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Minimally invasive fetal therapy

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The implementation of systematic pregnancy screening programmes, and the increased use and improving quality of medical imaging techniques, have lead to earlier detection and better understanding of the natural history of fetal anomalies. Where most fetal conditions are adequately treatable after birth, some disorders progress during fetal life and can lead to severe morbidity or fetal and neonatal demise. This inherently raises the question of prenatal therapy. Some fetal conditions are amenable for fetal surgical intervention, part of them by minimal access. We provide an overview of the rationale for, the technical aspects of, and (if available) the outcomes of the most common minimally invasive prenatal therapies. These include intrauterine transfusion, fetal cardiac procedures, interventions for lower urinary tract obstruction, thoracic and pulmonary pathology, fetoscopic laser of placental vessels for twin-to-twin transfusion syndrome, and selective reduction in complicated monochorionic twin pregnancies.

Introduction

Fetal therapy became a clinical reality after the introduction of high-resolution ultrasound. It has been boosted by the implementation of systematic pregnancy screening programmes that have led to

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the early detection and better understanding of the natural history of fetal anomalies. Only a limited number of fetal anomalies are progressive in nature, so that, when left untreated, they lead to fetal and neonatal demise, or severe morbidity. Prenatal intervention aims at halting or reversing the progression of these diseases and improving the postnatal outcome. Where some fetal conditions such as open neural tube defects,[1] large solid lung masses or sacrococcygeal teratomas[2] are still treated through maternal laparotomy and hysterotomy, we have witnessed an increased introduction of minimally invasive fetal therapeutic procedures over the past 2 decades. In this chapter, we present an overview of the rationale for, the technical aspects of, and outcomes of the most common minimally invasive prenatal therapeutic procedures. These procedures are reserved for well-selected fetuses at the most severe end of the spectrum, and are only offered in a limited number of centres. Optimal patient selection, expert counselling, rigorous clinical protocols, and experienced multidisciplinary teams are strict criteria for fetal therapy programmes.[3]

Intrauterine transfusion

Intrauterine transfusions are carried out for severe fetal anaemia and thrombocytopaenia. Technical aspects of the procedure are identical for both conditions. Given the relative rarity of fetal thrombocytopaenia, we refer for issues on current diagnosis and management to an excellent recent review [4] and restrict our discussion to fetal anaemia. The incidence of rhesus D (RhD) hemolytic disease haemolytic disease has decreased dramatically since the routine administration of anti-D immunoglobulins. As a consequence, other causes of fetal anaemia, such as feto–maternal haemorrhage twin anaemia polycythaemia sequence, parvovirus B19 infections and haemolytic disease, resulting from other than RhD red blood cell antigens, have gained in relative importance. The severity of anaemia in a fetus at risk can be assessed by non-invasive measurement of peak systolic velocity in the middle cerebral artery. Severe anaemia, mandating antenatal intervention, is present when the peak systolic velocity is consistently over 1.5 multiples of the median and shows an increasing trend.[5]

Intrauterine transfusions are usually carried out under local or locoregional anaesthesia, in an outpatient setting (Fig. 1).[6] The umbilical vein is punctured under ultrasound guidance with a 20 or 22 gauge amniocentesis needle, typically either in its intrahepatic portion or at the placental cord root. A

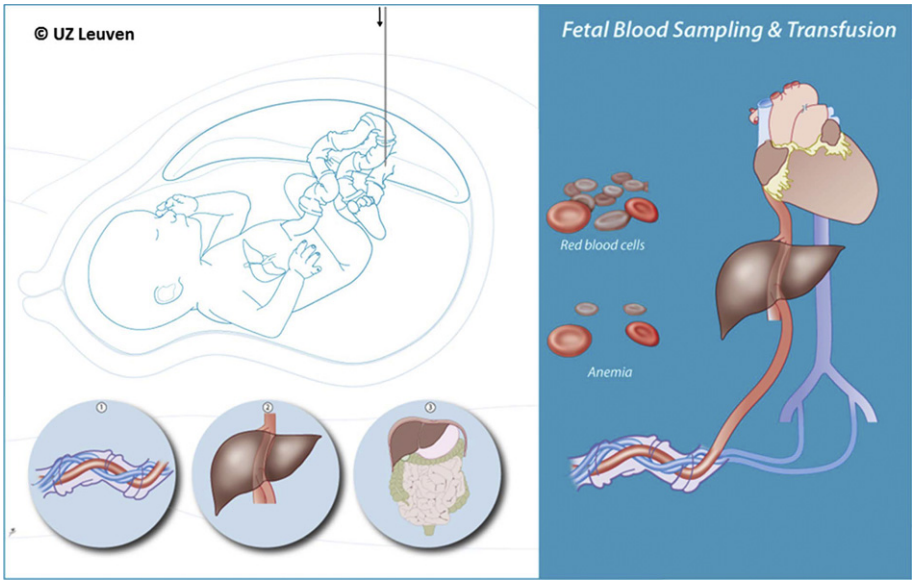

Fig. 1. Schematic representation of an intra-uterine transfusion. The fetal circulation typically is accessed at the level of the cord insertion (1), the intra-hepatic vein (2) or occasionally in the peritoneum (3).

free cord loop can also be used, but it is more fragile, and the insertion point may bleed on withdrawal of the needle. Intra-peritoneal transfusions are only rarely carried out, as the absorption of red blood cells from the peritoneal cavity is slow and unpredictable. At the start of the transfusion, a blood sample is drawn for haemoglobin and haematocrit measurement. Pancuronium can be administered to immobilise the fetus. O Rhesus negative blood with a haematocrit of 80%, which has been screened for the most common infectious diseases and irradiated to prevent graft versus host reaction, is transfused. The amount to be transfused can be calculated from the estimated feto–placental blood volume, the initial fetal haematocrit, and the target haematocrit, which is usually around 45%.[7] The final haematocrit is verified at the end of the procedure. In case of severe anemia, a single transfusion might not allow the target to be achieved without overfilling the fetus, and multiple transfusions with a few days interval may be necessary. After a successful transfusion, the peak systolic velocity in the middle cerebral artery decreases immediately. In case of persistent haemolysis, the fetal haematocrit drops around 1% per day. Therefore, repeated transfusions at 2–3 weeks interval are required in Rhesus alloimmunisation. The last transfusion is usually given around 34 weeks of gestation to allow for a delivery around 36–37 weeks.

In experienced hands, intrauterine transfusions are successful in over 97% of cases.[8] The rate of severe complications is 3% per procedure in RhD and the procedure-related fetal loss rate is 1.6%.[9,10] The latter increases to 10% in transfusions carried out before 22 weeks of gestation.[11] Overall survival after intrauterine transfusions for RhD is 75%, when the fetus is hydropic at the first transfusion and over 90% in non-hydropic fetuses.[8] A large follow-up study on neurologic outcomes after intrauterine transfusions for RhD shows a cerebral palsy rate of 2.1% and an overall risk for developmental delay of 4.8%.[12] Neurologic impairment is more likely if hydrops was present, which stresses the importance of close follow up in pregnancies with rhesus immunisation.

Fetal cardiac procedures

Despite improvements in neonatal (surgical) care and the development of dedicated follow-up programmes for infants with congenital heart disease, the outcome of fetuses with hypoplastic left heart syndrome remains poor. Postnatal surgery, which results in a far from optimal single ventricle Fontan-type circulation[13] has a considerable mortality rate, leading to a total survival of less than 65%.[14] Moreover, one-half of long-term survivors have poor neurodevelopmental outcome,[15] which may in part have an antenatal origin. Indeed, a preferential return of oxygenated blood towards the right ventricle and lower body rather than towards the left ventricle and the brain may lead to suboptimal brain oxygenation *in utero*.[16,17]

Hypoplastic heart can already be present in early pregnancy,[18] but about 5% develop in the second trimester and are progressive (Fig. 2).[14] In these cases, which are often due to outlet valve obstruction, fetal balloon valvuloplasties may allow for intrauterine ventricular recovery and growth, and increase the chance of a postnatal biventricular repair. Despite initial disappointing attempts with prenatal balloon valvuloplasty for aortic valve stenosis,[19] two groups[20,21] pursued the idea of prenatal intervention for severe aortic stenosis. They defined criteria for intervention (Table 1) and optimised techniques for needle-based access to the fetal heart. The technical aspects of the procedure are relatively standard and comparable between both groups.[20–22] The procedure may require general maternal anaesthesia for optimal fetal positioning, but most are done under local or locoregional anaesthesia. Initially, the laparotomy rate in the study by McElhinney et al.[21] was as high as 27%, but this dropped to 10% in their last 50 cases.[23] For hypoplastic left heart syndrome, an 18 or 19 gauge needle is inserted into the fetal left ventricle at the level of the apex and in alignment with the left ventricular outflow tract. A guide wire and a catheter with a coronary dilatation balloon are advanced through the aortic valve, which is dilated to 120% of the valve annulus (Fig. 2). Technical success, defined as successful inflation and dilatation, is achieved in 70% of cases. This can often be documented by the appearance of aortic regurgitation. Peri-operative complications are common. These include bradycardia necessitating fetal resuscitation (17–38%), haemopericardium (13%), ventricular thrombosis (15–20%) as well as fetal demise (8–13%).[24] Significant left ventricular growth may be observed *in utero*, yet only 33–67% of the technically successful procedures end up in a postnatal biventricular repair. Given the recent introduction of this procedure in fetal medicine, long-term outcomes are not yet available.

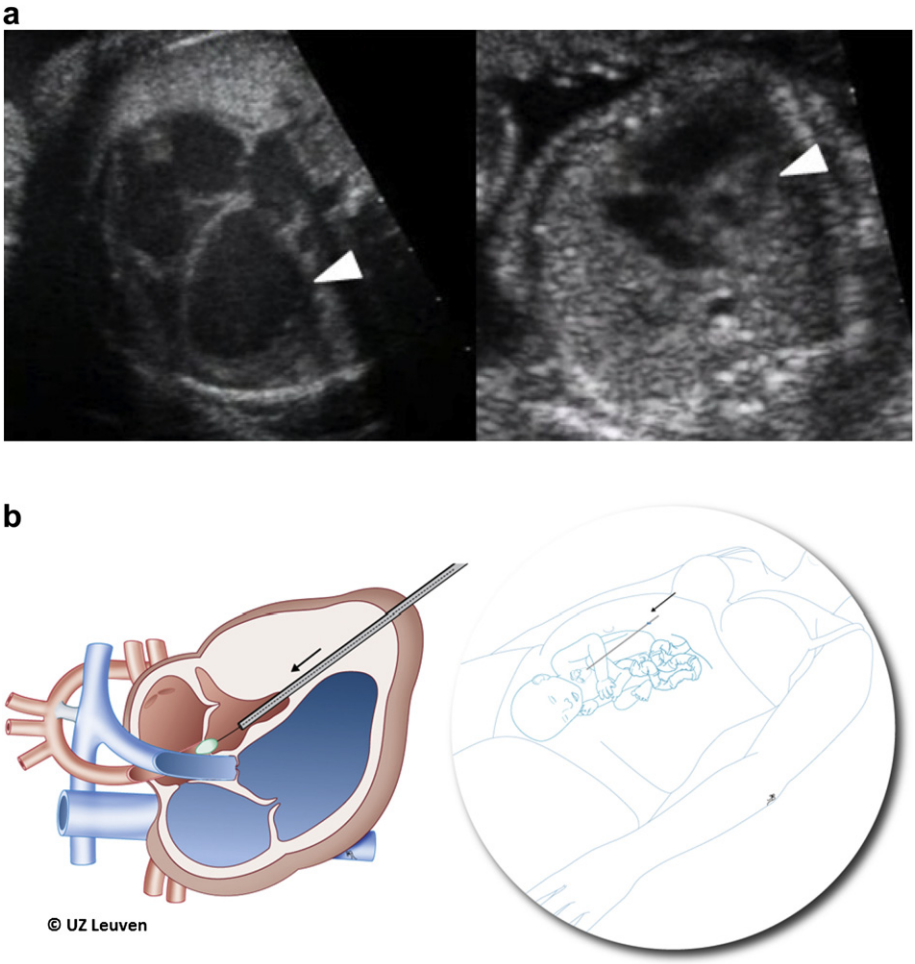

Fig. 2. (a) Ultrasound image on the left pane is a cross section at the level of the fetal chest, with four-chamber view in a fetus with aortic stenosis. Note that the left ventricle (arrowhead) is dilated, before becoming hypoplastic, as can be seen in another fetus in the right pane; (b). Percutaneous valvuloplasty, in this case of the left ventricular outlet tract.

Similar percutaneous cardiac balloon procedures have been proposed for hypoplastic left heart syndrome with a highly restrictive foramen ovale,[25] and pulmonary atresia with intact ventricular septum.[26] Data on these rarer cases are scarce, and virtually nothing has been published on longer-term outcomes.

Interventions for lower urinary tract obstruction

Fetal lower urinary tract obstruction (LUTO) occurs in about 2–3 per 10,000 pregnancies.[27] Most of these cases are caused by isolated posterior urethral valves or urethral atresia, but associated structural or chromosomal anomalies are present in 25%.[27] Untreated, the perinatal mortality of isolated LUTO is high, primarily resulting from pulmonary hypoplasia secondary to the oligohydramnion, but also from severe renal failure. Survivors have a high incidence of chronic renal failure, and up to 17% reach end-stage renal disease within 10 years.[28] Vesico-amniotic shunting has been proposed to improve the outcome of these fetuses. Evidence-based criteria on which fetuses should be considered eligible for in-

Table 1
Comparison of inclusion criteria and outcomes of fetal aortic valvuloplasty.[20,21]

	Arzt et al. ($n = 24$)[20]	McElhinney et al. ($n = 70$)[21]
Inclusion criteria	Left ventricle length z-score > -3 Aortic arch reversed flow Left to right shunt over foramen ovale Endocardial fibroelastosis	Left ventricle length z-score > -2 Aortic arch reversed flow or 2 of the following Left to right shunt over the foramen ovale Monophasic inflow left ventricle Bidirectional flow pulmonary veins Mitral valve z-score > -3 Depressed left ventricle function but conserved antegrade or retrograde flow
Gestational age at valvuloplasty in weeks (range)	26.6 (21.4–32.7)	23.2 (20–31)
Mini-laparotomy rate (%)	0	27
Technical success rate[a] (%)	70	74
Postnatal biventricular repair rate (%)	67	33

[a] Technical success defined as successful inflation of balloon.

utero treatment are lacking. Most centres require the presence of severe oligohydramnios and acceptable fetal renal function, based on a variety of diagnostic criteria.[29]

Vesico-amniotic shunting is a percutaneous procedure using a purpose-designed cannula and trocar with echogenic tip. The instrument is advanced through the fetal abdominal wall into the bladder to deploy a catheter allowing bladder drainage into the amniotic cavity.[30] Feasibility is highly dependent on fetal position. In case of complete anhydramnios, amnioinfusion may be required to allow for deploying the external loop of the shunt inside the uterus. The most frequent complication of vesico-amniotic shunting is preterm rupture of the membranes, leading to a mean gestational age at delivery of 34–35 weeks.[31] Shunt dislodgment, which occurs in 34%,[31] and obstruction, may mandate a repeat procedure. More severe complications, such as iatrogenic gastroschisis and chorioamnionitis, leading to maternal sepsis, are rare.[32] Some evidence shows that vesico-amniotic shunting improves neonatal survival, especially in fetuses with poor renal function.[33] Overall survival ranges between 50 and 90%, and one in three survivors has end-stage renal disease at a mean follow up of 5 years.[34] Survivors may also have other respiratory and growth problems, but their self-reported quality of life falls within the normal range.

More recently, intrauterine fetal cystoscopy has been proposed.[35] The procedure, which can be carried out as early as 16 weeks of gestation, allows a more robust diagnosis. In case of urethral valves, definitive treatment by laser fulguration may be attempted. A recent systematic review of four fetal cystoscopy studies[36] showed that the initial diagnosis of posterior urethral valves changed in 32% (six out of 19) of cases, typically towards urethral atresia. For postnatal survival, cystoscopic ablation of the valves was superior to expectant management yet comparable to shunting.[36] Long-term follow-up data for these cohorts on urinary or pelvic floor function are not available yet.

Interventions for fetal thoracic pathology

Pleural effusions

Fetal pleural effusions can either be isolated (primary hydrothorax or chylothorax) or secondary to other conditions, such as diaphragmatic hernia, bronchopulmonary sequestration, cardiac anomalies, fetal infections, metabolic, chromosomal or syndromal disorders. Mild-to-moderate primary hydrothorax, which does not lead to functional cardiac impairment, mediastinal shift or severe lung compression, has good outcomes when managed conservatively.[37] Expectantly managed fetuses with hydrops and severe pulmonary hypoplasia, however, only survive in 25%.[37]

Drainage of the effusion should theoretically alleviate intra-thoracic compression hence yield a better outcome. Such drainage can be achieved either by repeated thoracocentesis (the effusion

usually reaccumulates within 2 days), pleuroamniotic shunting or pleurodesis. A recent systematic review[38] showed that outcomes of thoracocentesis and shunting were similar, yet shunting is often preferred when more distant from term. The technical aspects of pleuroamniotic shunting are similar to vesico-amniotic shunting, and the same shunts are used. The lateral or posterior chest wall of the fetus are preferred for shunt insertion to avoid lesions to mammary gland and nipple (Fig. 3). Shunt migration or obstruction leads to the need for repeated procedures in 10–20% of cases. Preterm premature rupture of membranes and preterm delivery are common, with an average gestational age at delivery after pleuroamniotic shunting of 34–35 weeks. Yinon et al.[39] recently summarised a larger case study on shunting for hydrothorax. Neonatal survival was 55% in 206 hydropic fetuses, and 85% in 72 non-hydropic fetuses. Gestational age at birth and duration of shunting are both important predictors of outcome.[40]

In an attempt to avoid thoraco-amniotic shunting or repeated thoracocentesis, fetal pleurodesis can be attempted (e.g. by injecting OK-432[41,42]). OK-432 is an inactivated biological response modifier derived from *Streptococcus pyogenes*, and causes an inflammatory response through irritation of the pleura. Survival rate in the only two published studies is 75% (18 and 24%, respectively) in non-hydropic cases, and 21% (five out of 24) in hydropic fetuses. These results are not different from the natural history of the disease and are clearly inferior to what is seen with thoraco-amniotic shunting.

Pulmonary parenchymal lesions

Congenital cystic adenomatoid malformation of the lung (CCAM) arises from an overgrowth of the terminal respiratory bronchioles. In bronchopulmonary sequestration, non-functional pulmonary parenchyma is separated from the normal lung and receives its blood supply from the systemic circulation. CCAMs are classified as microcystic, macrocystic or mixed based on their appearance on ultrasound. Most commonly, CCAMs are small, and about 50% regress in the 3rd trimester of pregnancy.[43] Limited lesions do not compromise cardiac function or lung development, and have

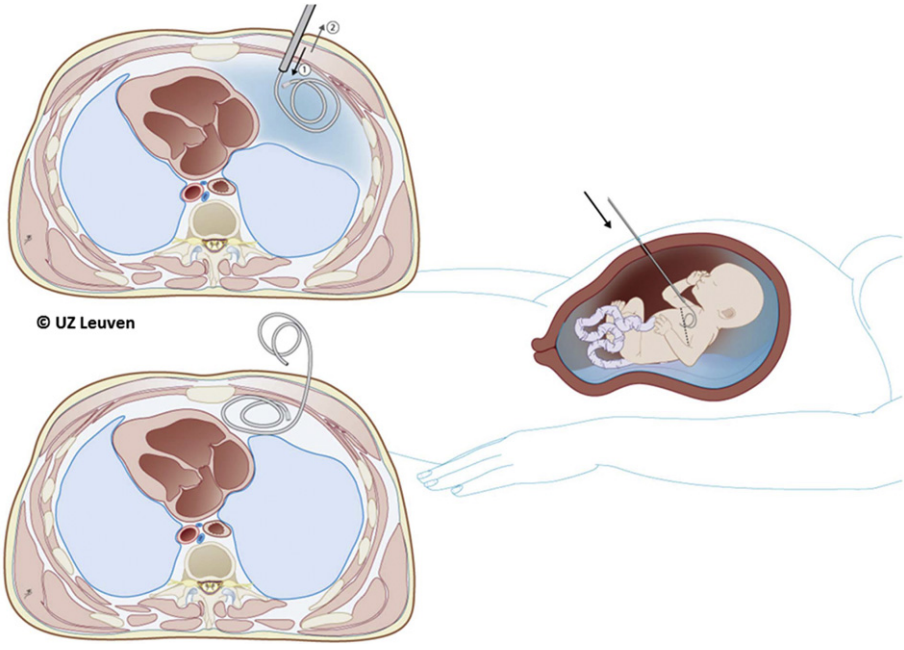

Fig. 3. Thoracic shunt being inserted (top left and right) and deployed (bottom left).

favourable outcomes with conservative prenatal management. Some can even be managed conservatively postnatally.[44]

More rare are the masses that grow very large and lead to pulmonary hypoplasia or hydrops, the latter being almost invariably fatal if left untreated.[45] In large macrocystic CCAMs, therapeutic size reduction can be obtained by thoraco-amniotic shunting of the larger cyst(s). Cavoretto et al.[43] summarised data on 24 non-hydropic fetuses who underwent thoraco-amniotic shunting at 27 weeks for CCAM causing severe mediastinal shift. Mean gestational age at delivery was 37 weeks and postnatal survival was 87.5%. For 50 hydropic cases, undergoing either thoracocentesis or thoraco-amniotic, survival was only 66%. Large microcystic CCAMs are considered not to be amenable for thoraco-amniotic shunting as mainly solid. Alternatively, they have been ablated using minimally invasive techniques (interstitial laser [$n = 5$], radiofrequency ablation [$n = 1$] or cyano-acrylate injection into the mass [$n = 1$]).[43,45–51] Of the six fetuses with reported neonatal outcomes, only two survived. Open fetal surgical lobectomy has a survival rate of 50%, yet at the cost of higher maternal morbidity.[2,52] More recently, the disappearance of hydrops and even regression of the microcystic mass has been reported after maternal administration of glucocorticoids (betamethasone 12 mg, twice). Current reports on fetuses with microcystic CCAM and associated effusions or hydrops are presented in Table 2.[53–55] The survival of 86% ($n = 18$ out of 21 fetuses) compares favourably to what is reported for other interventions.

In view of the potential of identifying a (systemic) feeding vessel to a bronchopulmonary sequestration, vascular occlusion techniques have been proposed as therapeutic options. Seventeen cases[43,56–61] were reported so far, either by injection of sclerosants ($n = 4$) or by interstitial laser coagulation ($n = 13$). Gestational age at delivery was greater than 34 weeks in all cases. One neonate died owing to a surgical complication at the time of sequestrectomy. All 16 others (94%) survived.

Pulmonary hypoplasia caused by congenital diaphragmatic hernia

Congenital diaphragmatic hernia occurs in 1 in 3000 pregnancies. Even when isolated (i.e. in the absence of other structural defects or chromosomal anomalies), this condition has high neonatal mortality and morbidity as a result of pulmonary hypertension and hypoplasia. The prognosis of an individual fetus can be predicted prenatally based on assessment of fetal lung size and liver position.[62,63] Although the overall neonatal survival of fetuses with isolated left-sided diaphragmatic hernia approaches 70–80% in high-volume centres, fetuses with liver herniation and a contralateral lung area less than 25% of the expected area for gestational age on ultrasound or a lung volume less than 35% of the expected total fetal lung volume on magnetic resonance imaging have a neonatal survival less than 25%.[64,65] Fetal lung growth can be stimulated *in utero* by tracheal occlusion (FETO). This procedure prevents the outflow of fluid produced by the lungs. As a consequence, the lungs are inflated and stretched, which is a proven strong stimulus for lung growth. Tracheal occlusion can be done fetoscopically under local or locoregional anaesthesia. After the fetus is anaesthetised and immobilised, a fetoscope[30] is introduced percutaneously, and the fetal trachea is accessed through the mouth (as for an intubation) (Fig. 4). A vascular occlusion balloon is delivered in the trachea, just below the vocal cords. As long as the tracheal balloon is *in situ*, the fetal airways are occluded, meaning that

Table 2
Outcomes of maternal corticosteroid therapy for microcystic congenital cystic adenomatoid malformation of the lung s with isolated fetal effusions or hydrops.

	N	Hydrops (n)	Isolated effusion (n)	Mean gestational age at steroids in weeks (range)	Resolution of effusion (n)	Survival (n)
Peranteau et al., 2007[53]	5	2	Two ascites, one scalp oedema	22.9 (19.4–25.60)	4	5[a]
Morris et al., 2009[54]	5	4	One ascites	25.4 (20.7–30.7)	4	4
Curran et al., 2009[55]	11	9	Two ascites	24.3 (22.4–26.6)	9	9
Total	21	15 (71.4%)	6 (28.6%)	24.3 (19.4–30.7)	17 (81.0%)	18 (85.7%)

[a] One fetus underwent open fetal surgery as effusions did not regress after corticosteroids.

normal respiration cannot take place at birth. We have proposed in-utero reversal at 34 weeks, which, in animal experiments, has been shown to promote lung maturation, but also allows vaginal birth and referral to a centre not familiar with FETO. Others remove the balloon at birth on placental circulation (ex-utero intrapartum treatment). The combined experience of three European centres offering FETO exceeds 200 cases.[66] The procedure is successful at first attempt in over 95% of cases, and mean operating time is around 10 min. The most important complications of FETO are preterm prelabour rupture of membranes and preterm delivery, which occurs on average at 35 weeks. Compared with an expectantly managed historical cohort, FETO improves survival of cases with severe isolated left-sided diaphragmatic hernia from under 25% to around 50% and decreases neonatal morbidity.[66,67] A similar increase in survival was observed by Ruano et al.,[68] and substantiated in a randomised-controlled trial on a population of left- and right-sided diaphragmatic hernia cases.[68] In that study, the survival rate was only 5% in expectantly managed cases, and 50% in cases that underwent FETO. Long-term follow-up studies on neurologic and pulmonary outcomes after FETO have not yet been published, but are urgently needed to gain insight into the extent of morbidity in survivors.

Fetoscopic laser coagulation of chorionic plate vessels

Twin-to-twin transfusion syndrome

Twin-to-twin transfusion syndrome (TTTS) affects 9% of monochorionic twins and usually presents between 16 and 26 weeks of gestation.[69] The exact pathophysiologic mechanism remains controversial, and was recently reviewed by Fisk et al.[70] Imbalances in vasoactive hormones and fluid shifts lead to one fetus being hypertensive and volume overloaded (the recipient fetus) and the other being volume depleted (the donor fetus). The diagnostic criteria for TTTS rely on the presence of polyuric polyhydramnios in the recipient fetus and oligouric oligohydramnios in the donor. Twin-to-twin transfusion syndrome is staged according to the Quintero criteria,[71] which rely on the presence (stage I) or absence (stage II) of bladder filling in the donor fetus, Doppler changes in one or both fetuses (stage III) and the presence of hydrops (stage IV). Intrauterine demise of one or both fetuses

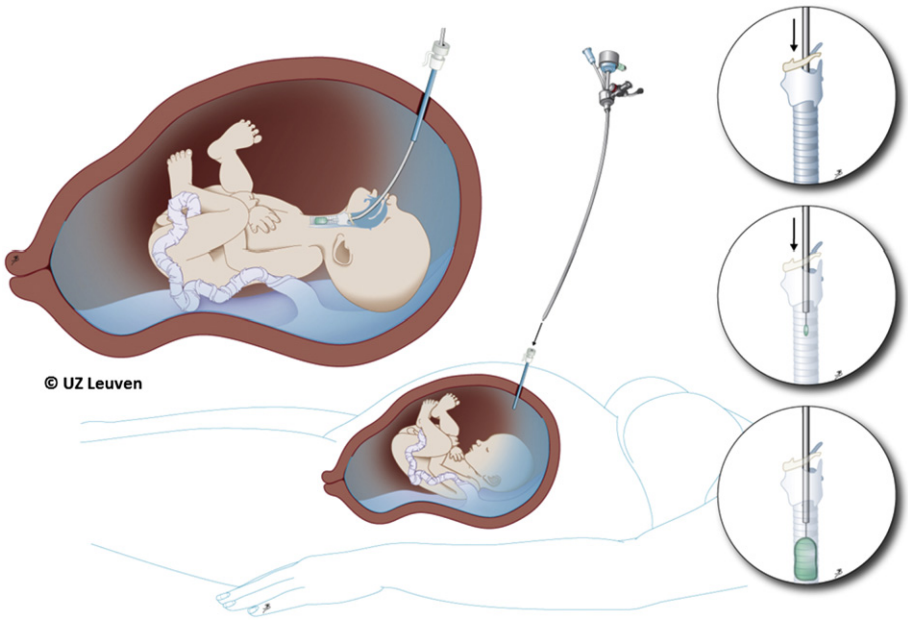

Fig. 4. Percutaneous insertion of a balloon into the fetal trachea. Inserts show the steps for positioning a detachable balloon.

corresponds to stage V disease. Others have suggested staging the disease based on the degree of cardiac dysfunction in the recipient, but at present the clinical relevance of this needs to be demonstrated.[71–74]

In a randomised-controlled trial, repetitive amniodrainages were compared with fetoscopic laser coagulation of the vascular anastomoses, the latter showing a better outcome.[75] Fetoscopic laser is carried out under local or locoregional maternal anesthesia. Fetoscopes with different diameters and a working channel for a laser fibre[30] are introduced into the recipient's sac (Fig. 5). The placenta, donor and recipient cord insertions and intertwin membrane are identified. All anastomosing vessels are coagulated under direct vision. The procedure is completed by amniodrainage. Postoperatively, improved diuresis in the donor and decreased diuresis in the recipient can be observed within days. Cardiac function in the recipient usually normalises within 6 weeks.[76] Transient signs of volume overload (subcutaneous oedema, reversed flow in ductus venosus) may appear in the former donor fetus.[77] Recurrent TTTS and twin anaemia-polycythaemia syndrome are relatively rare complications, but should actively be looked for in the first weeks after laser as they are amenable for therapy. Intrauterine fetal demise of one fetus, which is only partially predictable, occurs in about 15% of cases. In the earlier large studies, overall neonatal survival was around 55% and survival of one fetus or more around 70%[78]; these numbers increased to 70% and 80–90%, respectively, with increasing experience worldwide.[76,79] Mean gestational age at delivery after mid-trimester laser is 33–34 weeks.

A recent large multicentre follow-up study ($n = 287$ TTTS survivors) showed that, for long-term neurological outcome, the risk for cerebral palsy in survivors is 6%.[80] Severe mental delay is observed in 7%, and psychomotor impairment in 12%. This compares with the background risk of neurodevelopmental impairment (7%) and cerebral palsy (0.6%) in uncomplicated monochorionic twin pregnancies.[81] The major determinant of these adverse outcomes is prematurity,[82] yet advanced stage also plays a role.[82] Recipients have a 10–15% risk of (acquired) congenital heart disease,[83,84] which mainly consist in pulmonary stenosis and atresia (3–9%). Other cardiac lesions, such as atrial and ventricular septal defects, however, are also more common than in uncomplicated monochorionic twins.[83]

Selective intra-uterine growth restriction

Fetoscopic laser therapy has also been proposed for monochorionic twins with severe intrauterine growth restriction (sIUGR) with intermittent absent or reversed flow in the umbilical artery of the smaller twin. The rationale for the procedure is that it can protect the larger fetus from large volume

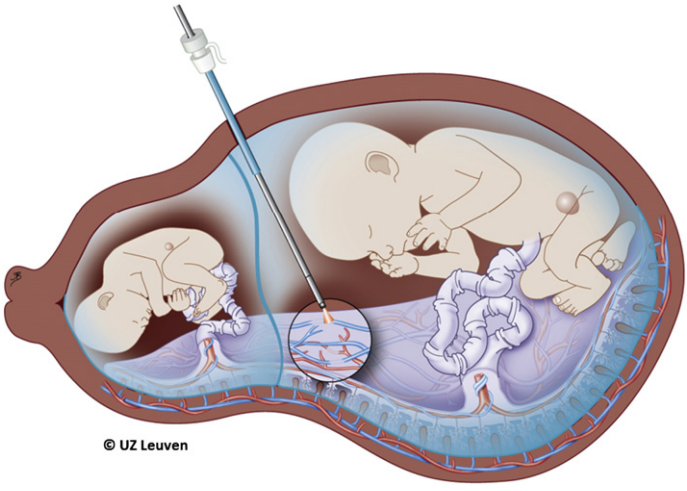

Fig 5. Fetoscopic laser coagulation of chorionic plate vessels for twin-to-twin transfusion syndrome.

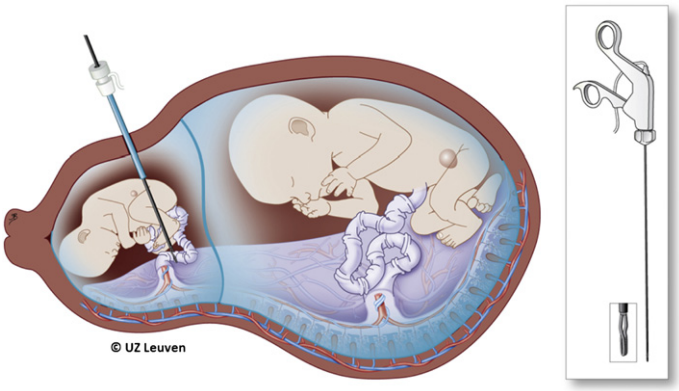

Fig. 6. Bipolar cord coagulation, using a bipolar forceps (insert).

shifts over the placental intertwin anastomoses, which may cause neurologic damage. Moreover, dichorionisation could protect it from the consequences of intrauterine fetal death of the smaller fetus, which occurs spontaneously in up to 15%.[85] Laser for IUGR is technically much more difficult than laser for TTTS. Gratacós et al.[86] compared 18 IUGR cases undergoing laser with 31 expectantly managed cases. They showed that neurologic damage to the recipient is indeed much less common after laser (4% compared with 20% in expectantly managed cases), but this apparent benefit is counterbalanced by an increased rate of donor fetus demise (67% after laser *v* 19% when managed expectantly) and increased rates of neurodevelopmental impairment in the surviving donors.[86] Outcomes of the remaining fetuses were better when cord occlusion was offered though at the expense of death of one of the fetuses.

Selective reduction in monochorionic twin gestations

In some monochorionic twin pairs, the condition of one fetus may pose a threat to the wellbeing of the other, owing to the presence of the placental anastomoses. Therefore, demise of one fetus in sIUGR, in TTTS, or in discordant congenital anomalies, can lead to severe hypovolaemia in the unaffected fetus, with an ensuing 15% risk of death and a 26% risk of neurologic impairment.[87] Other conditions, such as

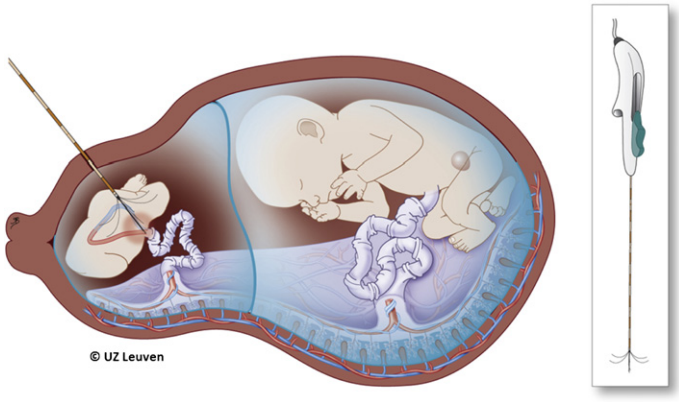

Fig. 7. Radiofrequency ablation using an radio frequency ablation device with its tines deployed.

Table 3
Most common fetal conditions amenable for treatment and outcome of interventions.

Pathology	Untreated leads to	Treatment	Gestational age at birth	Common complications	Outcome after treatment
Rhesus disease	High output cardiac failure and decreased tissue oxygenation	Intrauterine transfusion	36 weeks	IUFD 1.7% per procedure	Survival hydrops 74%, no hydrops 91%, cerebral palsy 2.1%, developmental delay 4.8%
Hypoplastic left heart syndrome	Postnatal demise, univentricular circulation	Balloon valvuloplasty	88% > 36 weeks	Intrauterine resuscitation 30%, IUFD 10%	33–67% biventricular repair
Posterior urethral valves	Renal failure, pulmonary hypoplasia	Vesico-amniotic shunting	34–35 weeks	Shunt dislodgment 34%	50–90% survival, 30-40% end stage renal failure
Pleural effusion	Cardiac failure, pulmonary hypoplasia	Thoraco-amniotic shunting	34–35 weeks	Shunt dislodgment 10–20%	Survival hydrops 55%, no hydrops 85%
Congenital diaphragmatic hernia	Pulmonary hypoplasia	Tracheal occlusion	35 weeks	Balloon deflation 8%	50% survival
Twin-to-twin transfusion syndrome	IUFD and preterm birth	Laser ablation of anastomoses	33–34 weeks	IUFD one fetus 15%, twin anaemia-polycythaemia sequence 10%	70% double survival, 80–90% survival ≥ one fetus, cerebral palsy 6%, mental delay 7%, motor delay 12%
Selective reduction in monochorionic twins	Neurologic damage or IUFD	Radiofrequency ablation and cord occlusion	34–35 weeks	Demise non target fetus 15%	85% survival non-target fetus

IUFD, intrauterine fetal demise.

twin reversed arterial perfusion, can put the healthy twin at risk of fetal demise owing to high output cardiac failure.[88] In these circumstances, controlled fetocide of the affected fetus, including obliteration of connecting vessels, has been advocated to protect the healthy twin. Simultaneous arterial and venous occlusion can be achieved by cord ligation or occlusion. Bipolar cord coagulation is carried out under local anaesthesia with ultrasound guidance (Fig. 6). This involves 2.5–3.3 mm instruments.[30] In early pregnancy, it can be done by laser. The fetoscopic technique has the advantage that the cord can be transected under direct vision, which may be required in monoamniotic twin pregnancies.[89] In contrast to bipolar coagulation and cord laser, radiofrequency coagulation is directed at coagulating intra-fetal vessels. A straight needle or a needle equipped with umbrella shaped tines is inserted into the abdomen of the target fetus, close to where the cord vessels branch at the level of the umbilicus (Fig. 7). High-frequency alternating current induces an increase in temperature around the vessels, leading to coagulation.[90] Cord coagulation and radio-frequency ablation are technically successful in 97% of cases. Outcomes are probably similar with both techniques[91] with survival of the non-target twin in about 80–85% of cases. Cases operated after 18 weeks do better than early cases.[92,93] Mean gestational age at delivery is 34–35 weeks, and neurologic outcome in survivors is good, with neurodevelopmental impairment in 2% of cases.[92,94]

Conclusions and future perspectives

Over recent years, the indications, as well as numbers of minimally invasive fetal interventions, have boomed. Some of them have been proven to improve fetal outcomes. Particularly, a large number

of studies have reported outcomes on intrauterine transfusions for RhD, fetoscopic laser for TTTS, selective fetocide, evacuation of pleural effusions, and fetal tracheal occlusion, so that reliable complication rates and short-term outcomes can be quoted. These are presented in Table 3. Level I evidence favours laser coagulation for TTTS over amniodrainage.

The fetal medicine community is currently engaging in sound randomised, multicentre studies that can provide data on patient selection and medium- to long-term outcomes of invasive fetal interventions. We are aware of a number of randomised trials. In the PLUTO trial (www.pluto.bham.ac.uk), fetuses with lower urinary tract obstruction underwent either vesico-amniotic shunting or expectant prenatal management. In parallel, a registry of fetuses treated on individual or clinician preference was kept. The trial has been completed, and results should soon become available.

A trial for women presenting with stage I TTTS, comparing expectant management with primary laser, is also ongoing (NCT01220011).[95] From a technical view point, the Solomon-trial[96] aims to compare selective fetoscopic laser of anastomoses with coagulation of the entire vascular equator, and hypothesises that the latter would decrease the risk of persistent anastomoses after laser.

The SIUGR RCT (NCT01177553)[95] aims to compare the neurologic outcome of monochorionic twins complicated by sIUGR with absent or reversed end diastolic flow in the umbilical artery of the smaller fetus, following either expectant prenatal management or fetoscopic laser of anastomoses.

In the TOTAL trials (NCT00763737 and NCT01240057)[97] the outcome of fetuses with severe or moderate pulmonary hypoplasia caused by congenital diaphragmatic hernia is being compared, following either fetoscopic tracheal occlusion or expectantly management during pregnancy.

Fetal medicine specialists should consider referring eligible women for participation in these trials, as (international) multicentric collaboration is the only way to recruit sufficient numbers of participants to answer these important questions on rare diseases.

Practice points

- Intrauterine transfusions have low complication rates and good long-term outcomes.
- Thoraco-amniotic shunting can be considered for large macrocystic CCAMs or pleural effusions.
- Large bronchopulmonary sequestrations can be treated by vaso-occlusive techniques.
- Fetoscopic laser is state-of-the-art treatment for TTTS.
- Double fetal survival after laser is 70% and survival of one of more fetus is 80–90%.
- Preterm delivery is the main complication of all invasive fetal interventions and affects neurologic outcome in survivors.

Research agenda

- Randomised comparison of prenatal valvuloplasty with postnatal therapy for hypoplastic left heart syndrome.
- Long-term follow up of survivors of prenatal valvuloplasty.
- Which fetuses are optimal candidates for vesicoamniotic shunting or cystoscopy?
- What is long-term outcome after prenatal intervention for LUTO?
- Randomised trial comparing fetoscopic tracheal occlusion with expectant prenatal management for congenital diaphragmatic hernia is under way.

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