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REVIEW OF CURRENT PRACTICE

The making of fetal surgery

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Fetal diagnosis prompts the question for fetal therapy in highly selected cases. Some conditions are suitable for *in utero* surgical intervention. This paper reviews historically important steps in the development of fetal surgery. The first invasive fetal intervention in 1963 was an intra-uterine blood transfusion. It took another 20 years to understand the pathophysiology of other candidate fetal conditions and to develop safe anaesthetic and surgical techniques before the team at the University of California at San Francisco performed its first urinary diversion through hysterotomy. This procedure would be abandoned as renal and pulmonary function could be just as effectively salvaged by ultrasound-guided insertion of a bladder shunt. Fetoscopy is another method for direct access to the feto-placental unit. It was historically used for fetal visualisation to guide biopsies or for vascular access but was also abandoned following the introduction of high-resolution ultrasound. Miniaturisation revived fetoscopy in the 1990s, since when it has been successfully used to operate on the placenta and umbilical cord. Today, it is also used in fetuses with congenital diaphragmatic hernia (CDH), in whom lung growth is triggered by percutaneous tracheal occlusion. It can also be used to diagnose and treat urinary obstruction. Many fetal interventions remain investigational but for a number of conditions randomised trials have established the role of *in utero* surgery, making fetal surgery a clinical reality in a number of fetal therapy programmes. The safety of fetal surgery is such that even non-lethal conditions, such as myelomeningocoele repair, are at this moment considered a potential indication. This, as well as fetal intervention for CDH, is currently being investigated in randomised trials. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: fetal surgery; fetoscopy; ultrasound; fetal therapy

INTRODUCTION

Prenatal diagnosis of a condition that cannot await therapy until after birth prompts the possibility of fetal therapy. This may be as simple as transplacental administration of glucorticoids to stimulate lung maturation, first described in 1972 (Liggins and Howie, 1972). Most fetal therapies need direct, invasive access to the feto-placental unit, requiring advanced technical skills, and are associated with procedure-related complications. The intervention can be as simple as insertion of a needle, as in intravascular transfusion. However, in the absence of ultrasound, fetal transfusion began in 1961 by blind, intra-abdominal administration of blood (Liley, 1963). Complete exchange transfusion, however, requires direct access to the fetal circulation, initially possible only through hysterotomy (Adamsons, 1966) or rod lens fetoscopic guidance (Rodeck *et al*., 1984). Around that time, considerable efforts were made to expand the field of fetal interventions. Thus, this chapter is a historical review of events leading to modern fetal surgery. It has been written by a number of physicians who contributed to its development. It does not claim to be comprehensive, nor does its limited author list pay sufficient respect to the many other pioneers and visionaries as well as uncountable young investigators who also contributed to these developments.

There is no doubt that the story of modern fetal surgery starts at the University of California at San Francisco (UCSF), in the person of Mike Harrison (Harrison, 2004). During his medical training, Mike had already become puzzled by congenital diaphragmatic hernia (CDH) (Harrison, 2010). As a surgical intern, he

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observed how Hardy Hendren at Massachusetts General Hospital elegantly repaired the diaphragmatic defect in newborns. These babies, however, continued to struggle for life because their main problem was pulmonary hypoplasia rather than the diaphragmatic hernia defect. Mike made an important second observation during his stay in Oslo. At that time, CDH mortality in Norway was as high as 50%. He saw that many babies with CDH never made it to the operating table, dying prior to referral. This left him with two conclusions: (1) what cannot be fixed after birth may benefit from a prenatal intervention and (2) in order to assess the need for the former, the true mortality of the condition needs to be defined. He referred to the discrepancy between the perceived and actual mortality as 'hidden mortality'. Later, other conditions became shortlisted as potentially benefitting from fetal intervention, in order to either save the life of the fetus or at least prevent permanent damage (Table 1). This might be either by anatomical correction of the malformation or by arresting the progression of the disease and leaving more definitive repair until after birth. The criteria for this concept were summarised in a consensus document drafted by the International Fetal Medicine and Surgery Society (IFMSS) (Harrison *et al.*, 1982; Table 2).

Although this story may have started in a small way at UCSF, many paediatric surgeons rotating through San Francisco became infected by the enthusiasm of Harrison and his co-workers, as well as by the early tangible results of surgically correctable birth defects in animal models. Several embarked on research fellowships and productive projects, becoming an indispensable pool of talent. Many of them, listed in detail elsewhere, had impressive careers, while enthusiastically spreading the seed of fetal therapy (Harrison, 2004). It was no different on the other side of the Atlantic, where fetal medicine was boosted by the team of Charles Rodeck at King's College Hospital, and later by Kypros Nicolaides at the Harris Birthright Centre (London). Once King's College, being a major fetal medicine training centre, embraced fetoscopy in the 1990s, operative fetoscopy spread quickly through Western Europe. This article briefly goes over the early experimentation leading to the advent of clinical fetal surgery, first by hysterotomy and then rekindled by the re-introduction of fetoscopy. We will elaborate more in detail on how fetal surgeons have struggled, and continue to do so, with one specific disease, that is, CDH. We have chosen this story as an example, because so many of us have dedicated a significant time in our careers to this yet unsolved problem. Fetal surgery for CDH was the first intervention to be evaluated in a randomised trial (Harrison *et al.*, 1997) and is actually today again under clinical investigation (Deprest *et al.*, 2009a). Randomised trials are the key for the advancement of medicine. Fetal therapy is

Table 1—Indications for fetal intervention (Deprest *et al.*, 2008)

Fetal surgery	Rationale for *in utero* therapy
Surgery on the fetus	
Congenital diaphragmatic hernia	Reversal of pulmonary hypoplasia and prevention of pulmonary hypertension
Sacrococcygeal teratoma	Cessation of steal phenomenon, reversal of cardiac failure and prevention of polyhydramnios
Thoracic space-occupying lesions	Prevention of pulmonary hypoplasia and/or reversal of cardiac failure
Lower urinary tract obstruction	Prevention of renal failure and pulmonary hypoplasia
Cardiac malformations	Prevention of hypoplasia or arrest of progressing damage to developing heart
Myelomeningocoele	Covering of exposed spinal cord, cessation of cerebrospinal fluid leakage to prevent/reverse hydrocephaly and hindbrain herniation
Surgery on the placenta, cord or membranes	
Complicated monochorionic pregnancies:	Arrest of feto-fetal transfusion and its consequences
Twin–twin transfusion syndrome (TTTS)	Preventing preterm delivery
Twin-reversed-arterial-perfusion sequence (TRAP) and other discordant anomalies	Prevention of potential damage to co-twin
Twin-anaemia polycythaemia sequence	In some conditions (TTTS/TRAP) reversal of cardiac failure and polyhydramnios
Selective intra-uterine growth restriction	In some conditions selective feticide is a goal in itself
Amniotic band syndrome	Prevention of deformities and functional loss
Chorioangioma	Prevention/reversal of cardiac failure, hydrops fetoplacentalis and polyhydramnios

Table 2—Criteria for fetal surgery

1. Accurate diagnosis and staging possible, with exclusion of associated anomalies.
2. Natural history of the disease is documented, and prognosis is established.
3. Currently no effective postnatal therapy.
4. *In utero* surgery proven feasible in animal models, reversing deleterious effects of the condition.
5. Interventions performed in specialised multidisciplinary fetal treatment centres within strict protocols and approval of the local Ethics Committee with informed consent of the mother or parents.

Adapted from Harrison *et al.* (1982).

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Table 3—Reported risks for PROM following fetoscopic procedures in selected case series

Conditions	Number of cases	Risk PROM (time point at assessment)	Diameter instrument	Reference
MMC	3	67%	3.8 mm	Kohl *et al*. (2006)
	4	33%	Three ports, largest 5.0 mm	Bruner *et al*. (2000)
LUTO	10	17%	1.3 mm	Welsh *et al*. (2003)
	13	13%	≤2.5 mm	Quintero *et al*. (1995)
ABS	2	100%	3.3 mm	Soldado (2009)
	2	100%	4.0 mm	Keswani (2003)
	2	50%	2.7 mm	Quintero (1997)
Fetoscopic laser	4 (TTTS)	75%	5.0 mm	Kohl *et al*. (2006) (secondary laser)
	6 (TTTS)	33%	3.3 mm	van Schoubroeck (2004) (triplets only)
	175 (TTTS)	28% (<34 weeks)	3.3 mm	Yamamoto and Ville (2005)
	20 (TTTS)	7% (<1 week)	3.3 mm	Crombleholme (2007)
	24 (TTTS)	5% (<28 weeks)	4.0 mm	Chang *et al*. (2006)
	6 (TRAP)	4%	2.0 mm	Quintero (2006)
		0% (<3 weeks)		
CO	80	38%	2.3 or 3.3 mm	Lewi *et al*. (2006)
	4	25%	2.7 mm	Ville *et al*. (1994) (laser)
	39	20% (<3 weeks)	3.5 mm	Quintero (2006)
	25	16% (<3 weeks)	3.5 mm (one or two ports)	Nakata (2004)
	12	8%	3.0 mm	Young (2005)
FETO	11	100%	5.0 mm (one or three ports)	Harrison *et al*. (2003)
	210	47%	3.0 mm	Jani *et al*. (2009)
		17% (<3 weeks)		

Rupture rates (%) are those reported ≤37 weeks, or at the time point specified (from Beck *et al*., 2010). ABS, amniotic band syndrome; CO, cord occlusion; FETO, fetoscopic endoluminal tracheal occlusion. References in last column can be found in the original publication (Beck *et al*., 2010).

no exception, but such trials are ethically challenging, difficult to organise and finance, and hard to execute effectively. This should, however, be no excuse (Chervenak and McCullough 1985).

HISTORICAL EXPERIMENTS

The history of fetal surgery is inherently one of *experimental* surgery. Its history was recently comprehensively reviewed by Jancelewicz and Harrison (2009). First, experiments were needed for the development of uterine access and fetal surgical techniques. Animal experimentation also established models of target diseases and possible therapies. Initially, this involved larger species such as dogs, sheep and rabbits, but later also included smaller species. The first experimental efforts were dedicated to achieving effective and safe access to the amniotic cavity. Ironically this remains an unfinished story, as post-operative rupture of the fetal membranes and preterm labour remain the Achilles' heel of the enterprise (Deprest, 1996; Table 3). Before the 2nd World War, Barron conducted a number of experiments on fetal lambs through a purse-string hysterostomy (referenced in Rosenkrantz *et al*., 1968). Direct fetal surgical manipulations had to wait until 1946, when Jost (1946) demonstrated in fetal rabbits that removal of the testes compromised normal endocrine development. Louw and Barnard (1955) reproduced intestinal atresia by mesenteric ischaemia, achieving the first experimental model of a human birth defect. Aortic coarctation and other heart defects, CDH and hydronephrosis, then followed. The models were first used to study the pathophysiology of diseases, but later also served for the study of candidate *in utero* therapies. Although controversial today, primate experiments were also a required step. It was shown that resorbable hysterotomy staples did not cause subsequent fertility problems, in contrast to metal staples. Non-human primates were also the only reliable model to study uterine contractility (Suzuki and Plentl, 1969) and we used them to demonstrate that fetoscopic access in mid-trimester Rhesus monkeys did not result in significant contractions 24 h post-operatively (van der Wildt *et al*., 1995). The potential of fetoscopy was further demonstrated by initial sheep experiments in Leuven, demonstrating less impairment of uterine flow by endoscopic rather than open uterine access (Luks *et al*., 1996a). Fetal lambs were also used to study the fetal effects of different distention media and to demonstrate the feasibility of complex fetoscopic surgeries (Deprest *et al*., 1995a) (Figure 1).

THE CHANGING ROLE OF OPEN FETAL SURGERY AND ITS DIFFERENTIAL UPTAKE OVER THE WORLD

LUTO and early applications of shunting

The first open clinical fetal surgical intervention at UCSF was a case of lower urinary tract obstruction (LUTO), not eligible for shunt placement. Instead, fetal ureterostomies were successfully created (Figure 2). There were no maternal complications, but unfortunately the fetus

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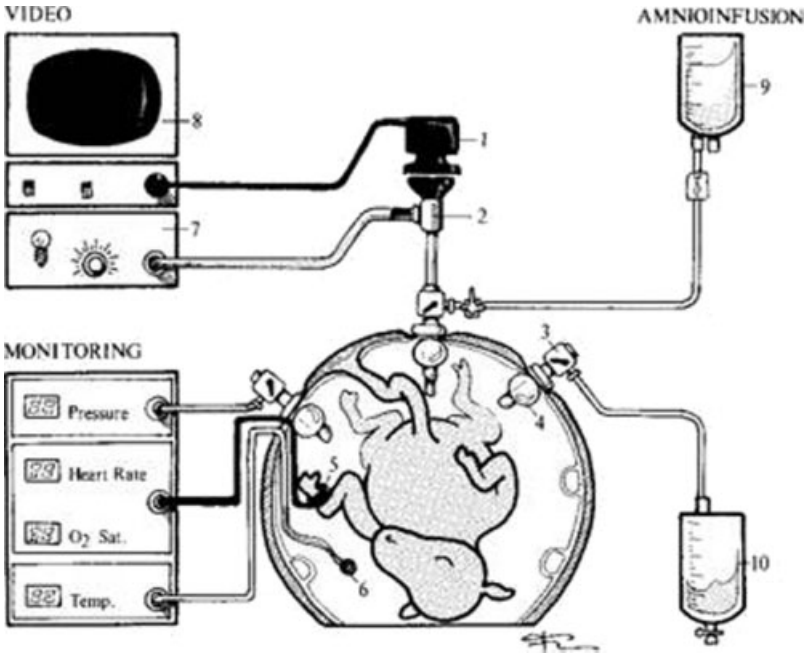

Figure 1—First description of lamb model for multiple access endoscopic *in utero* surgery. With permission, from Luks *et al.* (1994)

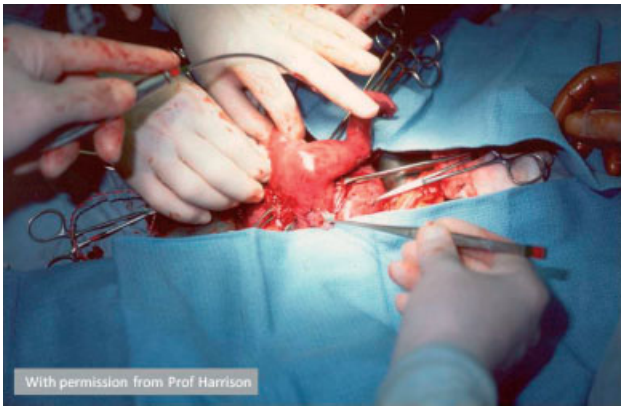

Figure 2—The first successful open fetal surgery at UCSF. The fetal lower torso is exteriorised through the hysterotomy and the urinary tract is decompressed surgically. With permission, from Harrison (1996, chapter 5, p. 76)

never produced any urine. The team from the Fetal Treatment Center team did not get discouraged by this outcome: the majority of patients with LUTO could be safely and effectively helped by shunt placement (Harrison *et al.*, 1981a,b). At that time these shunts were also proposed for *in utero* treatment of hydrocephalus until experimental work in fetal sheep and monkeys showed that such a treatment was ineffective (Clewell *et al.*, 1982). This is a good example of how, despite great initial enthusiasm, critical evaluation of results prompted reconsideration. The small circle of pioneers realised that the concept of fetal surgery was a precarious and vulnerable one because there was too much exposure, lack of clinical evidence, ethical issues and public perception. Therefore, they set up a network for sharing information, exchanging knowledge on new techniques, discussing treatment and frank disclosure of failures. They agreed on ethical guidelines, such as peer review publication *prior* to media exposure, and standards for fetal intervention. They first met in 1981 in Santa Ynez (California), where Sir William Liley was a keynote lecturer. The IFMSS was officially established 1 year later in Aspen (Colorado) and drafted the ethical framework that still applies today (Table 1). The society founded a journal, established a registry of interventions, and published a first report on intra-uterine shunting shortly thereafter (Manning *et al.*, 1986). Whereas shunts were successful for LUTO, the group agreed at that moment on a voluntary moratorium on shunting for hydrocephalus.

LUTO can be caused by stenosis of the urethral meatus, valves, urethral atresia, ectopic insertion of a ureter or even (peri)vesical tumours. Bladder shunts are effective for urine diversion, restoring amniotic fluid and thereby preventing pulmonary hypoplasia (recently reviewed by Mann *et al.*, 2010). Whether shunting effectively salvages renal function is uncertain. For that, prior accurate assessment of renal function is required. An important contribution to appropriate case selection was made by Johnson *et al.* (1995). They demonstrated the importance of serial vesicocentesis, and also reported on the long-term outcome of patients. The actual anatomical cause of LUTO proved to be an important predictor. Posterior urethral valves do much better in the long run, while babies with urethral atresias or the Prune Belly phenotype do less well (Biard *et al.*, 2005). Also, despite favourable prenatal renal function, up to half of the survivors still end up with chronic renal insufficiency (Holmes *et al.*, 2001, Clark *et al.*, 2003). However, the self-perceived quality of life of survivor falls within the normal range (Biard *et al.*, 2005). This type of long-term information is invaluable. That study also emphasises the need for better prenatal anatomical

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and functional evaluation. A recent advance in this respect is *in utero* cystoscopy. Although instruments remain far from ideal, the intervention can be extended to a therapeutic procedure. Both fetoscopic antegrade catheterisation and hydro- or laser ablation of urethral valves have been described (Quintero *et al*., 1995; Welsh *et al*., 2003). Ruano *et al*. recently reported a large series in this journal, so that this technique has also outgrown its infancy (Ruano *et al*., 2010).

Cystic lung lesions

Open fetal surgery was, and still is, being done for hydropic fetuses with microcystic congenital cystic adenomatoid malformation (CCAM) of the lung. Again, the meticulous documentation by researchers spinning off from UCSF, and later from the Children's Hospital of Philadelphia (CHOP) improved case selection. They described how growth of CCAM lesions is best followed up longitudinally. The volume of the lesion is expressed as a proportion of the head circumference (CCAM volume ratio—CVR) (Crombleholme *et al*., 2002). When the CVR is >1.6, the risk for hydrops is 80% and in those who develop hydrops, fetal intervention seems justified (Davenport *et al*., 2004; Wilson *et al*., 2006). *Microcystic* lesions can be treated by fetal lobectomy with a 50% survival rate ($n = 24$; Adzick, 2003; reviewed in Adzick, 2010a). When presenting late in pregnancy they can be resected while on placental circulation (Liechty, 2010). *Macrocystic* masses can be punctured or shunted. The largest experience with shunting was published by the CHOP group. In their experience, fetal intervention reduces the CCAM volume by 70%, reverses hydrops and results in a survival rate of 74% ($n = 23$; Wilson *et al*., 2004). This rate has since been confirmed by others (Knox *et al*., 2006). A recent advance is the use of maternal steroids, but its efficacy and wider place in management remains to be demonstrated (Tsao *et al*., 2003; Peranteau *et al*., 2007).

Sacrococcygeal teratoma

Whereas some sacrococcygeal teratomas (SCT) do not cause prenatal problems, larger and fast-growing tumours increase metabolic demands, cause fetal anaemia and act as a large arteriovenous shunt, eventually causing high-output cardiac failure. This leads to polyhydramnios, hydrops and eventually intra-uterine fetal death (IUFD). Furthermore, the mother may develop mirror syndrome. The groups from UCSF and CHOP demonstrated that fetal hydrops and placentomegaly are indicators of poor outcome (Bond *et al*., 1990; Westerburg *et al*., 2000). Others have proposed additional prognostic criteria such as rate of tumour growth based on which fetal intervention may be considered (Westerburg *et al*., 2000). In a Parisian series of 44 fetuses, pre- and perinatal losses were confined to those with larger, fast-growing tumours that had measurable impact on cardiac function ($n = 21$). These fetuses had a mortality rate of 52%. Four of six fetal deaths were also associated with hydropic signs (Benachi *et al*., 2006). Symptomatic interventions such as amniodrainage (polyhydramnios), intra-uterine transfusion (anaemia) and bladder shunting (urinary obstruction) have been reported as well. Open fetal resection of Type 1 or predominantly extra-pelvic tumours has been reported in five cases. Mean age at birth was 30 weeks and four survived long term (Hedrick *et al*., 2004). One survivor required postnatal treatment of pulmonary metastases of a germ cell tumour and at age of 11 years has no evidence of disease, but another had significant morbidity, probably related to emboli at the time of tumour resection. The other two survivors remain healthy. There is anecdotal experience of less invasive techniques, arresting flow in feeding vessels either by fetoscopic laser (Hecher *et al*., 1996), interstitial thermocoagulation (Makin *et al*., 2006) as well as radiofrequency ablation (Lam *et al*., 2002). The latter can cause collateral tissue damage (Paek *et al*., 2001). Needle-guided intravascular embolisation with alcohol or histoacrylor coils has been reported, but without measurable success (Benachi *et al*., 2006; Makin *et al*., 2006; Perrotin *et al*., 2006).

Myelomeningocoele and other open fetal surgical procedures

An important step was the addition of a *non-lethal condition* to the list of candidate indications for fetal intervention. Myelomeningocoele (MMC) can be staged by its extent or location and severe forms cause significant lifelong morbidity and burden. There is at present little prospect of improvements in postnatal management. Experiments and early clinical experience showed that prenatal intervention could improve outcome (Figure 3) (summarised by Adzick, 2010b) (Figure 4). Observational studies showed that prenatal microsurgical layered repair reverses hindbrain herniation, decreases the need for shunting, improves leg and bladder function, as well as later cognitive function (Bruner *et al*., 1999; Sutton *et al*., 1999; Danzer *et al*., 2008). The National Institutes of Health has sponsored the Management of Myelomeningocoele Study (MOMS) randomised trial (www.spinabifidamoms.org). The primary outcome is death or the need for shunting by the age of 1 year, and a secondary outcome is neurological and neurodevelopmental function at 2 years a 6 months and 2 years of age. This trial is interesting for many reasons. First, it has prevented the unfettered promulgation of this fetal operation in the USA. Second, centres with competing interests can be unified by a trial. Rivalry is avoided by geographical assignment of cases by a third party to one of the three treatment centres. Slow recruitment of the required 200 patients means that the trial may be completed years later than initially planned, but it will be worth waiting for. The only drawback is that it is not open to non-US citizens. Also such a trial might temporise the development of minimally invasive techniques. However, after initial clinical disappointment, others have mastered the technique. Using fetoscopy the defect is covered with a patch. This is not

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Table 4—Obstetrical and short-term outcomes in the CHOP and Vanderbilt series of MMC repair, this being the open fetal surgical procedure that has been most often reported

	CHOP ($n = 51$) (Johnson *et al.*, 2003)	Vanderbilt ($n = 178$) (Bruner and Tulipan, 2005)
Gestation at surgery (weeks)	23 + 0 (20 + 0 to 25 + 4)	(19 − 30); later on <26 weeks
Gestation at delivery (weeks)	34 + 4 (25 + 4 to 37)[a]	33 + 5 (25 − 38)
Postnatal shunt (postnatal age)	46% (21 weeks)	46% (12 weeks)
Perinatal losses	3/51 (5.8%; due to prematurity)	5/178 (2.8%; not specified)
Length of hospital stay	4 days	3.3 days (3–7)
Oligohydramnios	Not specified	25% early on; 30% readmission rate
Delivery <30 weeks	5/47 (10.6%)[b]	11.8%
Delivery >32 weeks	(40/47) 85%[b]	(not specified)
Maternal complications	None reported, including dehiscence or rupture; one amniotic fluid leak through hysterotomy	9 (5.1%) mild pulmonary oedema 1 bowel obstruction 4 (2.2%) dehiscence, asymptomatic in 3

[a] Includes all patients.
[b] Denominator denotes survivors only.

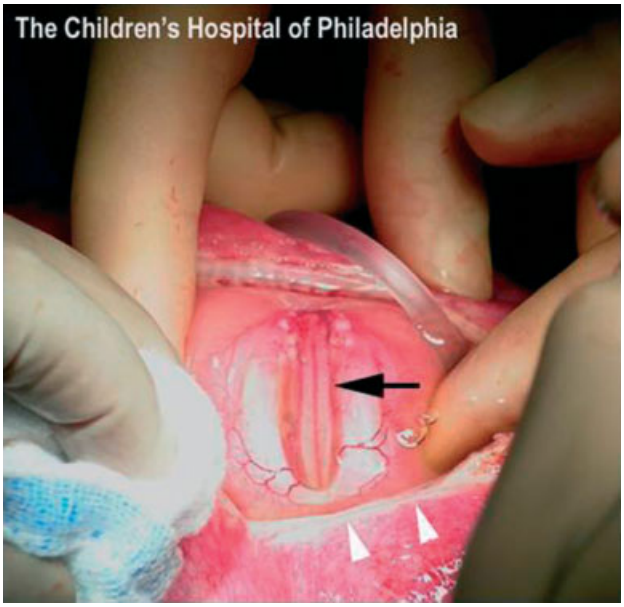

Figure 3—Open fetal neurosurgical repair of a thoraco-lumbo-sacral myeloschisis. Black arrow points to spinal cord tissue and white arrow heads to the uterine hysterotomy. This child is now 5 years old and walks with ankle braces (lower foot orthotics). Photo courtesy Mark Johnson, CHOP, with permission

exactly the same operation, so that results will have to show an equal efficacy (Bruner *et al.*, 2000; Kohl *et al.*, 2006).

Open fetal surgery is much less popular in Europe. Most centres limit themselves to procedures performed on placental support. The EXIT (*ex utero* intrapartum treatment) procedure was initially designed as a delivery technique for safely establishing upper airways following tracheal occlusion (Liechty *et al.*, 1997; Mychalishka *et al.*, 1997). The technical details of this treatment modality have been accurately detailed (Bouchard *et al.*, 2002; Liechty, 2010), and most fetal surgical centres should be able to offer this treatment modality safely. The time between induction of anaesthesia and cord clamping is kept as long as is clinically required. Using inhalational anaesthesia for maximal uterine relaxation, uteroplacental blood flow and gas exchange are maintained, and amnioinfusion and partial delivery of the fetus keep uterine volume within normal limits. The list of indications for using this technique has grown over the years but essentially includes airway obstruction due to laryngeal atresia, large tumours or iatrogenic tracheal occlusion. The procedure may also be used to create vascular access for extracorporeal circulation, such as for managing cardiac defects, severe CDH, lung lesions or conjoined twins (Kunisaki *et al.*, 2007).

Table 5—Recent series on postnatal outcome of isolated congenital diaphragmatic hernia

	Number of cases	TOP rate (%)	Survival rate (%)
Stege *et al.* (2003)	185	n.a.	70
Sartoris *et al.* (2006)[a]	244	n.a.	70
Gallot *et al.* (2007)	314	7	63
Hedrick *et al.* (2007)	89	n.a.	66
Datin-Dorrière *et al.* (2008)	99	20	63
Mettauer *et al.* (2009)[a]	147	n.a.	77
Grushka *et al.* (2009)[a]	121	n.a.	81

n.a., not available; TOP, termination of pregnancy.
[a] Units that report survival rates after transfer of the neonate and, therefore, do not include the hidden mortality.

Other open fetal surgical procedures are practised by a limited number of European centres. To our knowledge, some offer open surgical MMC repair. In the literature there is as of now little information on these few programmes, making it difficult to assess indications and trial design (Sroka *et al.*, 2007). Fetal lobectomy or sacrococcygeal teratoma resection has, to our knowledge, not yet been reported so far in Western Europe. In our opinion, the limited use of open fetal surgery is more a reflection of a physician's attitude than that the patient's perception of open fetal surgery. In fact, current data (Table 4) show that obstetric outcomes from open fetal surgery are very comparable to what is obtained by fetoscopy (Table 5). If the 'MOMS' trial demonstrates a decreased morbidity in survivors, open fetal surgery will inevitably be put back on the European agenda.

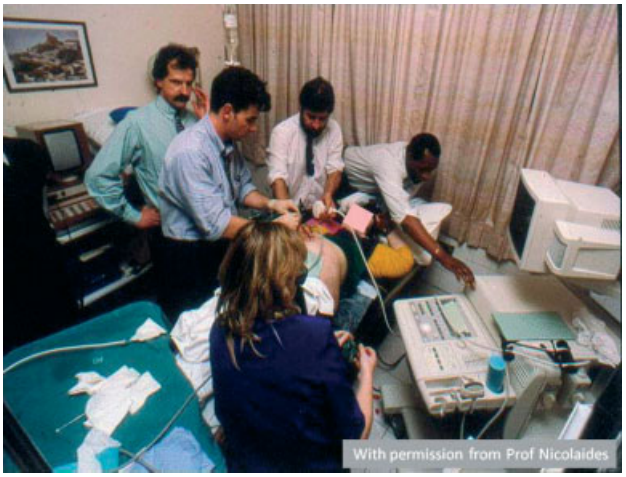

Figure 4—Fetoscopic laser coagulation for twin-to-twin transfusion syndrome in King's College Hospital in London; featuring from right to left Kypros Nicolaides, Yves Ville and Kurt Hecher (1992)

CLINICAL REVIVAL OF FETOSCOPY

Direct endoscopic visualisation of the embryo or fetus was introduced in the 1970s. It was done for diagnostic purposes, for example, to obtain fetal blood in the diagnosis of haemoglobinopathies, to visualise pathognomic malformations or to biopsy fetal skin, muscle or liver under direct vision. Therapeutic applications were mainly limited to intravascular transfusion under direct visual control. Fetoscopy was never widely implemented because of the skills required and its invasiveness. According to a report from the International Fetoscopy Group (1984) on about 3000 procedures, the fetal loss rate <28 weeks was 4%. With the widespread introduction of ultrasound, fetoscopy eventually became obsolete. In the 1990s, miniaturisation of cameras and development of small diameter (fibre) endoscopes allowed its revival (Estes *et al*., 1992; Luks and Deprest, 1993; Quintero *et al*., 1993). A boost was given by the European Commission with its funding of the 'Eurofoetus' project (Eurofoetus, 1998). It sponsored a consortium of fetal medicine units and a manufacturer of endoscopic instruments (Karl Storz, Tuttlingen, Germany) to design new endoscopes and instruments that would fulfil the needs of operating on the fetus (fetoscopic surgery) or on the placenta, membranes and umbilical cord (obstetric endoscopy) (Deprest and Gratacos, 1999). This resulted in an expanding line of instruments, with other manufacturers also adapting their instruments (Klaritsch *et al*., 2009).

Remarkably, surgery of the placenta and umbilical cord in *monochorionic* (*MC*) *twins* was not on the initial shortlist of paediatric surgeons interested in fetal surgery. The placenta is obviously not their usual habitat, and neither is there an effective animal model for twin-to-twin transfusion syndrome (TTTS). A potential surgical intervention for TTTS had already been suggested by Benirschke and Kim (1973). de Vore *et al.* (1983) proposed the use of laser energy for coagulation of placental anastomoses, but credit for the development of the original clinical technique must go to Julian De Lia (De Lia *et al*., 1990), who used mini-laparotomy for uterine exposure and insertion of a 5 mm hysteroscope through a purse-stringed hysterostomy. This procedure was not, to our knowledge, implemented in Europe until its percutaneous modification under local anaesthesia by Ville and Nicolaides made it acceptable (Ville *et al*., 1995) (Figure 4). Resistance to laser coagulation was initially strong and emotionally charged. Many doubted that anastomoses were even amenable to treatment while De Lia insisted from the beginning that eventually all vessels run on the placental surface at some point in their course (De Lia and Cruikshank, 1994). Coagulation of these anomalous vessels effectively arrests downstream flow. Although intuitively logical, it required experimental proof that in retrospect seems redundant (Van Peborgh *et al*., 1997; Dumitrascu-Branisteanu *et al*., 1999). The Eurofoetus project's highlight was the successful execution of a randomised trial on treatment for TTTS, so far the only one in fetal medicine. It showed that, compared with amniodrainage, fetoscopic laser coagulation increases survival by 25% and results in later delivery (33.3 vs 29.0 weeks) (Senat *et al*., 2004). In an early follow-up study from Germany, 167 children who underwent laser coagulation were evaluated at more than 3 years of age (Graef *et al*., 2006). Twelve infants (7.2%) had minor and 10 infants (6.0%) had major neurological abnormalities, without a difference between either former donors and recipients or between infants born as twins and those born as singletons. The 87% normal neurodevelopment was very reassuring, but unfortunately the amniodrainage cohort from the initial study could not be followed up. Lenclen *et al*. (2009) tried to overcome this shortcoming and evaluated a cohort of 21 children treated with amnioreduction and 88 with laser. They also used 222 dichorionic twins matching for gestational age at delivery. Normal development at 2 years of age was noted in 81% in the amnioreduction group, 88.6% in the laser group and 93.1% in the dichorionic twins. Major impairment was found in 9.5% following amnioreduction, in 4.6% after laser and in 3.4% of matched dichorionics. They used the Ages and Stages Questionnaire which is an evaluation method where parents score the functional outcome. The scores were lower and domains were more often abnormal following amnioreduction.

Prior to the Eurofoetus trial, the adoption of fetoscopic laser therapy at the 'traditional' fetal surgery centres was less enthusiastic, probably because of the limited involvement of obstetricians, concerns about maternal safety and efficacy of the procedure, but remarkably also because of difficulties in regulatory approval of these novel instruments in the United States. Although these regulations are obviously there to protect the patient from harm, it was difficult to understand from a European perspective why subtle variations of a generic instrument, such as an endoscope, had or have to be approved through such a long regulatory process.

Endoscopy was initially also used for umbilical cord occlusion in selected complications of MC twins. This was a welcome development, as ultrasound-guided embolisation was successful only in about a third of

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cases (Denbow *et al*., 1999). Early in gestation, fetoscopic laser was used (Ville *et al*., 1994; Hecher and Hackelöer, 1996b), but the cord was surgically ligated in older fetuses. For that purpose, fetoscopy replaced hysterotomy and extraction using a cordostat (Foley *et al*., 1995). The first endoscopic cord ligation was for an acardiac twin and done by the late Joel Childers (Tucson), who also pioneered laparoscopy in gynaecological oncology (McCurdy *et al*., 1993). Unfortunately, the pump twin died as well. Shortly thereafter, Rubèn Quintero from Wayne State University performed the first successful cord ligation (Quintero *et al*., 1994). In Europe, the Leuven team did the same a few months later, each group working in ignorance of the others' work (Deprest *et al*., 1996a). Upon compilation of all experience with fetoscopic cord ligation, the Preterm Prelabour Rupture of the Membranes (PPROM) rate of this procedure proved to be high and post-operative occurrence of amniotic bands was reported as well (Deprest *et al*., 1996a, 1998a). In 2000, Deprest *et al*. (2000) described the use of a 3.0 mm, and later a 2.3 mm, bipolar forceps. A recent modification of the bipolar forceps involves a built-in endoscope (Yamamoto *et al*., 2010). Meanwhile, monopolar needles (Rodeck *et al*., 1998) and radiofrequency energy using instruments as small as a 14 to 18 g needle were described (Lee *et al*., 2007; Moise *et al*., 2008).

The Eurofoetus group continued its work on MC twins, and meanwhile defined its natural history and outcome in apparently uncomplicated cases (Lewi *et al*., 2008; Ortibus *et al*., 2009). Gratacós *et al*. (2004, 2007) also proposed a classification for selective intra-uterine growth restriction (IUGR;14%) in MC twins, which is actually more common than TTTS (9%; Lewi *et al*., 2008). Selective IUGR with intermittently absent or reversed end diastolic flow in the umbilical artery, coinciding with the presence of arterio-arterial anastomosis, represents a particularly high risk. The place for fetoscopic intervention in this condition has yet to be determined. Laser has been proposed for that purpose but is more difficult than in TTTS (Quintero *et al*., 2001; Gratacós *et al*., 2008).

HISTORY OF EXPERIMENTAL FETAL SURGERY FOR CDH

CDH is in essence a pulmonary developmental problem. Campandale and Rowland (1995) first described the pulmonary hypoplasia which is more severe on the side of the lesion. Areechon and Reid (1963) planted the seed for the surgical management of CDH by suggesting that timely repair might lead to sufficient parenchymal growth. This disease has been, and still is being, studied in detail using experimental models that reproduce the pathology. In rodents the defect and hypoplasia are induced by a teratogen. In rabbits and sheep it is created surgically. Today, transgenic models are also available. The initial experiments were dedicated to reproduce both the abnormal anatomy and functional problems such as pulmonary hypertension and changes in lung compliance. To that end, the surgical defect needed to be created early in pregnancy (Adzick *et al*., 1985). A second step was to demonstrate that pulmonary hypoplasia could be reversed by an *in utero* intervention. The pulmonary hypoplasia was believed to be secondary to the space-occupying effect of the herniating viscera. Hypoplasia could indeed be reproduced by inflating an intrathoracic balloon (Haller *et al*., 1976), and reversed by its *in utero* deflation (Harrison *et al*., 1980a). Thoracic space can also be restored by anatomical repair of the defect, which worked in lambs (Harrison *et al*., 1980b). In the late 1980s, anatomical repair was first applied to patients in the USA (Harrison *et al*., 1990) and briefly in Paris (Esteve *et al*., 1992). For fetuses who did not have liver herniation, a 'two-step' repair (closure of the diaphragm and enlargement of the abdomen to accommodate the reduced viscera) allowed compensatory lung growth, improving survival after birth (Harrison *et al*., 1981a,b). A formal NIH-sponsored clinical trial in this 'liver down' group showed that although survival was high, it was no better than in the group of patients who were managed expectantly (Harrison *et al*., 1997). However, in the fetal surgery group there was a 21% neurological morbidity. Conversely, fetuses with liver herniated into the thorax were considered better candidates for fetal intervention as their survival with postnatal treatment was lower (Albanese *et al*., 1998). Prenatal reduction of the liver, however, acutely kinks the umbilical venous return, leading to fetal death (Harrison *et al*., 1993). These observations put a temporary end to open fetal surgery programmes.

A completely different approach was based on the rediscovery of observations made in 1965 by Carmel (Carmel *et al*., 1965). He showed that tracheal ligation, which prevents egress of lung, promotes lung growth. Conversely, chronic drainage of lung liquid leads to pulmonary hypoplasia. To our knowledge, DiFiore *et al*. (1994) first raised the concept of fetal tracheal obstruction to reverse lethal pulmonary hypoplasia due to CDH. This approach is often referred to as the PLUG (plug the lung until it grows) strategy (Hedrick *et al*., 1994). In the 1990s, a convoluted journey consisting of many experimental and clinical manipulations of fetal lung liquid started. Metal clips were used clinically for a while, because attempts at endoluminal occlusion with foam plugs were fraught with complications and were often not fully occlusive (Harrison *et al*., 1996). Groups from Leuven, Paris, San Francisco, Philadelphia and Providence independently explored *endoluminal* occlusion techniques, leading to a true 'Odyssey' of devices, ranging from cuffs, polymeric foam plugs, magnetic valves, umbrellas as well as vascular occlusive balloons (Bealer *et al*., 1995; Luks *et al*., 1996b). Concerns were clinical acceptability, accommodation of tracheal growth, reversibility at birth or *in utero*, and potential local side effects. Already, in 1995, we used a detachable endoluminal balloon which we could insert in lambs by fetoscopy (Deprest *et al*., 1995b; 1996b; Benachi *et al*., 1997; Flageole *et al*., 1997). Another important research topic was the exact timing and duration of the Tracheal Occlusion (TO). In brief, s*ustained* TO does increase lung mass, which temporarily improves gas exchange (DiFiore *et al*., 1994), but those lungs are depleted of

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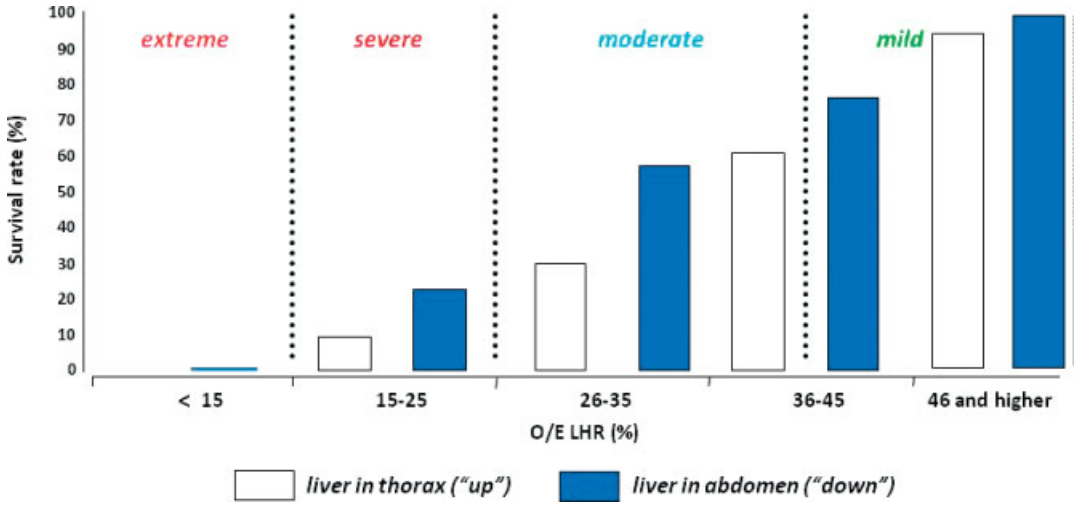

Figure 5—Survival rates of fetuses with isolated left-sided CDH depending on measurement of the observed/expected lung to head ratio (O/E LHR) measurements and liver position as in the antenatal CDH registry (Jani *et al*., 2006b); figure modified from Deprest *et al*. (2009)

alveolar type II cells (De Paepe *et al*., 1998) and surfactant (O'Toole *et al*., 1996). The Leuven group suggested to limit the latter effects by *reversal* of TO before birth (plug–unplug sequence) (Flageole *et al*., 1998). However, functional studies still demonstrate that the response was better but not yet ideal (Luks *et al*., 2000; Davey *et al*., 2003). Nearly normal lung growth and maturation was achieved in sheep by a cyclical occlusion protocol, that is, a 47 h occlusion period altered by 1 h release, and this between 110 and 138 days (Nelson *et al*., 2005). For further details on these and other studies related to experimental tracheal occlusion, we refer to some comprehensive reviews (Nelson *et al*., 2006; Khan *et al*., 2007).

CLINICAL EXPERIENCE WITH PRENATAL INTERVENTION FOR CDH

The rationale for fetal surgery for CDH is that its natural history can be defined, and that a subset of fetuses die in the postnatal period despite optimal care. Although the latter number remains undefined, recent data indicate that the condition is lethal in 10 to 30% of cases (Stege *et al*., 2003; Javid *et al*., 2004; Sartoris *et al*., 2006; Gallot *et al*., 2007; Hedrick *et al*., 2007; Datin-Dorriere *et al*., 2008) (Table 5). Further, this subset must be identifiable prior to birth. In the last decade considerable effort has been made to validate prognostic markers that predict lung size and determine position of the liver. The best validated prognostic method in use today is the lung-to-head-ratio (LHR), which involves standardised 2D-ultrasound measurement of the contralateral lung at the four-chamber view of the heart (Jani *et al*., 2006a). When expressed as a proportion compared to what is expected in a normal fetus (observed/expected LHR), this prediction is independent of gestational age (Jani *et al*., 2007a). Although the position of the liver is correlated with survival, it remains controversial that this is an independent variable. In Europe, we currently use a combination of both variables to define poor prognostic groups (Figure 5). In the near future, we expect magnetic resonance imaging (MRI) volumetry to play a more important role, because it has less maternal limitations and it can reliably and accurately measure *total* rather than unilateral lung size as well as quantifying the amount of liver herniated into the thorax (Cannie *et al*., 2006, 2008a,b; Jani *et al*., 2007b). It is also hoped that measurements of the pulmonary circulation will be predictive of pulmonary hypertension, as this is the second most important cause of death in CDH (Ruano *et al*., 2006; Sokol *et al*., 2006; Done *et al*., 2007; Moreno-Alvarez *et al*., 2010).

TO was first clinically achieved by laparotomy, hysterotomy, neck dissection and tracheal clipping (Flake *et al*., 2000). In the CHOP experience, a variable lung response and a survival rate of 33% were observed, but four out of the five survivors had serious neurological morbidity. UCSF later reported a 75% survival rate. They related it to the use of endoscopic uterine access. However, this still meant uterine exposure by laparotomy, the use of multiple cannulas and endoscopic tracheal dissection and clipping (Harrison *et al*., 2003). An endoluminal balloon was also used as first experimentally described by the European group (Deprest *et al*., 1996b, 1998b) but clinically using a single port of 4.5 mm diameter following laparotomy for uterine exposure (Harrison *et al*., 2001). The first *percutaneous* endoluminal occlusion was reported by Quintero *et al*. (2000). Unfortunately, the device failed to occlude and the baby died in the postnatal period. In Europe, the so-called Fetal Endoscopic Tracheal Occlusion—Task Force (Figure 6) developed a clinical technique via 3.3 mm percutaneous access with balloon removal initially at the time of an EXIT procedure (Bouchard *et al*., 2002; Deprest *et al*., 2004; 2006). General anaesthesia was used at first but we soon moved to regional and local anaesthesia with fetal sedation and immobilisation. We also reversed the occlusion *in utero* either by ultrasound-guided puncture or fetoscopy. This allows for vaginal delivery, and early return of the patient to the referring

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Figure 6—One of the first fetoscopic endoluminal tracheal occlusion procedures in 2001, performed by the FETO consortium, with Jan Deprest, Eduardo Gratacos and Kypros Nicolaides (from left to right). Courtesy: Geo Magazin, Germany, Dr A Vinciano. © Thomas Ernsting, Agentur für Photos & Reportagen gmbh

institution. These technical modifications occurred during the course of a randomised controlled trial (RCT) sponsored by the NIH (Harrison *et al*., 2003), which did not show any benefit from fetoscopic endoluminal tracheal occlusion (FETO) over standard postnatal care, mainly because of an unexpected high survival rate in the group that was expectantly managed (Table 6).

Since the majority of patients in the NIH trial did not meet the severity criteria used in Europe, the FETO task force continued its programme. The European FETO Task force recently reported its entire experience ($n = 210$) up to 2008 (Jani *et al*., 2009). PPROM within 3 weeks occurred in 16.7% cases, far less than the earlier experience in the NIH trial (Harrison *et al*., 2003). Delivery took place at a median of 35.3 weeks, but 30.9% of patients delivered before 34 weeks. Forty-eight per cent of infants were discharged from the hospital alive. On the basis of stratified data from the prenatal CDH registry, FETO therefore increased survival in severe cases with left-sided CDH from 24.1 to 49.1%, and in right-sided from 0 to 35.3% ($p < 0.001$) (Jani *et al*., 2006a). The strongest predictors of survival are observed/expected LHR *prior* to the procedure, the absence of PPROM and gestational age at delivery (Jani *et al*., 2007b, 2009). The early clinical experience has shown few demonstrable clinical side effects of the balloon on the developing trachea perhaps, except in very early occlusions and complications arising at the time of removal (Deprest *et al*., 2010; Fayoux *et al*., 2010; McHugh *et al*., 2010).

Intuitively, FETO later in gestation would reduce the risk for preterm birth, but yields a lesser lung response (Cannie *et al*., 2009). For that reason, we offer late TO only to moderately severe cases (Deprest *et al*., 2006, 2009b). Meanwhile, in Europe we finally moved to a randomised trial comparing expectant management during pregnancy to late (30–32 weeks) FETO in cases of moderate hypoplasia, and more recently, FETO at 28 to 30 weeks for severe cases. The balloon is removed at 34 weeks. Postnatal management of this multicentre trial is standardised by a consensus protocol (Deprest *et al*., 2009c). Although difficult, it is our hope that North American centres can also join the list of several European centres endorsing this trial.

THE FUTURE

This historical review has not described one of the most exciting advances in fetal therapy in recent years, that is, percutaneous fetal valvuloplasty or cardiac septostomy (Allan, 2010). The potential for fetal cardiac intervention opens completely new doors and a new society was even proposed (Jacobs *et al*., 2008). In other areas progress continues. Further evolution in the techniques used to treat TTTS may yet increase survival rates. Coagulation should be done as sparingly as possible, but not at the expense of leaving anastomoses that cause recurrence, IUFD or fetal anaemia (Lewi *et al*., 2006; Robyr *et al*., 2006; Stirnemann *et al*., 2008). Lasering the arteriovenous anastomoses from the donor to the recipient first ('sequential lasering') may improve haemodynamic status and decrease the risk of demise of the donor twin (Quintero *et al*., 2007). Currently there is much debate on how the condition should best be staged, so that therapy can be tailored to individual needs. Most describe TTTS using the Quintero-staging system, based on either the presence of amniotic fluid discrepancy (stage I–II) or the presence of haemodynamic changes without (stage III) or with hydrops (stage IV) (Quintero *et al*., 1999). Indeed, survival is stage dependent, but the system has no therapeutic implications, as therapy remains invariably laser coagulation (Huber *et al*., 2006). Some propose to incorporate fetal cardiac function assessment,

Table 6—Fetal surgery for CDH—trends in clinical experience

	Harrison *et al*. (2003)	FETO consortium (2009)
Criteria for surgery	LHR < 1.4 and liver 'up'	LHR < 1.0 and liver 'up'
Anaesthesia	General	Loco-regional or local
Access through abdominal wall	Laparotomy	Percutaneous
Access diameter	5 mm cannula	3.3 mm cannula
Occlusive device	Clip or endoluminal balloon	Endoluminal balloon
Reversal of occlusion	EXIT delivery	*In utero* reversal
PPROM < 34 weeks	100%	25%
Mean gestational age at birth	30.8 (28–34)	35.3 weeks (25.7–41.0)
Survival following TO (LHR < 1.4)	73% ($n = 11$) (controls: 77%)	TO not performed in this group
Survival following TO (LHR < 1.0)	33% ($n = 3$) (left CDH)	Left-CDH: 49% Right-CDH: 35%

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because it better reflects the pathophysiology of the condition (Anderson *et al*., 2006; Michelfelder *et al*., 2007; Rychik *et al*., 2007; Ville, 2007; Van Mieghem *et al*., 2009). It remains unclear whether or how this will change therapy. Meanwhile, the Eurofoetus group is currently designing an open multicentre trial that will evaluate the place of laser for stage I disease, which may be treated conservatively.

Another evolution in fetal medicine is that we are moving away from surgery *per se* towards a lesser invasive, even medical, approach with current research efforts focused on stem cell and gene therapy (Roybal *et al*., 2010). Initially, these methods may play a role as an adjunct to the surgical management of the perinatal patient. As an example, tissue engineering using fetal cells is conceptually very attractive for reconstruction of congenital birth defects. The amniotic fluid is an obvious source of rapidly expanding fetal cells, wherein multipotent mesenchymal stem cells have been demonstrated (Kaviani *et al*., 2003; Gucciardo *et al*., 2009). As amniocentesis is typically part of the initial assessment; these cells are readily available. They can be used to engineer homologous 'biological' grafts while the pregnancy continues and the fetal patient awaits postnatal therapy. The European Union has recently funded a research programme to explore the broader potential of tissue engineering for several congenital defects (Eggink *et al*., 2008; Roelofs *et al*., 2008a,b; Hosper *et al*., 2010). Using our index condition as an example, diaphragmatic reconstruction might be undertaken using a collagen matrix, seeded with native fibrous or muscular cells. Fauza *et al*. (2001) already suggested this 10 years ago, hoping this would create a more functional substitute than the inert synthetic grafts currently in use (Kunisaki *et al*., 2006). These strategies may also be used to create a matrix for stimulating fetal membrane healing (Ochsenbein-Köble *et al*., 2007; Mallik *et al*., 2007).

The practice of fetal surgery today floats on a permanent conflict between what is optimal quality and how it can be guaranteed, versus widespread access and sufficient quantity of patients (Chescheir, 2009). It also needs to remain open for innovation and alternative approaches with researchers questioning the dogmas of the past. Here we need a balance of appropriate regulation and concern for patient protection versus sufficient space for enthusiastic new scientists and clinicians who may be the pioneers of the future. It is our personal belief that such a balance is best made within a few leading centres, which have the necessary resources, case-load, senior scientists and multidisciplinary research groups, who are willing to stay of the beaten path. The North American Fetal Therapy Network (NAFTNet) has tried to merge efforts from leading centres (Johnson, 2009). At the same time, mainstream fetal procedures for common indications need to be brought closer to the patient. Who and where is a matter of debate, and probably difficult at present to judge in an evidence-based manner.

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