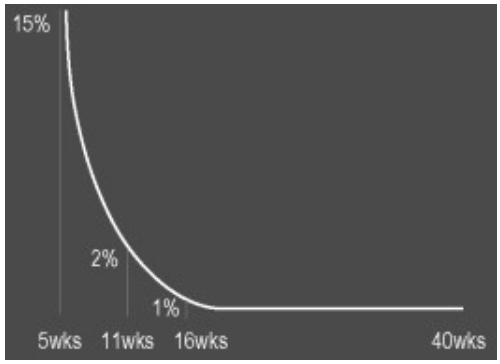

Fig. 12.1. Spontaneous fetal loss rate throughout gestation.

(Reproduced with permission from Hook EB. Down syndrome live births and spontaneous abortions of unknown karyotype. Prog Clin Biol Res 1985;163C:21–24.)

Non-specific risks involve fetal loss which may be idiopathic or may occur as a result of direct fetal injury with subsequent exsanguination or infection. Preterm delivery, intra-amniotic haemorrhage and chorioamnionitis also contribute to the morbidity of invasive procedures. Adequate methodology should include registration of the outcome of all pregnancies without excluding any complication from a causal relationship with the procedure performed.

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Prenatal Treatment of Genetic Diseases in the Unborn

E.J.T. Verweij, D. Oepkes, in Noninvasive Prenatal Testing (NIPT), 2018

Counseling and Ethical Issues for Fetal Genetic Therapy

There seems to be little doubt that in the near future, following improved diagnostic techniques, genetic disease will be treated before birth. The unique feature of fetal therapy is not that the mother needs to decide for her fetus and future child (many other examples of patients unable to decide for themselves exist), but that there is the accepted alternative, at least in many countries, to elect for termination of pregnancy. The other option, to choose for expectant management and if possible, postnatal treatment is rarely controversial, and should perhaps be regarded as standard of care.

In the many examples of prenatally diagnosed genetic diseases where standard care means lifelong severe handicaps, the parents-to-be have to weigh this prospect, both for their future child itself, as well as for themselves and their family, against the also often lifelong burden of possible feelings of doubt and guilt associated with termination of pregnancy. The third option, fetal therapy, would be an easy and logical one if this intervention would be 100% safe and effective, leading to curing the disease completely in all cases, without risks for the fetus and without side effects to the mother. This, however, is rarely if ever the case.

In counseling parents on the option fetal therapy, as an additional choice next to the traditional options, expectant management and termination of pregnancy, a major challenge is to make sure parents understand all possible scenarios, their likelihood and their long-term consequences. Any new treatment, in particular presented by enthusiastic innovative clinician-researchers, bears the risk of being presented or perceived in an overoptimistic way. Obviously, there is hope that the new treatment will lead to a better prognosis, however, by definition there is still little experience, long-term follow-up studies are lacking and both parents and caregivers do not like to emphasize the (often distinct) possibility that the outcome may actually be worse than with standard care. One way to reduce the risk of nonobjective counseling is, in particular in trials, to have the counseling performed by well-informed but independent counselors, supported by properly designed written or online decision aids. Although patients entered in trials generally do better than those not participating (irrespective of the trial arm they are in), it is important to minimize the risk of "therapeutic misconception," emphasizing that a trial by definition means that there is insufficient evidence for the studied treatment.

In their comprehensive review on the scientific and ethical issues of gene editing, the European Society of Human Genetics [48] presented three crucial areas that they thought needed the most attention at this stage in the responsible development and use of gene editing technologies, particularly for uses that directly or indirectly affect humans:

1. Conducting careful scientific research to build an evidence base
2. Conducting ethical, legal and social issues (ELSI) research
3. Conducting meaningful stakeholder engagement, education, and dialogue (SEED).

Especially the last part, involving stakeholders including patient representatives and the general public, seems to gain popularity and acceptance. Since these processes are often time consuming (and thus expensive), they may not be able to keep up with the speed of technical advances. The target group of the treatment options, in particular families carrying genetic diseases, may have difficulties waiting for prolonged comprehensive assessments of all safety issues if there is hope for relief of their burden. Still, scientists and especially the eager, innovative clinicians and their professional societies need to guard their responsibility for careful introduction of these therapies. Preferably, in our view, without the need for legal or governmental control, although this may in many countries be unavoidable.

In the undoubtedly very promising field of gene editing, the main and most complex challenge is how to deal with germ line editing. Although curing a disease not only in the actual patient, but at the same time in his or her offspring seems a great prospect, politicians, lawyers, and the lay public are scared by terms such as "genetically modified children." de Wert and colleagues carefully unravel all legal and ethical aspects in their background document to the ESHRE statement on germ line editing [49].

At this point in time, the debate concentrates on whether or not, and if so what type of germ line editing can be allowed for science to progress. Even early stage preimplantation embryo gene editing will likely result in mosaic embryos and off-target effects that will be hard to detect. To reduce the mosaic risk, gene editing of the sperm cell or oocyte, or their precursors, or even stem cells that differentiate into sperm or oocyte, seems attractive. de Wert et al. state that "whereas most countries currently prohibit germline modification, many of the concepts used in relevant legal documents are ill-defined and ambiguous, including the distinction between research and clinical applications and basic definitions" [49].

We agree with the conclusion from these authors, who represent the European Society of Human Genetics (ESHG) and the European Society for Human Reproduction and Embryobiology (ESHRE), when they state that "from an ethical point

of view, scientists and clinicians must respect the legal and regulatory framework in their country. They also have an important responsibility to help society understand and debate the full range of possible implications of the new technologies, and to contribute to regulations that are adapted to the dynamics of the field while taking account of ethical considerations and societal concerns."

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Tuberous Sclerosis

Sara Shelley, Katherine R. Goetzinger, in Obstetric Imaging: Fetal Diagnosis and Care (Second Edition), 2018

Prenatal

Cardiac rhabdomyomas diagnosed in the fetus tend to regress in early childhood, whereas cerebral lesions tend to progressively increase in size and number over time.[20] There are no known fetal therapies that alter progression of the disease. In families with a known TSC mutation, the identification of cardiac rhabdomyomas on US should prompt further imaging and prenatal genetic testing, keeping in mind that 70%–80% of TSC mutations are sporadic.[3] Prenatal diagnostic testing is available by gene sequencing for a suspected diagnosis of TSC or is available if a known mutation has been identified in the proband. Perinatal morality is significantly increased in cases complicated by fetal dysrhythmia and hydrops fetalis.[27]

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Prenatal Diagnosis and Fetal Therapy

Hanmin Lee, ... Michael R. Harrison, in Pediatric Surgery (Seventh Edition), 2012

Management of Mother and Fetus

Breaching the uterus, whether by puncture or incision, incites uterine contractions. Despite technical advances, disruption of membranes and preterm labor are the Achilles' heel of fetal therapy. Although halogenated inhalation agents provide satisfactory anesthesia for mother and fetus, the depth of anesthesia necessary to achieve intraoperative uterine relaxation can produce fetal and maternal myocardial depression and affect placental perfusion.[10] Indomethacin can constrict the fetal ductus arteriosus and the combination of magnesium sulfate and betamimetics

can produce maternal pulmonary edema. The search for a more effective and less toxic tocolytic regimen led to the demonstration in monkeys that exogenous nitric oxide ablates preterm labor induced by hysterotomy.[32] Intravenous nitroglycerin is a potent tocolytic but requires careful control to avoid serious complications.[1]

Postoperative management is dictated by the degree of intervention. Open fetal surgery by maternal laparotomy and hysterotomy is usually performed with the patient under general anesthesia. Fetal well-being and uterine activity are recorded externally by tocodynamometer. Extensive monitoring, both fetal and maternal, continues postoperatively. Patient-controlled analgesia or continuous epidural analgesia, or both, ease maternal stress and aid tocolysis. After contractions are controlled, monitoring and tocolysis continue and fetal sonograms are obtained at least weekly. Open hysterotomy requires cesarean delivery in this and future pregnancies because of the potential for uterine rupture.[33,34] The most common immediate maternal complication is pulmonary edema due to the administration of perioperative tocolytic agents and intravenous fluids. The incidence was as high as 28% in previous experiences, but with refinement of surgical techniques and tocolytic management the incidence is now approximately 5%.[35] Bleeding that requires transfusion is an infrequent but significant complication of open fetal surgery. Preterm labor and membrane rupture are the most significant complications throughout the remainder of the pregnancy. Close monitoring for contractions, amount of amniotic fluid, membrane disruption, and cervical shape and length must be performed throughout pregnancy.

Patients who undergo percutaneous procedures, performed either with fetoscopic guidance or with image guidance using 1- to 3-mm-diameter devices, usually receive regional or local anesthesia. The requirement for tocolytic therapy is significantly less than for open fetal surgery, and most patients can be safely discharged from the hospital within 24 to 48 hours after the procedure.[35] Maternal bleeding and pulmonary edema are rare. However membrane rupture and preterm labor remain significant complications,[22] and close monitoring is required throughout the remainder of pregnancy.

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Cell-Free DNA-Based Noninvasive Prenatal Testing and Society

Carla van El, Lidewij Henneman, in Noninvasive Prenatal Testing (NIPT), 2018

Being Prepared for the Birth of a Handicapped Child

Prenatal screening for fetal anomalies aims to provide autonomous reproductive choices to the pregnant couple including termination of pregnancy, preparing for having a child with a condition and, in some cases, fetal therapy. Fetal therapy offers an intervention before birth for the purpose of correcting, treating, or diminishing the deleterious effects of a fetal condition. Though the idea may be appealing, fetal therapy is still in its infancy [63] (see Chapter 20). Most parents decide to terminate the pregnancy of a child with a congenital and/or genetic condition after the diagnosis is confirmed but there are differences between countries [5,38,64]. Some current studies on decisions after cfDNA NIPT testing, however, mentioned that parents increasingly choose to use the test results to prepare for a child with a condition and not necessarily for decision-making about termination of pregnancy [65,66]. Thus while the uptake of screening may increase with cfDNA NIPT, either as contingent test or as a first-line test, the impact of the introduction of this new technology on the live birth prevalence of Down syndrome may be less linear than expected.

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