Antenatal screening and fetal intervention

Brian W Davies

Abstract

Congenital malformations are a common cause of reduced life expectancy and disability and can affect all body systems, thus are relevant to all surgeons. One in fifty children will have a major or significant congenital anomaly at birth. Since the advent of antenatal ultrasound there has been the potential to diagnose many congenital anomalies before birth. This can forewarn parents and clinicians, so that treatment can be started promptly following birth rather than waiting for the baby to become symptomatic. It has also raised the possibility of treatment in utero with the goal of stopping or reversing the pathological effects of the anomaly on the developing tissues, which will, hopefully, reduce morbidity and mortality once the baby is born and thus improve outcomes. This article focuses on congenital anomalies relevant to surgeons, initially looking at screening and diagnosis and how this may affect treatment and surgery following delivery. The second part will look at some of the interventions that have been tried to treat 'surgical' congenital anomalies in utero.

Keywords Antenatal screening; antenatal ultrasound; congenital diaphragmatic hernia; lower urinary tract obstruction; spina bifida

Screening

In the UK, antenatal screening is offered to all pregnant women. This involves;

- Blood tests to look for red cell anomalies (sickle cell, thalassaemia), blood bourn infections (syphilis, hepatitis B, HIV) and red cell antibodies and rhesus status in the mother and, in combination with an early pregnancy ultrasound, the potential risk that the baby has a trisomy chromosomal anomaly.
- US scanning. They are offered an early (at 11–14 weeks' gestation) and detailed structural (at 18–21 weeks) US scan to look for congenital anomalies.

It is vital for both clinicians and parents to appreciate that these tests:

- Will not detect all anomalies, and a number of serious life-limiting conditions cannot be detected until after birth.
  - This is also true for the infant with multiple congenital anomalies, where one or two anomalies maybe been seen, but the tests may not be able to detect the other anomalies, thus the parents and clinician may not have the full picture of the child's diagnosis until after birth. For example, in the VACTERL association (Vertebral, Ano-rectal, Cardiac, Trachea-oEsophageal, Renal and Limb), the cardiac, vertebral, limb and some of the renal anomalies can often be seen on the 20-week scan; however, oesophageal atresia and ano-rectal anomalies probably will not be able to be seen.
- That not all anomalies seen will have an impact on the child, and the scan may find some incidental conditions that will resolve spontaneously or will not require any treatment nor limit life in any respect.
- Have varying degrees of accuracy (i.e. sensitivity and specificity)
  - Some it can detect with high precision, for example, gastroschisis where the intestines are seen within the amniotic fluid.
  - In other conditions, US may be suggestive. For example, the combination of polyhydramnios and minimal or no fluid seen within the fetal stomach may be indicative of oesophageal atresia; however, this will need post-natal tests to confirm or refute. This is more likely to be seen later in pregnancy, rather than on an 18–21 week scan.
  - The scan may see markers that can in some cases indicate pathology. For example, 'echogenic' bowel, when the intestines look brighter than usual, in approximately 50% this indicates intestinal pathology of a variety of causes, including meconium ileus due to cystic fibrosis, but in the other 50% the children have normal intestinal function and growth.

Further tests used are selectively dependent upon the results of the above, or if the parents' family history indicates that other tests are needed. These can involve testing the parents (e.g. if the scan shows features that may be consistent with cystic fibrosis [CF], both parents can be tested to see if they are carriers of the common mutations of the CF gene) or the baby.

The baby's chromosomes can be checked by invasive tests including chorionic villus biopsy or aminocentesis. Both these have a quoted 1% risk of inducing a miscarriage, thus cannot be taken lightly. More recently, testing for cell-free fetal DNA (cffDNA) within a blood sample taken form the mother has been developed. This looks for fragments of DNA that have come from the placenta. It can be done relatively early in the pregnancy (from 10 weeks). As this has no risk of miscarriage, this technology is developing rapidly. There are plans to adopt cffDNA screening for common aneuploidies (trisomy 13, 18, 21 and Turner's syndrome [XO]) into the UK screening programme, initially for women whose hormone tests have suggested an increased risk. Many private providers are offering these tests in the UK. Presently it has a 0.3% false positive rate, thus positive tests should be confirmed by invasive tests. It has a 2% false negative rate and in 4% the results are inconclusive. Testing for single gene defects from cffDNA is underdevelopment.

Direct fetal blood sampling is possible in later pregnancy and can be done at the same time giving intravenous treatment to the baby. Most commonly this would be for in-utero blood transfusions in cases of fetal anaemia.

Fetal magnetic resonant imaging MRI scans are possible and can add detail to the findings of antenatal US. This is most commonly performed when there are concerns about brain development (Table 1).

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Complications of antenatal screening

Complication	Causes	Significance
Miscarriage	Chorionic villus biopsy Aminocentesis	Death of fetus
Unnecessary parental distress	False positives; lack of precision/specificity of 'markers' of anomalies	Psychological distress and sometimes clinical depression
Unnecessary invasive tests	False positives; lack of precision/specificity of 'markers' of anomalies	Potential for miscarriage
Missed diagnoses[a]	False negatives	Baby presents with symptoms and suffers complications that might have been avoided if treatment had commenced earlier
Reduction in society's value of people with disabilities	Emphasis on in-utero diagnosis with potential termination of pregnancy for serious disabilities	Parents who chose to continue with pregnancy feel under pressure to undergo a termination Patients may not feel valued
Termination of pregnancy based on gender alone	Society/family preference (parents learn the likely sex of baby from a sonographer and seek a termination from another provider)	Large number (millions) of 'missing' girls in some societies Beware this occurs in most countries

[a] Conditions that can often be diagnosed on routine screening (i.e. excludes conditions that can't be seen at 18–21 weeks).

Table 1

Antenatal counselling

Once an antenatal anomaly has been detected then this will need to be confirmed and explained to the parents. Initially this will be by the local obstetrician or screening midwife. Following this a prompt referral to a regional fetal medicine department is usually made where they can meet with a feto-maternal obstetrician and ideally a clinician who has experience of looking after children born with that condition. This gives the opportunity for them to meet one of the team who will continue to be involved in the care of their child following birth. Following this, plans for ongoing care of both mother and baby, including timing, mode and place of delivery can be made (Table 2).

Counselling aims to inform the mother/parents of the condition, the treatment required and the impact on the child both initially and lifelong. Uncertainties in either the diagnosis or possible associated other anomalies need to be discussed. A balance of the potential risks of mortality and morbidity, versus the potential for a good outcome needs to be struck. It is important to remember that at the diagnosis the parents will go through a bereavement-like process as their dreams of their perfect baby will have been broken. They thus will only remember some of what is said, especially on the day of diagnosis, thus written information and possibly multiple appointments will be required. Similarly, this group of patients will nearly always have looked up the condition on-line before subsequent appointments.

My practice has been to see mothers/couples on their second visit to the feto-maternal clinic. I find it helpful to watch the relevant part of the US as in many conditions this helps me to know what end of the spectrum of complexity of the condition this infant is likely to be following delivery. For example, a small exomphalos would usually be repaired with a single operation, whereas a large one may need staged management, thus by observing the scan I can assess which method is more likely to be suitable for this baby. I would, of course, mention the range of potential surgical options.

I start the counselling by asking how much they understand of the problem. This is really helpful, so that I can start from where they are at, and clarify any misunderstandings they may have from the start. For some conditions, photographs of previous babies are very useful, for example, gastroschisis, where the intestines are eviscerated through a small defect in the abdominal wall adjacent to the umbilical cord, but remember that not all will want to see them. They will want to know practicalities, including confirmation of the diagnosis, timing of surgery, likely length of stay and follow-up. Similarly, the surgeon can reinforce the importance of breast milk and how this can still make a real difference to the baby especial if they have a gastrointestinal anomaly. By mentioning the importance of post-operative pain relief, you will demonstrate that you are concerned about the things that they are worried about and will help reduce their fears. Parents will often have a lot of questions, thus it is important to plan enough time and not appear rushed. I summarize the conversation in a letter to the lady/couple.

Fetal intervention

In-utero treatment has been tried for various congenital anomalies. The following three conditions illustrate well the rational for and the challenges of fetal intervention.

Congenital diaphragmatic hernia (CDH)

Relevant to paediatric surgery (and potentially ENT, thoracic and general surgery)

This is a severe malformation with up to 40% mortality. This significant mortality is due to poor development of the lungs which, at birth, are both small and immature. In view of this high mortality rate, surgeons have investigated the possibility of intervening in utero to try to allow better in-utero lung development, so that, by birth the baby has adequate lung function to survive, then thrive. It is important to appreciate there is a wide spectrum of the lung hypoplasia from relatively mild to fatal. Similarly, some infants with CDH have other serious anomalies, particularly cardiac or chromosomal, that will impact survival.

In the 1980s and 1990s techniques were developed to perform open fetal surgery, aiming to perform the same operation as postnatally. This involved opening the uterus at approximately

Conditions seen by a paediatric surgeon in a feto-maternal clinic

Diagnosis	Percentage incidence[a]	Action AN	Delivery plan	Neonatal plan
Gastroschisis	31%	Surveillance of fetal health and growth	Aim for induced vaginal delivery at 37–38 weeks in paediatric surgery centre	Cover intestines at birth (plastic bag/ cling film) iv fluids and NGT, maintain temperature Early surgical reduction or placement of intestines into silo bag
Exomphalos	11%	Look for other anomalies	Minor: await spontaneous labour Major: elective caesarean section to avoid trauma	Look for, assess and treat other anomalies Minor: surgical repair at 24–48 hours of age Major: surgical repair or staged management
Congenital diaphragmatic hernia (CDH)	11%	Look for other anomalies	Aim for vaginal delivery a close to term as possible at paediatric surgery centre	Immediate neonatal intensive care focusing on optimizing respiratory and cardiac function Surgical repair, if stable (usually 2–7 days of age)
Duodenal or jejunal atresia	7%	Consider amino-drainage if severe polyhydramnios	Await spontaneous labour, delivery at paediatric surgery centre	NGT and iv fluids Abdominal X-ray at 4–6 hours to confirm diagnosis Surgery at 24–48 hours
Oesophageal atresia (possible)	6%	Consider amino drainage if severe polyhydramnios	Await spontaneous labour	Midwife to pass stiff NGT prior to first feed to confirm/refute diagnosis
Congenital lung lesions[b]	13%	Very few require in-utero intervention	Await spontaneous labour Small: local delivery Large: regional centre	If no respiratory signs or distress, nurse with mother, X-ray at 36–48 hours, then review in out patients Symptomatic may need early surgical intervention/excision
Intra-abdominal cysts	7%	Monitor size of cyst	Await spontaneous labour Small: local delivery Large: regional centre	If no intestinal signs or distress, nurse with mother, home 48 hours, US at 1–2 weeks, then review in out patients Symptomatic may need early surgical intervention/excision
Teratomas and other masses	3%	Monitor growth of mass	Sacrococcygeal teratomas; caesarean section	Will need surgical assessment Sacrococcygeal tetratomas will need early excision
Other	11%			

[a] Incidence based on author's own experience on counselling 531 mothers/couples with paediatric surgical conditions (NB, practise in Nottingham is that renal anomalies are seen by a paediatric nephrologist, cardiac anomalies by a paediatric cardiologist & neurological anomalies by a neurosurgeon).
[b] Congenital pulmonary airways malformations (cPAM), sequestrations, and other lung anomalies.

Table 2

25 weeks' gestation via a classical vertical hysterotomy, partially delivering the baby to expose the left chest and abdomen, but keeping the head in the uterus. Both a thoracotomy and laparotomy were required to reduce the viscera (unlike the post-natal operation which only requires one incision), and a patch repair of the diaphragm performed. The abdominal incision was closed with a patch to prevent increased intra-abdominal pressure. It was not possible to reduce the liver without affecting the blood flow in the umbilical vein; thus, cases where the liver was seen to be herniated were excluded. This is important as these are often the more severe cases. This approach was abandoned following a small trial showing the outcome was no better than post-natal management.[1] This trial illustrated some major challenges of fetal intervention. First, prematurity; the intervention group had a mean gestation of 32 weeks compared to 38 weeks in the compassion group. Second, exclusion; in this trial many cases (40 of 55) were excluded due to liver herniation, i.e. it wasn't suitable for potentially the most severe cases.

Since then researchers have focused first on trying to assess the potential severity of the lung disease on ante-natal imaging and second on less invasive in-utero interventions that can be applied to the most severe cases.

Assessing potential post-natal severity is important, so that cases likely to survive are managed with post-natal intervention, thus avoiding the complications of in-utero therapy, targeting in-utero therapy on cases unlikely to survive postnatally. Two factors have been extensively investigated and seem to correlate to postnatal outcome. These are measuring the size of the contralateral lung and whether or not the liver is herniated into the thorax. Measuring the volume of a complex and compressed three dimensional structure is challenging. As a marker comparing the cross-sectional measurements of the contralateral lung and comparing these to the size of the baby's head have been developed (so-called lung–head ratio [LHR]). This is then compared to a normal range for the baby's gestation and expressed as a percentage of normal. It is important to remember that the lungs are not just small, but also have a varying degree of immaturity, which scanning does not assess, thus it can only be an estimate of predicted survival. Combining this and whether or not the liver is herniated then can be compared to survival rates from previous infants.

It has been observed that in fetuses/babies with complete tracheal occlusion, the lungs are very big. This observation led researchers to try to temporarily occlude the trachea in utero in fetuses with severe CDH in the hope that the lungs would become bigger. Initially this was performed by tying or clipping the trachea in utero, requiring a reversal ± tracheostomy at birth while the baby is still attached to the placental circulation. This has been refined to a fetal endoscopic procedure, where a bronchoscope is introduced though a fetoscope allowing placement of a balloon in the baby's trachea (Figure 1). This can be removed by a further fetoscopic procedure or at birth. This has seen increased size of the lungs at birth with apparent improved survival. However, a randomized controlled trial (RCT) performed in the USA (1999–2001) was terminated early as, on interim analysis, there was no difference in survival rates, mainly due to a better than expected survival in the control group.[2] This led to the technique being abandoned in the USA; however, in Europe researchers have persisted with trying to refine the technique, the selection process and the timing of the intervention or reversal. Further trials are ongoing, with a trial in 'moderate lung hypoplasia' just finished recruiting (May 2019) and in 'severe lung hypoplasia' ongoing (website http://www.totaltrial.eu).

Pharmacological treatment for antenatally diagnosed CDH has also been considered; however, so far none has been found to be beneficial.

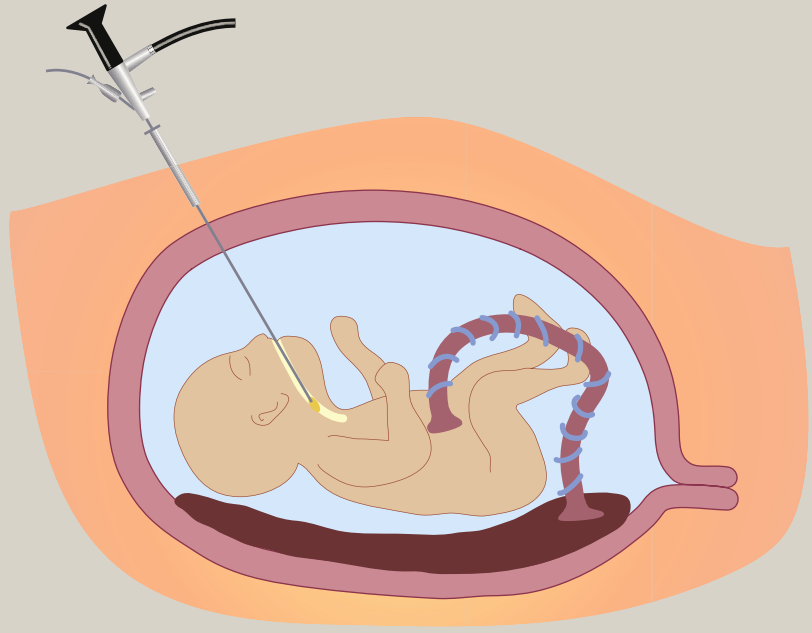
In summary, in cases of antenatally diagnosed CDH, despite much research and some initial promising results, in-utero treatment remains experimental, thus needs to be limited to formal research trials.

Spina bifida (myelomeningocele)

Relevant to: neurosurgery, orthopaedics, urology and paediatric surgery/urology

In spina bifida, the problem is not primarily about mortality, as most babies will survive, but about the lifelong morbidity;

Fetal endoscopic tracheal occlusion (feto) for in-utero treatment of congenital diaphragmatic hernia



Some centres use a flexible endoscope for the fetal bronchoscopy, rather than a rigid scope as illustrated above.

From the Japan Fetal Therapy Group (http://en.fetusjapan.jp/method/method-68). With kind permission

Figure 1

neurological impairment/deficit below the level of the lesion with paralysis, bowel and bladder incontinence and associated hydrocephalus and hindbrain herniation (so called Arnold-Chiari II malformation). The rational of repairing the defect in utero is to preserve more of the neurological function below the level of the lesion and to prevent or reverse the hindbrain herniation, with the hope to lessen the incidence of hydrocephalus and improve intellectual performance.

After developing the technique of open in-utero repair of spina bifida, a multicentre RCT was performed; the Management of Myelomeningocele Study (MOMS).[3] This study is worth reading as it shows the thoroughness needed for a surgical RCT to be successful. They reviewed outcomes at three points: early neonatal, 12 months and 30 months. They noted in the discussion the importance of on-going long-term follow-up. In all, 183 mothers were randomized over 7.75 years, one of whom declined prenatal surgery after initially consenting. Of note is that a further 299 women declined to participate or refused to consent. Prenatal surgery was performed before 26 weeks' gestation. The trial was stopped early after interim analysis showed improved outcome with prenatal surgery. Both of the researchers primary outcome measures; the risk of death or need for ventricular-peritoneal shunting by the age of 12 months and scores on a composite measure of mental and motor function, with adjustment for lesion level, at 30 months of age, were improved in the prenatal surgery group. There were two deaths in each group. In the prenatal surgery group these were one in-utero fetal death and one extreme prematurity death, both occurring on the fifth post-operative day. In the post-natal surgery group, two infants died due to complications of a severe Arnold-Chiari II malformation.

Prenatal surgery also improved several secondary outcomes, including the degree of hindbrain herniation associated with the Chiari II malformation, motor function and the likelihood of being able to walk independently, as compared with postnatal surgery.

Maternal and neonatal complications were increased in the prenatal surgery group, especially premature delivery and uterine dehiscence at delivery.

In summary, in-utero surgery for spina bifida has shown an improvement in the short and medium term outcomes, but with increased complications to both mother and baby. This is now being performed in the UK with the first babies born in 2018.

Severe lower urinary tract obstruction (LUTO)

Relevant to: paediatric urology, urology, transplantation

Severe obstruction of the lower urinary tract in utero leads to oligohydramnios or even anhydramnios. This in turn leads to pulmonary hypoplasia, which is often fatal in the perinatal period. Also the obstruction causes renal damage with survivors often having poor renal function that progresses to end-stage renal failure in infancy or childhood. The cause of the obstruction is usually either severe posterior urethral valves or urethral atresia.

Fetal intervention aims to relieve the obstruction, with the hope that the pulmonary hypoplasia and renal damage are preventable or reversible. A shunt can be placed under ultrasound guidance between the bladder and the amniotic cavity (a vesico-amniotic shunt). To be effective, it is likely that this will need to be relatively early in pregnancy during the canalicular phase of lung development (16–24 weeks' gestation).

The percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO) study was set up to test the effectiveness of these shunts in males. This was a multicentre, international RCT. The literature review and power calculation concluded that 150 mothers/infants would be required to take part for the trial to be statistically robust. Unfortunately, after 4 years the study had only recruited 31 mothers/infants. Thus although shunting seemed to give better post-natal outcomes, at the cost of increased fetal death, this was not statistically significant.[4]

Looking at the reasons for poor recruitment in this study reveals three key reasons:

- First, after being thoroughly counselled to the prognosis, many mothers/couples opted for termination of the pregnancy (68, i.e. more than double those who took part).
- Second, 45 mothers/couples or their feto-maternal obstetrician, decided not to be randomized, but chose one or other of the treatment options. A separate publication showed that these tended to be less severe cases, thus with increased doubt about the benefits of intervention.
- Third, many centres struggled to get local approval or sponsorship, thus were delayed in being able to take part, thus only seven of the 21 hospitals taking part managed to recruit any patients.

In summary, a vesico-amniotic shunt may have a role in improving the outcome in severe LUTO, however, this hasn't been proven, which gives mothers/couples and their doctors a dilemma when considering in-utero treatment for this condition where there is significant mortality and morbidity to the infant without it (Table 3).

Other fetal interventions

Other interventions have been developed or tried and often it is the most minimally invasive that have been most successful.

Fetoscopic lasering of abnormal blood vessels on the placenta has shown to be beneficial to both twins in twin-to-twin transfusion syndrome.

Most congenital lungs lesions do not cause problems in utero or at birth, thus they do not require fetal intervention. However, in a few, fetal hydrops (i.e. fetal cardiac failure that usually leads to in-utero death) develops before the baby is mature enough for delivery and neonatal surgery/intervention. In this situation, survivors have been reported following open fetal surgery and lobectomy, laser ablation of feeding vessels (in pulmonary sequestration), and aspiration and/or shunting of large cysts.

Treatment of fetal anaemia by in-utero transfusion is well established.

Although not an invasive intervention, the single biggest intervention that affects paediatric surgeons in terms of numbers of children, is the administration of antenatal steroids when there is threatened or likely premature delivery. This has made a marked improvement to neonatal respiratory management and outcome, improving survival of extreme prematurity such that they are more infants who will survive to then suffer the surgical complications of prematurity (e.g. necrotizing enterocolitis, retinopathy of prematurity).

Complications of fetal intervention

Complication	Causes	Significance
Prematurity	The human uterus tolerates intervention poorly: • Inducing preterm labour • Premature rupture of membranes • Chorioamnionic separation • Placental abruption • Infection; chorioamnionitis • Oligohydraminos	Baby at risk of the complications of prematurity as well as the complications of the congenital anomaly
In-utero fetal death	Various maternal & fetal causes	Death
New complications (i.e. unexpected complication caused by interfering with in-utero development)	For example, a case series of significant tracheal dilatation following fetal endoscopic tracheal occlusion (FETO) has been reported	Baby needs treatment for a further problem (e.g. a few infants requiring tracheostomy following FETO) Importance of long-term follow-up to refining techniques
Maternal complications	Complications of GA in pregnancy (if required) Venous thombo-embolism Uterine rupture (open fetal surgery) Scaring – increased risk of maternal transfusion at delivery	Increased morbidity to both mother and baby
Impact of future fertility	Scaring to uterus, particularly with open interventions	Potential reduction in fertility, however, recent studies suggest that this can be avoided by improved techniques
Impact on subsequent pregnancies	Open fetal surgery requires classical vertical hysterotomy (rather than 'lower segment')	Risk of uterine rupture and requirement for Caesarean delivery of all subsequent pregnancies (increased morbidity to both mother and baby)
Socio-Economic	Fetal therapy often involves travel to distant super-specialist hospital and long-periods of ante-natal hospitalization or limitations on maternal activity	Mother/families chose not to have treatment or default from follow-up, thus local hospital may have to treat complications that they are not equipped to manage
Ethical challenges	• One patient undergoing invasive treatment for the benefit of another patient • Potential impact on third patient (future pregnancies)	Consent more complex Research approval more complex

Table 3

Conclusion

The surgeon needs to be aware of which conditions they treat postnatally can potentially be diagnosed antenatally, so that they can work with obstetricians to counsel parents accurately. For those conditions with a poor prognosis, research is on-going to see if therapy given in utero improves outcomes. ◆

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