Fetal surgery

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Abstract

Fetal medicine is a super-specialty enterprise and a technology-driven field. The growth and interest in fetal surgery can be largely attributed to advances in fetal imaging and bespoke instruments for in utero intervention. Previously fatal fetal conditions are now being treated using open surgery, minimally invasive procedures, and percutaneous fetal technologies. Several fetal conditions, including myelomeningocele and twin-to-twin transfusion syndrome, have been tested rigorously in RCTs. However, as the specialty of fetal surgery grows, a robust evidence base with long-term follow-up is obligatory for every procedure. This article offers an overview of fetal surgery and antenatal intervention. As more cutting edge therapies come into clinical practice, growing public opinion and medical ethics will play a significant role in the future of this multidisciplinary specialty.

Introduction

Although the eponym is based in antiquity (performed post-mortem in an attempt to save the baby over 2000 years ago), the earliest known record of a caesarean section where the mother survived was in the 16th century. Operating to alter fetal abnormalities remains at the frontier of medical innovation. Understanding of fetal development and disease has been advanced significantly by in utero imaging and animal models. Ultrasonography has thus enabled ‘access into the womb’ for diagnosis and staging of the condition, and documentation of the natural history of the disease. Currently, there are several medical and surgical conditions that can be treated by intrauterine intervention. Careful consideration of the risks and benefits is necessary as intervention has a significant impact not only the fetus but also the health of the mother. Centres performing fetal intervention need to be prepared for emergency preterm delivery with attendant fetal and maternal morbidity. Specialist multidisciplinary teams are essential, not only for the skilled delivery of fetal therapy but also to share expert ‘non-directive’ antenatal counselling with expectant parents.

The unborn patient

Fetal therapy comprises several types of intervention.

Open surgery

Open operations are performed via a hysterotomy while maintaining the placental circulation. In the vast majority of cases, the fetus is returned to the uterus and the pregnancy continues until near to term. Open surgery provides excellent surgical exposure to the fetus, but there is a significant risk of maternal morbidity and premature labour.

Minimally invasive surgery

Minimally invasive surgery encompasses ultrasound-guided percutaneous intervention and fetoscopic surgery. For the latter, case selection is critical because, although there is a reduced risk of maternal haemorrhage and early labour, the working field for the operator is far more limited. EUROFETUS funded by the European Commission has been working closely with leading world manufacturers in improving and adapting instruments for fetoscopic surgery.

Medical intervention

Medicines administered to the mother can have a therapeutic effect on the fetus. Examples are antenatal corticosteroids to promote fetal lung development and, perhaps more experimentally, stem cell and gene therapy delivery.

Ex utero intrapartum therapy

Congenital compressive lesions of the fetal airway can be catastrophic. Ex utero intrapartum therapy (EXIT) was developed as a controlled way to provide access to the fetus with a critical airway. During the EXIT procedure, the head and neck of the fetus are delivered through a hysterotomy while retaining the maternofetal circulation. An airway is secured either by intubation, resection of a compressive lesion, or placement of extracorporeal membrane oxygenation catheters for life support. Once the procedure has been completed safely, the umbilical

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cord is divided, and the baby is delivered and stabilized. Unlike caesarean section, in which uterine contraction and haemostasis is desired, uterine hypotonia is fundamental in maintaining the uteroplacental circulation. Therefore, a rapid reversal of uterine relaxation is vital to prevent maternal haemorrhage after delivery. A full antenatal work-up incorporating parental counselling, fetal ultrasonography, fetal MRI, echocardiography, and karyotyping analysis is performed before EXIT. A highly skilled multidisciplinary team including radiologists, obstetricians, neonatologists, anaesthetists, ear, nose and throat specialists, and paediatric surgeons is crucial to its success.

### Intrauterine transfusion

Fetal anaemia can be a cause of significant perinatal morbidity and mortality. Despite the introduction of RhD immunoglobulin prophylaxis, alloimmunization remains a leading cause of fetal anaemia. Although the majority of pregnancies with mild fetal anaemia are managed with careful monitoring, severe anaemia can be treated with intrauterine transfusion (IUT) of red cells. Transfusions are administered between 18 and 35 weeks via the umbilical vein. Complications include infection, premature rupture of membranes, preterm labour, and umbilical cord haematoma. Fetal transfusions here highlight the benefit of exposure to high procedure numbers in improving outcomes. Zwiers and colleagues examined outcomes from over 1600 cases of IUT in a single centre; fetal loss declined from 4.7 per cent to 1.8 per cent over 15 years of experience. An overall survival rate of 90 per cent has been reported in moderate to severe fetal anaemia, with small numbers experiencing any long-term morbidity.

### Twin-to-twin transfusion syndrome

Twin-to-twin transfusion syndrome (TTTS) is a fascinating condition. Occurring in 1 in 40 monozygotic monochorionic twin pregnancies, it is a progressive disorder caused by abnormal perfusion across an unbalanced placental anastomosis. If left untreated, severe TTTS carries a mortality rate of 60–100 per cent. In 2004, the EUROFETUS group published results from an RCT comparing conventional serial amnioreduction therapy with endoscopic laser ablation of aberrant vessels in the placenta. It demonstrated higher rates of perinatal survival in the laser group (57 versus 41 per cent), higher rates of survival at 6 months, later date of delivery with higher birth weights, and reduced neurological morbidity at aftercare follow-up. Selective fetal laser ablation has now become the primary therapy for TTTS. The importance of exploring long-term outcomes was discussed in a 2014 Cochrane review. This showed that, although there were no differences in overall death rates between amnioreduction and laser coagulation, more babies were alive and well at 6 years’ follow-up without neurological abnormality in the laser-treated group.

### Fetal shunts

Dilatation of the fetal urinary tract is seen in 1 per cent of all routine antenatal scans. In the majority of mild cases, this has resolved by birth. Severe lower urinary tract obstruction (LUTO) can lead to renal dysplasia, oligohydramnios, and pulmonary hypoplasia in the fetus. The most common underlying causes of LUTO are posterior urethral valves in the male fetus and urethral atresia in both sexes. Although often occurring in isolation, 10 per cent of urinary tract obstructions are associated with syndromes such as VACTERL sequence (vertebral, anorectal, cardiac, tracheo-oesophageal fistulas, renal and limb abnormalities). Investigation for associated anomalies is essential as this may preclude any fetal intervention.

Intrauterine shunting for LUTO aims to decompress the dilated urinary tract to protect renal function. Restoring renal function should improve reduced amniotic fluid production and in turn promote lung development. Harrison and colleagues described the first intrauterine shunting operation at the University of California San Francisco in 1981. The procedure involves inserting an ultrasound-guided percutaneous pigtail catheter into the fetal bladder, which then communicates with the maternal amniotic cavity. Procedure numbers have grown steadily over recent decades. However, postnatal clinical outcomes in shunted cases remained similar to those in untreated control cohorts.

The PLUTO (Percutaneous vesicoamniotic shunting for fetal Lower Urinary Tract Obstruction) study was a UK-led randomized, multicentre trial comparing watchful waiting conservative management with percutaneous vesicoamniotic shunt placement. Owing to many challenges in recruitment (31 maternal–fetal cases recruited of a required 150) the trial was not completed, although anecdotally there may have been improved survival at 1 year with vesicoamniotic shunting. Fetal intervention for obstructive uropathy, therefore, currently lacks robust level 1 evidence.

Fetal pleural effusions can occur in isolation or secondary to pathological lung malformations, associated congenital heart defects, and acquired infection. Placement of a pigtail chest drain catheter—a thoracoamniotic shunt—under ultrasound guidance as a potential therapy has been explored. Although there is currently no level 1 evidence comparing serial thoracocentesis and pleural shunting, several large case studies have shown markedly improved outcomes when pleural shunting is deployed in the hydropic fetus.

### Myelomeningocele

Myelomeningocele (MMC) or open spina bifida is the most common severe neural tube defect compatible with life, affecting 1 in 2000 live births. MMC can be detected with greater than 90 per cent sensitivity at the 20-week fetal anomaly scan. Raised levels of acetylcholine and α-fetoprotein in amniotic fluid are further diagnostic tools available. The condition is characterized by incomplete closure of the caudal spinal canal. The exact cause of MMC is still not fully understood; however, a two-hit hypothesis likely explains the human phenotype: first, extrusion of the meninges through the structural defect, which is then compounded by contact of the exposed spinal cord with the chemical effects of amniotic fluid in utero. Infants born with MMC suffer hydrocephalus, debilitating urinary and faecal incontinence, varying degrees of lower limb paralysis, and cerebral cognitive impairment. Treatment strategies previously available were termination of pregnancy or postnatal repair of the defect. In 1995, Meuli and colleagues showed in an MMC lamb model that prenatal closure of the neural tube defect could reduce exposure of the spinal cord to amniotic fluid while dramatically improving neurological outcome postnatally. Open, fetoscopic, and hybrid techniques for in utero repair have consequently developed. Human prenatal repair involves maternal hysterotomy with primary or patch dura repair fetal wound skin closure.

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MOMS (Management of Myelomeningocele Study)\textsuperscript{31}, published in 2011, was the first prospective RCT comparing prenatal MMC repair with a conventional postnatal repair. The trial, which ran over some 7 years and included 183 women, showed a significant reduction in ventriculoperitoneal shunting in babies who underwent prenatal repair. Long-term effects on mental development and motor function were also notably more favourable in the prenatal surgery group ($P=0.007$). Prenatal intervention was, however, associated with a higher incidence of premature delivery and maternal morbidity\textsuperscript{31,32}.

The next exciting steps in evolution of MMC management are focused on developing alternatives to open repair to reduce fetal–maternal morbidity. The CECAM (Chirurgia Endoscopica para Correccion Antenatal da Meningomielocele) trial\textsuperscript{33} is in a phase 2 stage, and uses a biocellulose patch in place of open surgical closure. The utility of stem cell therapy in MMC is also being investigated by groups in California and Boston, USA, with promising results emerging from experimental models\textsuperscript{34,35}.

Progress and outcomes of these ongoing studies are awaited with keen interest.

**Congenital diaphragmatic hernia**

Congenital diaphragmatic hernia (CDH) is characterized by herniation of the abdominal organs through a diaphragmatic defect into the thoracic cavity. In most instances, this is associated with severe lung hypoplasia and pulmonary hypertension. Surgery with reduction of the viscera and repair of the diaphragmatic defect in newborns has an overall survival rate of 70 per cent\textsuperscript{36}. It was thought for some years that in utero repair of CDH may rescue abnormal lung growth and hence achieve better survival. Although prenatal CDH repair had some early success, high-risk fetuses there remained, however, a dismal prognosis\textsuperscript{36,37}.

Fetal tracheal occlusion, initially by tracheal clipping and then by internal balloon occlusion, was pioneered as a new way of rescuing abnormal lung development in CDH in the 1990s. Harrison and colleagues published the first RCT of fetal tracheal occlusion versus elective delivery of newborns with CDH treated using standard postnatal care therapy. Patient enrolment was terminated early by the steering trial committee owing to failure to show significant improvement(s) in mortality or morbidity among the two experimental cohorts. Subsequent work with minimally invasive fetoscopy-guided technology (fetal endoscopic tracheal occlusion) has now claimed improving outcome(s) with fetal tracheal occlusion\textsuperscript{38} (Fig. 2).

The EUROFETUS group led by Jan Deprest at the University of Leuven, Belgium, is currently undertaking the TOTAL (Tracheal Occlusion to Accelerate Lung Growth) RCT\textsuperscript{39} to evaluate outcomes more conclusively. At the time of writing this article, the results are awaited with much interest in the next year or so (J. Deprest, personal communication).

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**Fig. 1 Antenatal uropathy and vesicoamniotic shunting**

\textbf{a} MRI T2-weighted sagittal image of abdominal cavity in a hydropic fetus showing ascites (yellow arrow) and a hydronephrotic kidney (white arrow). \textbf{b} Schematic drawing of vesicoamniotic shunting; double-ended pigtail shunt drains urine from obstructed bladder into amniotic sac. Images courtesy of Editor-in-Chief, Rickham’s Neonatal Surgery, 2018, PD Losty, Flake AW, Rintala RJ, Hutson JM, Iwai N (eds). Copyright UZ Leuven and J. Deprest.

**Fig. 2 Percutaneous fetoscopic endoluminal tracheal occlusion for congenital diaphragmatic hernia**

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IUT, intrauterine transfusion; TAPS, Twin Anaemia Polycythaemia Sequence; OR, odds ratio; TTTS, twin-to-twin transfusion syndrome.
Medical therapy

Alongside current developments in fetal surgery, medical interventions have shown benefit for many fetal diseases. Administration of corticosteroids to women in preterm labour to accelerate lung maturation and improve survival in premature newborns has had notable landmark success in obstetrics and neonatology. A Cochrane review of almost 30 trials convincingly showed that a single corticosteroid course given during preterm labour significantly reduced the overall health burden of neonatal pulmonary disease. A possible antenatal medical therapy for pulmonary hypertension in CDH is the phosphodiesterase inhibitor sildenafil. Early experimental studies have shown improved lung parenchymal development. The care provided based evaluation of fetal therapy. Centralization of fetal services, ethical approval, and large-scale funding. Alongside RCT validation, techniques and interventions improve, well designed RCTs are essential. Establishing and running robust clinical trials will present further challenges to researchers, including recruitment, ethical approval, and large-scale funding. Alongside RCT validation, long-term follow-up is crucial to establish a true evidence-based evaluation of fetal therapy. Centralization of fetal services will permit a higher caseload with better specialization and experience for medical professionals, which in turn will improve the care provided.

Future directions

Current evidence for fetal therapy is summarized in Table 1. With the ongoing development and innovation of new technologies, fetal surgery will no doubt continue to grow. As the available techniques and interventions improve, well designed RCTs are essential. Establishing and running robust clinical trials will present further challenges to researchers, including recruitment, ethical approval, and large-scale funding. Alongside RCT validation, long-term follow-up is crucial to establish a true evidence-based evaluation of fetal therapy. Centralization of fetal services will permit a higher caseload with better specialization and experience for medical professionals, which in turn will improve the care provided.

Disclosure. The authors declare no conflict of interest.

References

2. de Lorimier AAD. Hypoplastic lungs in fetal lambs with surgically produced congenital diaphragmatic hernia. Surgery 1967; 62:12–17