Fetal Surgery

K Sampat1, PD Losty\*1 2

1. Department of Paediatric Surgery, Alder Hey Children's Hospital, Liverpool UK
2. Institute of Child Health, Alder Hey Children's Hospital, Liverpool UK

\*Corresponding Author:

Paul D Losty MD FRCSI FRCS(Ed) FRCS(Eng) FRCS(Paed) FEBPS

Professor Of Paediatric Surgery

Alder Hey Children's Hospital NHS Foundation Trust

Department Of Women's and Children's Health

Faculty Of Health And Life Science

University Of Liverpool, UK

Email; paul.losty@liverpool.ac.uk

No funding declared

Manuscript category: Review (By invitation BJSurg Editors Office)

Paper is notbased on previous communication(s) to a Society or Meeting.

# Summary

Fetal medicine is a super speciality 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 through open, minimally invasive procedures and percutaneous fetal technologies. Several fetal conditions, including myelomeningocele and twin to twin transfusion syndrome, have been rigorously tested in randomised controlled trials. However as the speciality 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 speciality.

# Introduction

Our fascination with the unborn is not a new phenomenon. Since the earliest record of a successful caesarean section, in the 16th century, fetal intervention has evolved into a medical field of its own. (1) Fetal surgery now operates at the frontier of medical innovation with cutting edge technology, genetic and stem cell research.

Our understanding of fetal development and disease was significantly advanced with animal models alongside progress made with *in utero* imaging. In the 1960s, a congenital diaphragmatic hernia (CDH) lamb model was established at the University of California San Francisco (UCSF). The model provided vital comparative data on the pathophysiology and lethality of the human condition. (2) This enterprise greatly influenced many aspects of current management of CDH including in utero diagnosis, perinatal care plans and timing of surgery in the newborn. Prenatal ultrasonography has dramatically changed the face of fetal therapy. As a result of more accurate imaging, there is now a better understanding of fetal pathology with earlier diagnosis of progressive, debilitating conditions. Ultrasonography has thus enabled ’access into the womb' for diagnosis and therapy. As outlined in establishing the criteria for fetal intervention by Harrison et al., successful fetal therapy should include accurate diagnosis and staging of the condition, a well documented natural history of the disease, an absence of effective postnatal treatments and supporting evidence from animal studies. Careful consideration of risks and benefits is necessary as intervention poses a significant impact not only the fetus but also the health of the mother. (3)

Currently, there are several medical and surgical conditions which can be treated by intrauterine intervention. Centres performing fetal intervention need to be prepared for emergency preterm delivery, 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 parent(s). Not all fetal treatments have been placed under the scrutiny of randomised controlled trials, perhaps understandably given the hurdles to overcome, but this is changing. This article makes effort to provide an overview of fetal intervention procedures.

## The Unborn Patient

Fetal therapy includes :

1. **Open surgery** – performed via a hysterotomy while maintaining the placental circulation. In the vast majority of cases, the fetus is returned to the uterus and 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.
2. **Minimally invasive surgery** - Encompassing ultrasound-guided percutaneous intervention and fetoscopic surgery. With the latter, case selection is critical as 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)
3. **Medical intervention** - Medicines administered to the mother can have therapeutic effect on the fetus, e.g. antenatal corticosteroids to promote fetal lung development and, perhaps more experimentally, stem cell and gene therapy delivery.

# Ex Utero Intrapartum Therapy (EXIT)

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 whilst retaining the materno-fetal circulation. An airway is secured either through intubation, resection of a compressive lesion or the placement of ECMO catheters for life support. Once the procedure is safely completed, the umbilical cord is divided, the baby delivered and stabilised. Unlike a caesarean section, where uterine contraction and haemostasis is desired, uterus 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 workup incorporating parental counselling, fetal ultrasound, fetal MRI, echocardiography and karyotype analysis is performed before EXIT. (7) A highly skilled multidisciplinary team including radiology, obstetrics, neonatology, anaesthetists, ENT and paediatric surgeons is crucial to its success. (8)

In a retrospective study of 31 EXIT procedures performed at the world-renowned Children's Hospital Philadelphia, USA, there was only a single fatality recorded in a fetus due to inability to secure the airway with two maternal complications from bleeding and wound dehiscence. (6)

Intrauterine transfusion

Fetal anaemia can be a cause of significant perinatal morbidity and mortality. Despite the introduction of RhD immunoglobulin prophylaxis, alloimmunisation remains a leading cause of fetal anaemia. (9) While 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 18-35 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 case numbers in improving outcomes: Zweirs et al. examined outcomes from over 1600 cases of IUT in a single centre; where fetal loss declined from 4.7% to 1.8% over 15 years of experience. (12) An overall survival rate of 90% is reported in moderate to severe fetal anaemia(s), with low 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 1:40 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%. In 2004 the EUROFETUS group published results from a randomised controlled trial comparing conventional serial amnioreduction therapy with endoscopic laser ablation of the aberrant vessels in the placenta. It demonstrated higher rates of perinatal survival in the laser group (57% vs 41%), higher rates of survival at six months, later date of delivery with higher birth weights and reduced neurological morbidity at aftercare follow up. (17) Selective fetal laser ablation (S-FLA) has now become primary therapy for TTTS. The importance of exploring long term outcomes was presented in a 2014 Cochrane review; This showed although there were no differences in overall death rates comparing amnioreduction and laser coagulation, more babies were alive and well at six years follow up without neurological abnormality in the laser-treated group. (18)

# Fetal Shunts

Dilatation of the fetal urinary tract is seen in 1% 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 (PUV) in the male fetus and urethral atresia in both sexes. (21) Although often occurring in isolation, 10% of cases of urinary tract obstruction are associated with syndromes such as VACTERL sequence (vertebral, anorectal, cardiac, tracheoesophageal fistulae, renal and limb abnormalities). Investigation for associated anomalies is essential as this may preclude any fetal intervention.

Intrauterine shunting for LUTO is aimed at decompressing the dilated urinary tract to protect renal function. Restoring renal function should improve reduced amniotic fluid production and in turn promote lung development. Michael Harrison described the first intrauterine shunting operation at UCSF in 1981. (3) The procedure involves inserting an ultrasound-guided percutaneous pigtail catheter into the fetal bladder, which then communicates with the maternal amniotic cavity. (21) Case numbers have grown steadily over recent decade(s). However, postnatal clinical outcomes in shunted cases remained similar to untreated 'control' cohorts. (22)

The PLUTO (Percutaneous vesico-amniotic shunting for fetal Lower Urinary Tract Obstruction) study was a UK led randomised, multicentre trial comparing 'watchful waiting' conservative management and percutaneous vesico-amniotic shunt placement. (23) Due to many challenges in recruitment (31 maternal-fetal cases recruited out of a required 150) the trial was not completed, although anecdotally there may have been improved survival at one year with vesico-amniotic shunting. (23) Fetal intervention for obstructive uropathy, therefore, currently lacks robust level 1 evidence.

**Figure 1**

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 option was 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) (26,27)

# 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 >90% sensitivity at the 20-week fetal anomaly scan. Raised levels of acetylcholine and alpha-fetoprotein in amniotic fluid are further diagnostic tools at our disposal. (28) The condition is characterised 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. Firstly the extrusion of the meninges through the structural defect, which is then compounded by contact of the exposed spinal cord to the chemical effects of amniotic fluid in utero. (29) . Those 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. Meuli and colleagues (1995) showed in an MMC lamb model that prenatal closure of the neural tube defect could reduce the exposure of the spinal cord to amniotic fluid while dramatically improving neurological outcome postnatally. (30) Open, fetoscopic and hybrid techniques for in utero repair have consequently developed. Human prenatal repair involved maternal hysterotomy with primary or patch dura repair fetal wound skin closure.

The Management of Myelomeningocele Study (MOMS trial) published in 2011 was the first prospective randomised controlled trial comparing prenatal MMC repair with a conventional postnatal repair. The trial, which ran over some seven 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)

Next exciting steps in evolution of MMC management are focused at developing alternatives to open repair to reduce fetal-maternal morbidity. The Chirurgia Endoscópica para Correção Antenatal da Meningomielocele (CECAM) trial is in a phase 2 stage utilising a biocellulose patch in place of 'open surgery' closure. (33) The utility of stem cell therapy in MMC is also being investigated by groups in California and Boston, USA, with promising results emerging in animal models. (34)(35) Progress and outcomes of these ongoing studies are awaited with keen interest.

# Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is characterised by herniation of abdominal organs through a diaphragmatic defect into the thoracic cavity. In most cases, this is associated with severe lung hypoplasia and pulmonary hypertension. Surgery with viscera reduction and repair of the diaphragmatic defect in newborns has an overall survival rate of 70%. (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. (37) (36)

Fetal tracheal occlusion, initially with tracheal clipping and then with internal balloon occlusion, was pioneered as a new way to rescue abnormal lung development in CDH in the 1990s. Harrison et al. published the first randomised controlled trial of fetal tracheal occlusion vs elective delivery of CDH newborns with standard postnatal care therapy(s). Case enrolment was terminated early by the steering trial committee for failure to show significant improvement(s) in mortality or morbidity among the two experimental group cohorts. Subsequent work with minimally invasive fetoscopy guided technology (FETO) claims improving outcome(s) now with fetal tracheal occlusion. (38)

**Figure 2**

The EUROFETUS group led by Jan Deprest at the University of Leuven, Belgium is currently undertaking the RCT TOTAL trial (Tracheal Occlusion to Accelerate Lung Growth) to evaluate outcomes more conclusively. (39) At the time of writing this BJS article results are awaited with much interest in the next year or so (Jan Deprest Personal communication, 2020).

# Fetal Medical Therapy

Alongside current developments in fetal surgery, medical interventions show benefit for many fetal diseases.

Corticosteroids administered to women in preterm labour to accelerate lung maturation and improve survival in premature newborns is a 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. (40) A possible antenatal medical therapy for the pulmonary hypertension in congenital diaphragmatic hernia is phosophodiesterase inhibitor sildenafil. Early animal studies have shown improved lung parenchymal development. (41)

Stem cell and gene therapy(s) 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 are undoubtedly a new frontier in fetal medicine.

# Future Directions

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, the need for well designed randomised controlled trials 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 followup is crucial to establish a true evidence-based evaluation of the fetal therapy. Centralisation of fetal services will permit a higher caseload volume with better specialisation and experience for medical professionals, which in turn will improve the care provided. (45)

**Table 1**

References:

1. Cesarean Section - A Brief History: Part 1 [Internet]. [cited 2020 Jun 9]. Available from: https://www.nlm.nih.gov/exhibition/cesarean/part1.html

2. de Lorimier AA DFT. Hypoplastic lungs in fetal lambs with surgically produced congenital diaphragmatic hernia. Surgery. 1967;(62):12–7.

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. 1982 Mar 11;306(10):591–3.

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. Vol. 11, Seminars in Fetal and Neonatal Medicine. 2006. p. 398–412.

5. Deprest JA, Gratacos E. Obstetrical endoscopy. Vol. 11, Current Opinion in Obstetrics and Gynecology. 1999. p. 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(3):418–26.

7. Hedrick HL. Ex utero intrapartum therapy. Semin Pediatr Surg. 2003;12(3):190–5.

8. Mychaliska GB, Bealer JF, Graf JL, Rosen MA, Adzick NS, Harrison MR. Operating on placental support: The ex utero intrapartum treatment procedure. In: Journal of Pediatric Surgery. 1997. p. 227–31.

9. Moise KJ. Fetal anemia due to non-Rhesus-D red-cell alloimmunization. Semin Fetal Neonatal Med. 2008 Aug 1;13(4):207–14.

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 of Systematic Reviews. 2008.

11. Papantoniou N, Sifakis S, Antsaklis A. Therapeutic management of fetal anemia: Review of standard practice and alternative treatment options. Vol. 41, Journal of Perinatal Medicine. 2013. p. 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(2):180–6.

13. IT L, VE S-W, JM van K, Verduin E, IL van K, FJ W, et al. Long-term neurodevelopmental outcome after intrauterine transfusion for hemolytic disease of the fetus/newborn: the LOTUS study. In: American Journal of Obstetrics & Gynecology [Internet]. 2012. p. 141.e1-8. Available from: https://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=104508181&site=ehost-live

14. Schumacher B, Moise KJ. Fetal transfusion for red blood cell alloimmunization in pregnancy. Vol. 88, Obstetrics and Gynecology. 1996. p. 137–50.

15. Lutfi S, Allen VM, Fahey J, O’Connell CM, Vincer MJ. Twin-twin transfusion syndrome: A population-based study. Obstet Gynecol. 2004;104(6):1289–97.

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(5):328–35.

17. Senat M-V, 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 [Internet]. 2004;351(2):136–44. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa032597

18. Roberts D, Neilson JP, Kilby MD, Gates S. Interventions for the treatment of twin-twin transfusion syndrome. Vol. 2014, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2014.

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(1):F31–4.

20. Fetal anomaly screening: programme handbook - GOV.UK [Internet]. [cited 2020 Jun 8]. Available from: https://www.gov.uk/government/publications/fetal-anomaly-screening-programme-handbook

21. Ruano R. Fetal surgery for severe lower urinary tract obstruction. Vol. 31, Prenatal Diagnosis. 2011. p. 667–74.

22. Elder JS, Duckett JW, Snyder HM. Intervention for Fetal Obstructive Uropathy: Has It Been Effective? Vol. 330, The Lancet. 1987. p. 1007–10.

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(9903):1496–506.

24. Smith RP, Illanes S, Denbow ML, Soothill PW. Outcome of fetal pleural effusions treated by thoracoamniotic shunting. Ultrasound Obstet Gynecol. 2005;26(1):63–6.

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(6):2047–50.

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 Jul;36(1):58–64.

27. Peranteau WH, Scott Adzick N, Boelig MM, Alan W. F, 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 Feb 1;50(2):301–5.

28. Cameron M, Moran P. Prenatal screening and diagnosis of neural tube defects. Vol. 29, Prenatal Diagnosis. Prenat Diagn; 2009. p. 402–11.

29. Korenromp MJ, Van Gool JD, Bruinese HW, Kriek R. Early Fetal Leg Movements in Myelomeningocele. Vol. 327, The Lancet. 1986. p. 917–8.

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(4):342–7.

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 [Internet]. 2011 Mar 17 [cited 2020 Jun 9];364(11):993–1004. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1014379

32. Scott Adzick N. Fetal surgery for spina bifida: Past, present, future. Semin Pediatr Surg [Internet]. 2013 Feb [cited 2020 Jun 26];22(1):10–7. Available from: /pmc/articles/PMC6225063/?report=abstract

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(1):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 Jan 1;53(1):183–8.

35. Shieh HF, Tracy SA, Hong CR, Chalphin A V., Ahmed A, Rohrer L, et al. Transamniotic stem cell therapy (TRASCET) in a rabbit model of spina bifida. J Pediatr Surg. 2019 Feb 1;54(2):293–6.

36. Losty PD. Congenital diaphragmatic hernia: Where and what is the evidence? Semin Pediatr Surg. 2014;23(5):278–82.

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(10):1411–8.

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. Vol. 264, Annals of Surgery. Lippincott Williams and Wilkins; 2016. p. 929–33.

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(9):619–24.

40. JP N. Cochrane update: antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Obstet Gynecol [Internet]. 2007;109(1):189–90. Available from: http://oxfordbrookes.idm.oclc.org/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cin20&AN=106267006&site=ehost-live

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;

42. Sagar R, Götherström C, David AL, Westgren M. Fetal stem cell transplantation and gene therapy. Vol. 58, Best Practice and Research: Clinical Obstetrics and Gynaecology. Bailliere Tindall Ltd; 2019. p. 142–53.

43. Wagner AM, Schoeberlein A, Surbek D. Fetal gene therapy: Opportunities and risks. Vol. 61, Advanced Drug Delivery Reviews. 2009. p. 813–21.

44. Roybal JL, Santore MT, Flake AW. Stem cell and genetic therapies for the fetus. Semin Fetal Neonatal Med. 2010 Feb;15(1):46–51.

45. Kaviani A, Guleserian K, Perry TE, Jennings RW, Ziegler MM, Fauza DO. Fetal tissue engineering from amniotic fluid. Vol. 196, Journal of the American College of Surgeons. 2003. p. 592–7.