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Review Article

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[1]. 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[2]. 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[3]. 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[4]. EUROFETUS funded by the European Commission has been working closely with leading world manufacturers in improving and adapting instruments for fetoscopic surgery[5].

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[6]. A full antenatal work-up incorporating parental counselling, fetal ultrasonography, fetal MRI, echocardiography, and karyotype analysis is performed before EXIT[7]. A highly skilled multidisciplinary team including radiologists, obstetricians, neonatologists, anaesthetists, ear, nose and throat specialists, and paediatric surgeons is crucial to its success[8].

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[9]. 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[10,11]. 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[12] 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[13,14].

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[15,16]. If left untreated, severe TTTS carries a mortality rate of 60–100 per cent. In 2004, the EUROFETUS group published results from an RCT[17] 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[18]. 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[19,20]. The most common underlying causes of LUTO are posterior urethral valves in the male fetus and urethral atresia in both sexes[21]. 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[3] 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[21]. Procedure numbers have grown steadily over recent decades. However, postnatal clinical outcomes in shunted cases remained similar to those in untreated control cohorts[22].

The PLUTO (Percutaneous vesicoamniotic shunting for fetal Lower Urinary Tract Obstruction) study[23] was a UK-led randomized, multicentre trial comparing watchful waiting conservative management with percutaneous vesicoamniotic shunt placement (*Fig. 1*). 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[23]. 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[24]. 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[25–27].

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[28]. 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*[29]. 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[30] 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.

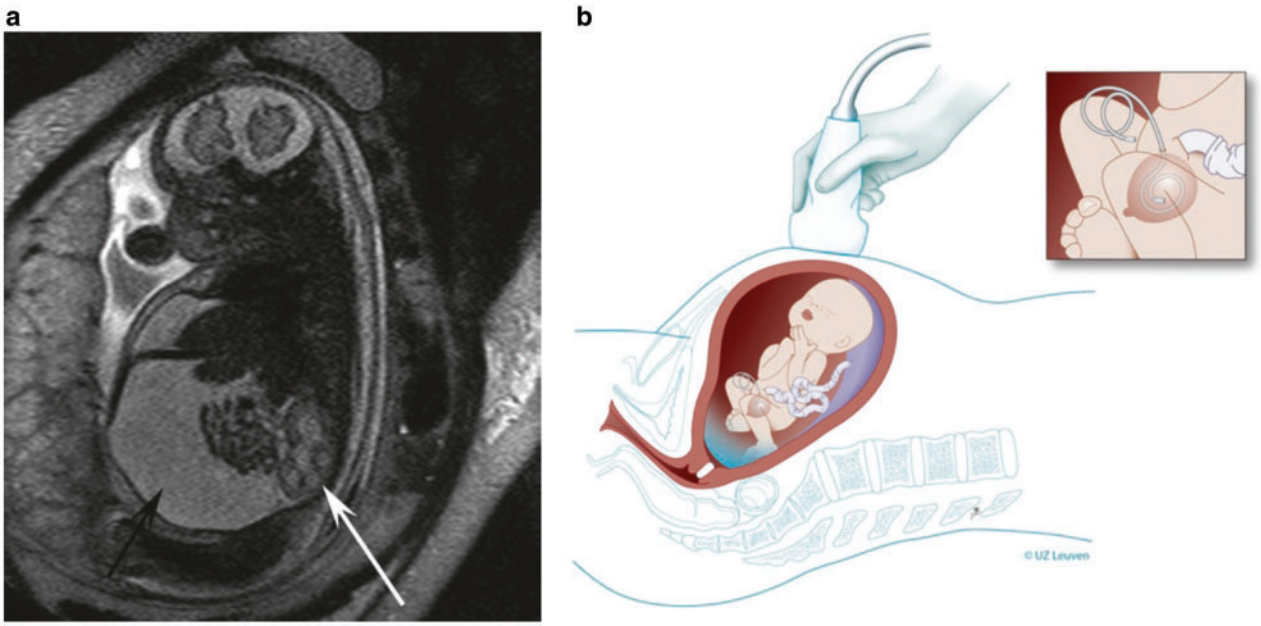

Fig. 1 Antenatal uropathy and vesicoamniotic shunting

a MRI T2-weighted sagittal image of abdominal cavity in a hydropic fetus showing ascites (yellow arrow) and a hydronephrotic kidney (white arrow). **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.

MOMS (Management of Myelomeningocele Study)[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[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 Endoscópica para Correção Antenatal da Meningomielocele) trial[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[34,35]. Progress and outcomes of these ongoing studies are awaited with keen interest.

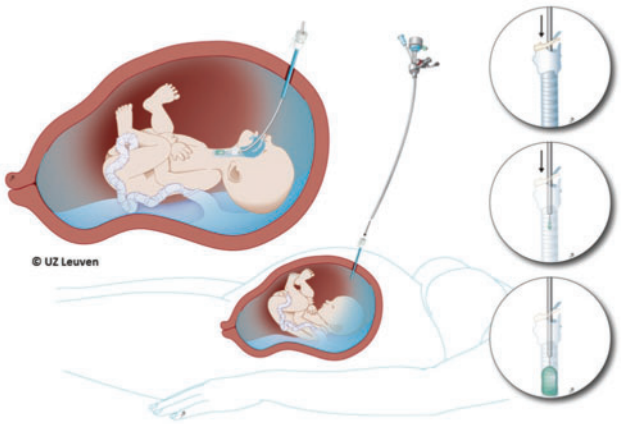

Fig. 2 Percutaneous fetoscopic endoluminal tracheal occlusion for congenital diaphragmatic hernia

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.

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[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, in high-risk fetuses there remained, however, a dismal prognosis[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[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[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).

Table 1 Summary of current evidence in fetal therapy

Condition	Therapy	Study	Study period	No. of patients	Results	Type of study	Reference
Fetal anaemia	IUT	Case series of intrauterine transfusions from 1 institution	1998–2015	1678	Procedures performed after 2011: 97% survival; 3.3% procedure-related complication per fetus; 1.8% perinatal loss per fetus	Case series	Zwiers *et al.*[12]
		LOTUS: long-term follow-up after IUT	1987–2008	291	4.8% risk of neurodevelopmental impairment after IUT	Observation	Lindenburg *et al.*[13]
TTTS	Laser ablation therapy	Endoscopic laser therapy *versus* serial amnioreduction	1999–2002	142	Higher likelihood of survival of at least 1 twin to 28 days ($P = 0.009$) and 6 months ($P = 0.002$) in laser therapy group; higher likelihood of being free from neurological complications at 6 months of age (52 *versus* 31%; $P = 0.003$)	RCT	Senat *et al.*[17]
		Selective vessel coagulation Solomon technique *versus* placental equator ablation	2008–2012	274	Reduced incidence of TAPS in selective laser coagulation group (3 *versus* 16%; OR 0.16); reduced recurrence of TTTS (1 *versus* 7%; OR 0.21); no difference in perinatal mortality and neonatal morbidity	RCT	Slaghekke *et al.*
Twin reversed arterial perfusion sequence	Radiofrequency ablation		2007–2010	7	57% risk of preterm premature rupture of membranes; 1 intrauterine death; 71% survival at 6 months	Case series and systematic review	Cabassa *et al.*
	Intrafetal laser ablation		2000–2013	17	82% survival; 18% intrauterine deaths	Case series	Pagani *et al.*
Lower urinary tract obstruction	Vesicoamniotic shunting	Conservative management *versus* shunt placement	2006–2010	31 (suspended early owing to recruitment issues)	8 of 12 live births alive at 28 days in shunt group *versus* 4 of 12 in conservative management group; 7 of 12 *versus* 3 of 12 at 1 year	RCT	Morris *et al.*[23]
Pleural effusions with hydrops	Thoracoamniotic shunting	Review of outcomes with shunt placement	1998–2013	75	68% survival of fetuses with hydrops; 36 of 75 born prematurely	Retrospective review	Peranteau *et al.*[27]
			1997–2003	21	44% survival of fetuses with hydrops; 8 intrauterine deaths; 3 neonatal deaths; 70% preterm delivery	Retrospective review	Smith *et al.*[24]
Myelomeningocele	Prenatal surgical repair of defect	MOMS: randomized trial of prenatal *versus* postnatal repair of myelomeningocele		183 (153 evaluated)	40% shunt placement in prenatal surgery *versus* 82% in postnatal repair ($P = 0.001$). Improved mental development and motor function at 30 months ($P = 0.007$). Gestational age at delivery 34 *versus* 37 weeks	RCT	Adzick *et al.*[31]
Congenital diaphragmatic hernia	Fetal tracheal occlusion	TOTAL trial (TOTAL clinical trials identifier NCT01240057 Randomized Intervention Clinical Trial)			Results awaited		

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[40] 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[41].

Stem cell and gene therapies offer hope for a wide range of human pathology, from haemoglobinopathies and osteogenesis imperfecta to regenerative fetal medicine technologies with tissue engineering[42]. The majority of these therapies are at an early experimental phase; however, they undoubtedly represent a new frontier in fetal medicine.

Future directions

Current evidence for fetal therapy in summarized in *Table 1*. With the ongoing development and innovation of new technologies, fetal surgery will no doubt continue to grow[43,44]. 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[45].

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References

1. U.S. National Library of Medicine. Cesarean Section—A Brief History: *Part 1*. https://www.nlm.nih.gov/exhibition/cesarean/part1.html (accessed 9 June 2020)
2. de Lorimier AAD. Hypoplastic lungs in fetal lambs with surgically produced congenital diaphragmatic hernia. *Surgery* 1967; **62**:12–17
3. Harrison MR, Golbus MS, Filly RA, Callen PW, Katz M, de Lorimier AA *et al.* Fetal surgery for congenital hydronephrosis. *N Engl J Med* 1981;**306**:591–593
4. Deprest J, Jani J, Lewi L, Ochsenbein-Kölble N, Cannie M, Doné E *et al.* Fetoscopic surgery: encouraged by clinical experience and boosted by instrument innovation. *Semin Fetal Neonatal Med* 2006;**11**:398–412
5. Deprest JA, Gratacos E. Obstetrical endoscopy. *Curr Opin Obstetr Gynecol* 1999;**11**:195–203
6. Bouchard S, Johnson MP, Flake AW, Howell LJ, Myers LB, Adzick NS *et al.* The EXIT procedure: experience and outcome in 31 cases. *J Pediatr Surg* 2002;**37**:418–426
7. Hedrick HL. *Ex utero* intrapartum therapy. *Semin Pediatr Surg* 2003;**12**:190–195
8. Mychaliska GB, Bealer JF, Graf JL, Rosen MA, Adzick NS, Harrison MR. Operating on placental support: the *ex utero* intrapartum treatment procedure. *J Pediatr Surg* 1997;**32**:227–231
9. Moise KJ. Fetal anemia due to non-Rhesus-D red-cell alloimmunization. *Semin Fetal Neonatal Med* 2008;**13**:207–214
10. Dodd JM, Windrim RC, Van Kamp IL. Techniques of intrauterine fetal transfusion for women with red-cell isoimmunisation for improving health outcomes. *Cochrane Database Syst Rev* 2012; (9)CD007096
11. Papantoniou N, Sifakis S, Antsaklis A. Therapeutic management of fetal anemia: review of standard practice and alternative treatment options. *J Perinatal Med* 2013;**41**:71–82
12. Zwiers C, Lindenburg ITM, Klumper FJ, de Haas M, Oepkes D, Van Kamp IL. Complications of intrauterine intravascular blood transfusion: lessons learned after 1678 procedures. *Ultrasound Obstet Gynecol* 2017;**50**:180–186
13. Lindenburg IT, Smits-Wintjens VE, van Klink JM, Verduin E, van Kamp IL, Walther FJ *et al.* Long-term neurodevelopmental outcome after intrauterine transfusion for hemolytic disease of the fetus/newborn: the LOTUS study. *Am J Obstet Gynecol* 2012; **206**:141.e1–141.e8
14. Schumacher B, Moise KJ. Fetal transfusion for red blood cell alloimmunization in pregnancy. *Obstet Gynecol* 1996;**88**:137–150
15. Lutfi S, Allen VM, Fahey J, O'Connell CM, Vincer MJ. Twin–twin transfusion syndrome: a population-based study. *Obstet Gynecol* 2004;**104**:1289–1297
16. Hoek G, Brunekreef B. Acute effects of a winter air pollution episode on pulmonary function and respiratory symptoms of children. *Arch Environ Health* 1993;**48**:328–335
17. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery *versus* serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J Med* 2004;**351**: 136–144
18. Roberts D, Neilson JP, Kilby MD, Gates S. Interventions for the treatment of twin–twin transfusion syndrome. *Cochrane Database Syst Rev* 2014;(**1**)CD002073
19. Dudley JA, Haworth JM, McGraw ME, Frank JD, Tizard EJ. Clinical relevance and implications of antenatal hydronephrosis. *Arch Dis Child Fetal Neonatal Ed* 1997;**76**:F31–F34
20. GOV.UK. Fetal Anomaly Screening: Programme Handbook—GOV.UK *[Internet]*. https://www.gov.uk/government/publications/fetal-anomaly-screening-programme-handbook (accessed 8 June 2020)
21. Ruano R. Fetal surgery for severe lower urinary tract obstruction. *Prenat Diagn* 2011;**31**:667–674
22. Elder JS, Duckett JW, Snyder HM. Intervention for fetal obstructive uropathy: has it been effective? *Lancet* 1987;**330**:1007–1010
23. Morris RK, Malin GL, Quinlan-Jones E, Middleton LJ, Hemming K, Burke D *et al.* Percutaneous vesicoamniotic shunting *versus* conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. *Lancet* 2013;**382**:1496–1506
24. Smith RP, Illanes S, Denbow ML, Soothill PW. Outcome of fetal pleural effusions treated by thoracoamniotic shunting. *Ultrasound Obstet Gynecol* 2005;**26**:63–66
25. Picone O, Benachi A, Mandelbrot L, Ruano R, Dumez Y, Dommergues M. Thoracoamniotic shunting for fetal pleural effusions with hydrops. *Am J Obstet Gynecol* 2004;**191**:2047–2050
26. Yinon Y, Grisaru-Granovsky S, Chaddha V, Windrim R, Seaward PGR, Kelly EN *et al.* Perinatal outcome following fetal chest shunt insertion for pleural effusion. *Ultrasound Obstet Gynecol* 2010;**36**:58–64
27. Peranteau WH, Adzick NS, Boelig MM, Flake AW, Hedrick HL, Howell LJ *et al.* Thoracoamniotic shunts for the management of fetal lung lesions and pleural effusions: a single-institution review and predictors of survival in 75 cases. *J Pediatr Surg* 2015;**50**: 301–305

28. Cameron M, Moran P. Prenatal screening and diagnosis of neural tube defects. *Prenat Diagn* 2009;**29**:402–411
29. Korenromp MJ, Van Gool JD, Bruinese HW, Kriek R. Early fetal leg movements in myelomeningocele. *Lancet* 1986;**327**:917–918
30. Meuli M, Meuli-Simmen C, Hutchins GM, Yingling CD, Hoffman KM, Harrison MR *et al. In utero* surgery rescues neurological function at birth in sheep with spina bifida. *Nat Med* 1995;**1**:342–347
31. Adzick NS, Thom EA, Spong CY, Brock JW, Burrows PK, Johnson MP *et al.* A randomized trial of prenatal *versus* postnatal repair of myelomeningocele. *N Engl J Med* 2011;**364**:993–1004
32. Adzick NS. Fetal surgery for spina bifida: past, present, future. *Semin Pediatr Surg* 2013;**22**:10–17
33. Pedreira DAL, Zanon N, Nishikuni K, Moreira De Sá RA, Acacio GL, Chmait RH *et al.* Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial. *Am J Obstet Gynecol* 2016;**214**:111.e1–111.e11
34. Chen YJ, Chung K, Pivetti C, Lankford L, Kabagambe SK, Vanover M *et al.* Fetal surgical repair with placenta-derived mesenchymal stromal cell engineered patch in a rodent model of myelomeningocele. *J Pediatr Surg* 2018;**53**:183–188
35. Shieh HF, Tracy SA, Hong CR, Chalphin AV, Ahmed A, Rohrer L *et al.* Transamniotic stem cell therapy (TRASCET) in a rabbit model of spina bifida. *J Pediatr Surg* 2019;**54**:293–296
36. Losty PD. Congenital diaphragmatic hernia: where and what is the evidence? *Semin Pediatr Surg* 2014;**23**:278–282
37. Harrison MR, Adzick NS, Flake AW, Jennings RW, Estes JM, MacGillivray TE *et al.* Correction of congenital diaphragmatic hernia *in utero*: VI. hard-earned lessons. *J Pediatr Surg* 1993;**28**:1411–1418
38. Al-Maary J, Eastwood MP, Russo FM, Deprest JA, Keijzer R. Fetal tracheal occlusion for severe pulmonary hypoplasia in isolated congenital diaphragmatic hernia: a systematic review and meta-analysis of survival. *Ann Surg* 2016;**264**:929–933
39. DeKoninck P, Gratacos E, Van Mieghem T, Richter J, Lewi P, Ancel AM *et al.* Results of fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia and the set up of the randomized controlled TOTAL trial. *Early Hum Dev* 2011;**87**:619–624
40. Neilson JP. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Obstet Gynecol* 2007;**109**:189–190
41. Russo FM, De Bie F, Hodges R, Flake A, Deprest J. Sildenafil for antenatal treatment of congenital diaphragmatic hernia: from bench to bedside. *Curr Pharm Des* 2019;**25**:601–8
42. Sagar R, Götherström C, David AL, Westgren M. Fetal stem cell transplantation and gene therapy. *Best Pract Res* 2019;**58**:142–53
43. Wagner AM, Schoeberlein A, Surbek D. Fetal gene therapy: opportunities and risks. *Adv Drug Deliv Rev* 2009;**61**:813–821
44. Roybal JL, Santore MT, Flake AW. Stem cell and genetic therapies for the fetus. *Semin Fetal Neonatal Med* 2010;**15**:46–51
45. Kaviani A, Guleserian K, Perry TE, Jennings RW, Ziegler MM, Fauza DO. Fetal tissue engineering from amniotic fluid. *J Am Coll Surg* 2003;**196**:592–597