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Fetal Surgery for Congenital Diaphragmatic Hernia Is Back from Never Gone

Jan A. Deprest[a] Kypros Nicolaides[b] Eduard Gratacos[c]

[a]Division Woman and Child, University Hospitals KU Leuven, Leuven, Belgium; [b]King's College Hospital, Harris Birthright Centre for Fetal Medicine, London, UK; [c]Hospital Clinic-Idibaps, University of Barcelona and CIBER-ER, Barcelona, Spain

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Congenital diaphragmatic hernia · Fetal intervention · Endoscopic tracheal occlusion, fetal · Fetoscopy · Pulmonary hypoplasia

Abstract
Over half of the cases of congenital diaphragmatic hernia are picked up prenatally. Prenatal assessment aims to rule out associated anomalies and to make an individual prognosis. Prediction of outcome is based on measurements of lung size and vasculature as well as on liver herniation. A subset of fetuses likely to die in the postnatal period is eligible for a fetal intervention that can promote lung growth. Two randomized trials have shown that fetal surgery using open anatomical repair or tracheal occlusion via hysterostomy has no benefit. Since then, a percutaneous fetoscopic technique has been introduced, which has been shown to be safe and seems to improve survival when compared to historical controls. Rupture of the fetal membranes and early delivery, nevertheless, remain an issue, but are less likely as compared to earlier experience. Improved outcomes are confirmed in two other studies published in this issue of *Fetal Diagnosis and Therapy*. This paper summarizes the experimental and clinical history of fetal surgery for congenital diaphragmatic hernia. It stresses the need for another randomized trial. This trial started in Europe and patients should be asked whether they would like to participate.

Introduction

Congenital diaphragmatic hernia (CDH) is a congenital birth defect which occurs in 1/3,000 to 1/5,000 live births [1]. This number includes what has been called the 'hidden mortality', such as stillbirths or neonatal death before transfer to a tertiary care centre, so that a more accurately estimated incidence of CDH is believed to be 1 in 2,200 live births [2, 3]. Eurostat counted 5,420,900 live births in the European Union (EU-27) in 2008. As a consequence, this means that in absolute numbers at least every 4 h one new case is born alive [4]! According to a meta-analysis, up to 40% of cases have associated problems [5]. These can occur in the absence or presence of identified syndromes or other genetic problems. Their presence is an independent predictor of neonatal death. The majority thus are apparently isolated. The surgical defect is typically left sided, but 10% are right sided and 2% are bilateral. Though CDH is a surgically correctable defect, neonates may not make it to the operation because of the pulmonary underdevelopment that is invariably present. It affects both airways and vessels, leading to variable degrees of ventilatory insufficiency and/or pulmonary hypertension (PHT). Pulmonary hypoplasia is more prominent on the side of the lesion, but both lungs are affected.

The authors founded the FETO Task Force.

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Jan Deprest, MD, PhD
Division Woman and Child, Department Women
University Hospitals Leuven
BE–3000 Leuven (Belgium)
Tel. +32 1634 4215, Fax +32 1634 4205, E-Mail jan.deprest@uzleuven.be

In case of prenatal diagnosis, in utero transfer is therefore recommended to ensure optimal neonatal management. Since the 1990s postnatal management has shifted from emergency repair, aggressive ventilation and hyperoxygenation to gentle ventilation followed by delayed surgery, together with measures for control of PHT [6]. 'Gentilation' with permissive hypercapnia and minimal sedation must avoid baro- and volutrauma of the lung. Over the course of years other novel neonatal strategies, such as the use of inhaled nitric oxide and prostaglandins (for PHT), high-frequency oscillatory ventilation, extracorporeal membrane oxygenation and even liquid ventilation (for ventilator insufficiency) have been embraced, with the hope to improve survival; however, this was in vain [7]. It is extremely difficult to compare results from different centres, as case load, case mix and neonatal management may be significantly different. It seems, however, fair to say that mortality rates for prenatally diagnosed, isolated left-sided CDH are still as high as 30% in tertiary centres [8]. As postnatal strategies may fall short, prenatal therapy has been suggested as early as 1963 to treat (nearly) lethal pulmonary hypoplasia [9]. CDH has always been high on the fetal surgery agenda, but its story followed certainly cycles of hope and despair. Over the last decade, we have seen a renewed interest because of a coinciding improvement in prenatal diagnostic tools, as well as the introduction of (yet another) prenatal intervention.

A Special Issue on CDH

It is a great pleasure to see that *Fetal Diagnosis and Therapy* devotes a special issue to recent progress in the field of CDH. Since the focus of the readership of *Fetal Diagnosis and Therapy* is in essence clinical, the stress is on clinical applied research. This issue contains information relevant to all physicians dealing with CDH in fetuses or newborns. It looks at the different aspects of making a more precise prenatal diagnosis of CDH. Indeed, parents expect caregivers not only to make the diagnosis in good time but also to provide them with comprehensive information on the impact of the condition after birth. In reality they expect clinicians to predict the outcome of their baby; in other words, they expect an individualized prognosis (fig. 1). Such an individualized management requires in utero referral to a specialized multidisciplinary team at a tertiary care centre, familiar with the pre- and postnatal management of the disease. In view of the increasing spectrum of prenatal options, physicians less familiar with this condition should refrain from making statements about the potential prognosis, in order not to compromise future options [10]. As will be explained below, CDH is no longer a 'black box'. In this issue both evaluation of airway development as well as pulmonary vasculature is being reviewed [11, 12]. This means that the prenatal decision-making process can now be objectivized.

This issue of *Fetal Diagnosis and Therapy* will also deal with fetal surgery for highly selected patients. Several groups have enthusiastically explored the potential of fetal therapy over the last 20 years. Between 1980 and 1989, 61 clinical papers on CDH were published in English, which also mentioned (the potential of) fetal therapy. This increased to 205 by 1999, and by another 40% to 286 by October 2010 [13]. In recent years, it has become apparent that fetal intervention can be offered through minimally invasive access and is safe for the mother. *Fetal Diagnosis and Therapy* now publishes 2 additional clinical series with percutaneous fetoscopic endoluminal tracheal occlusion (FETO), suggesting an increased survival rate after fetal surgery [14–17]. Though the published experience seems to demonstrate variable degrees of benefit of fetal therapy, one should remember this remains an experimental procedure, in the sense that it is not a therapy with proven efficacy (as is the case for many other fetal therapies). Simplification of the antenatal intervention by the development of minimally invasive instruments and the use of local anaesthesia may make the procedure appear trivial. A new hammer, however, should not make everything look like a nail. FETO should only be offered within a precise trial protocol by an experienced multidisciplinary team in accordance with the criteria for fetal surgery defined by the International Fetal Medicine and Surgery Society [18]. Actually, the time has come to offer this fetal procedure within a randomized trial, testing the hypothesis whether FETO truly improves outcome as compared to expectant management during pregnancy [19]. In order to update the interested reader who is less familiar with fetal surgery, we describe below the odyssey of fetal surgery for this condition. It may show us that perceived advances in fetal therapy have to be substantiated by hard evidence prior to a change in clinical practice.

The History of Experimental Fetal Surgery for CDH

Different experimental models were designed to reproduce the pathophysiology of CDH. In rodents, the diaphragmatic defect and pulmonary hypoplasia are typically induced by a teratogen or dietary changes [20]. The literature on nitrofen-exposed rodents is huge, and several

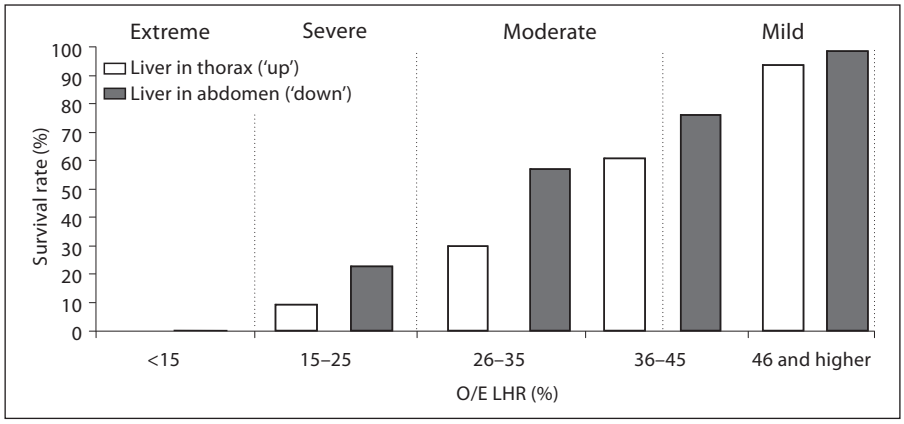

Fig. 1. Survival rates of fetuses with isolated left-sided CDH, depending on measurement of the observed/expected (O/E) LHR and position of the liver as in the antenatal CDH registry [adapted from 124].

good reviews are available [21]. Today, transgenic models are also available. In rabbits and sheep, the defect is typically created surgically, though space occupation by a balloon also provokes pulmonary hypoplasia [22]. De Lorimier et al. [23] were the first to surgically induce a diaphragmatic defect in lambs in order to reproduce problems with lung development. However, it was late in pregnancy so that the effects were minimal. Kent et al. [24] then created it in the late second trimester, with subsequent PHT, right-to-left shunting, hypoxia, hypercarbia, acidaemia, and a decreased total lung-to-body weight ratio. Adzick et al. [25] created the defect as early as at 65 days, which in lambs is in the pseudoglandular phase. This resulted in parenchymal and vascular changes similar to those seen at autopsy of babies with CDH. The functional impact of these morphological changes was later demonstrated by the groups from Boston and Buffalo [26, 27].

The concept of a prenatal surgical intervention was already raised in 1963 by Areechon and Eid [9]. They suggested that 'timely repair' could lead to sufficient parenchymal growth. Harrison et al. [28] proved the principle of this concept by deflation of a previously inflated intrathoracic balloon. This increased lung weight, air capacity and cross-sectional area of the pulmonary vascular bed with improvement in pulmonary compliance. The same group also demonstrated the efficacy of in utero anatomical diaphragmatic repair. In the late 1980s and early 1990s, this approach was applied clinically, first in the USA [29] and then briefly in Paris [30]. For fetuses without liver herniation, a 'two-step' repair consisting of closure of the diaphragm and enlargement of the abdomen yielded compensatory lung growth [31]. A formal NIH-sponsored clinical trial in humans showed that in the 'liver-down' group an unexpectedly high survival rate obtained in the expectantly managed group, without a further increase in those treated by fetal surgery [32]. Additionally, the fetal surgery group had a high rate of neurological morbidity. Fetuses with liver herniated into the thorax are theoretically better candidates for fetal intervention since their survival is lower. However, when doing an anatomical repair in this group, reduction of the liver is required. This acutely kinks the umbilical venous return, leading to fetal death [33]. These observations put a (temporary) end to open fetal surgery programs based on anatomical repair.

A completely different approach was based on the rediscovery of observations made in 1965 by Carmel et al. [34]. During fetal life the lungs are important contributors to amniotic fluid volume. Lung-liquid volume and intratracheal pressure are maintained within precise limits by opening and closing of the larynx [35]. The prenatal airway pressure is determined by the balance of forces generating the elastic recoil of the lungs and the thoracic wall. The fetal chest wall is relatively stiff, whereas the lungs are more compliant, creating a negative intrapleural pressure of 0.2–0.7 Torr [36]. The intratracheal pressure varies with fetal breathing movements: in their absence, pressure under the glottis is 1.8–2.0 Torr above that of the amniotic fluid cavity [37, 38]. In other words, during fetal apnoea there is a net transpulmonary pressure of about 2.7 Torr, which stents the airways and promotes lung growth [39]. Fetal breathing leads to the opening of the vocal cords, and levels the airway pressure to that of the amniotic cavity. Chronic drainage of lung liquid leads to pulmonary hypoplasia, while its entrapment causes increased lung growth despite moderate effects on intratracheal pressure [40–42].

Better insight into the role stretch plays in fetal airway development started a convoluted journey consisting of many experimental and clinical manipulations of fetal

lung liquid. To our knowledge, DiFiore and Wilson [26] first suggested the use of fetal tracheal ligation to reverse lethal pulmonary hypoplasia due to CDH. Tracheal occlusion (TO) is also referred to as the PLUG (plug the lung until it grows) strategy [43]. Clips were first used because an endoluminal foam plug induced tracheal side effects or was not completely occlusive [44]. Groups from Leuven, Paris, San Francisco, Calif., Philadelphia, Pa. and Providence, R.I. independently explored endoluminal occlusion techniques, leading to a true 'odyssey' of devices, ranging from cuffs and polymeric foam to magnetic valves, umbrellas and vascular occlusive balloons [45–48]. The varying occlusion methods have different occlusive performance, clinical acceptability, accommodation of tracheal growth, reversibility at birth or in utero, and local side effects. As early as in 1995, we used a detachable endoluminal balloon which we could insert in lambs by fetoscopy. This balloon system is currently still in clinical use and prevailed over the other methods for a variety of reasons. First, balloon occlusion allows for tracheal growth. Second, it avoids neck dissection and external clipping, thereby preventing its inherent morbidity [49]. Third, percutaneous access is feasible in over 95% of cases [15]. Finally, experimentally tracheal side effects were limited to mild local tracheal changes, consisting of loss of epithelial folding, squamous metaplasia and focal defects without damage to the cartilage [50].

The eventual effect of TO is dependent on timing, duration and reversal of the occlusion. The literature on this topic has been summarized elsewhere by Khan et al. [51] and Nelson et al. [52]. Briefly, TO increases DNA synthesis, which peaks after 2 days and is largely complete by 4 days [53]. Thereafter, growth falls back to control rates [54]. TO for 1 week induces pulmonary hyperplasia, but effects are more important after 3 weeks of obstruction [55, 56]. Gestational age at occlusion is another important determinant [57]. Lung growth is primarily driven by the volume of lung liquid rather than by tracheal pressure. As a consequence, the rate of lung growth is greater late in gestation, because of the higher lung liquid secretion in older fetuses, together with higher chest wall compliance [53, 58, 59]. However, growth rate is not the only concern: lung size which can eventually be achieved at birth is as critical. Therefore, earlier intervention may lead to larger lung size than late TO. Lipsett et al. [60] demonstrated the beneficial effect of early TO (101 days of pregnancy in sheep; canalicular phase; term = 145 days) over late TO (129 days; saccular phase). Sustained TO may increase lung mass and temporarily improve gas exchange [26], but TO lungs are depleted of alveolar type II cells [61] and surfactant [62] and there is PHT after birth. Our group proposed that these effects should be limited by reversal of TO before birth (plug-unplug sequence) [63]. One of the most comprehensive experiments in fetal lambs was that by Nelson et al. [64]. A cyclical occlusion protocol with a 47-hour occlusion and 1-hour release performed between 110 and 138 days provided ideal lung growth. Unfortunately, this intermittently active occlusion device has yet to be produced for clinical use. Temporary TO also leads to more normal muscularization of pulmonary arterioles. However, the functional impact is not very obvious [65, 66].

The above is mainly a summary of ovine experiments, but rabbits with CDH have also been used to study airway and vascular changes by TO. Rabbits have a pulmonary development that largely mimics that of the human lung. Alveolization occurs prior to birth so that at term, rabbit lungs are in the terminal air sac stage. Rabbits have a relatively short gestational period (term = 31 days) and a large litter size so that they are practical for fetal surgical experiments. The pseudoglandular phase stretches proportionally far in pregnancy so that fetal surgery on a reasonably sized animal can be done. We demonstrated that surgical induction of CDH at day 23 of gestation leads to progressive and severe pulmonary hypoplasia and vascular changes [67–69]. TO reverses this process in part, in particular late in pregnancy, and steroids may have a beneficial effect [70, 71]. In utero, a reversal has not been described in this animal. Nitrofen rats have also been used to study the effect of TO [72, 73]. These animals, however, have a different lung development and surgery is more difficult. Very sophisticated experiments have made it possible to unravel gene expression following TO in these animals, while pharmacologic agents that may induce lung growth, with or without TO, are being tested as well. For instance, osmotic active agents may trigger lung growth as demonstrated in rats [74] as well as sheep. Perfluorocarbons may be used as well. They have a high density and viscosity and in fetal rabbits with normal lungs, we together with others have shown that perfluorooctyl bromide can trigger lung growth [75, 76]. Perfluorooctyl bromide-treated animals also had improved neonatal lung mechanics and normal type II pneumocyte density [76].

Prenatal Diagnosis and Prediction of Outcome

One of the criteria for fetal surgery is that an accurate diagnosis can be made and the natural history of the condition can be predicted. Wide availability of high-resolu-

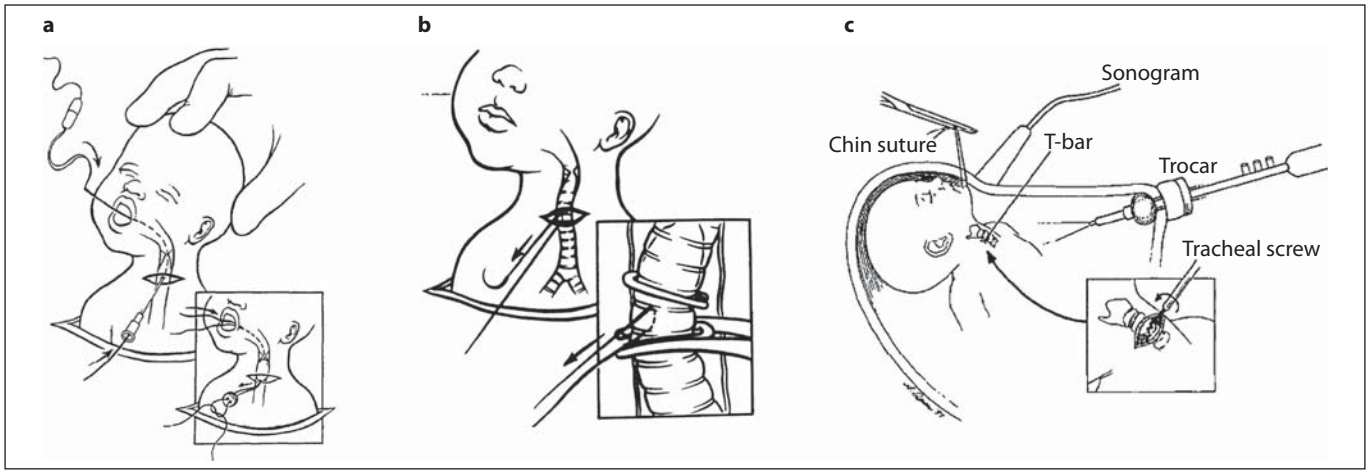

Fig. 2. Clinical TO techniques using a foam plug (**a**), an external clip (**b**) [44], and the same but applied by fetoscopy (**c**) [101]. Reproduced with permission.

tion ultrasound and increasing access to prenatal screening have made it possible in western countries to diagnose 2 cases out of 3 antenatally [77]. Following diagnosis, additional imaging methods and genetic studies allow to rule out the vast majority of associated anomalies, which have a proven negative effect on postnatal outcome. Karyotyping is an essential step in the work-up of the fetus with CDH, but its resolution may fall short of excluding underlying genetic problems. Modern techniques are, therefore, increasingly being used, also to better understand the aetiopathogenesis of CDH [78, 79]. In this issue, Brady et al. [80] review these new approaches that are slowly introduced into the clinic. They recently designed a purpose-designed array, targeting genes previously linked to CDH, and applied it to fetuses with apparently isolated CDH [81]. They hypothesized that even in those isolated cases, there might be underlying genetic causes resulting from copy number variants. Indeed, in nearly 4% of the samples a genomic imbalance was detected, and 2 out of 3 located on genes earlier tied to CDH. This underscores the need for further investigation of the genetic basis of this condition, including in cases phenotypically presenting as isolated CDH. Today, genome-wide comparative hybridization is technically feasible and we are integrating it into our assessment of anomalies like CDH [82]. However, the interpretation of the detected copy number variations (particularly those that exhibit reduced penetrance or with variable expression), incidental findings not clearly related to the anomaly involved or unclassified variants remains difficult. Therefore, these novel techniques have to be used with caution within research protocols [83].

Apart from genetic analyses, structural evaluation is used to rule out associated anomalies which include in descending order cardiac defects (52%), genitourinary (23%), gastrointestinal (14%) and central nervous system anomalies (10%) [5]. In this issue of *Fetal Diagnosis and Therapy*, Claus et al. [12] review the different imaging methods that provide anatomical assessment of the fetus presumably with CDH. Though ultrasound remains the basis of prenatal diagnosis, fetal MRI may play an increasingly important role. However, its added value may be difficult to prove. When after scrutinous assessment the condition seems isolated, parents will ask for an estimation of the chances of survival. This may help them with further decision making. This includes termination of pregnancy, which in most countries is legally and ethically acceptable. Therefore, survival chances and morbidities should be predicted on the basis of objective information. In other words, prenatal prediction of outcome has become an issue for any fetal medicine specialist, even if there were no fetal surgery option. In this issue, both the assessment of the developing airways as well as of the pulmonary vasculature and knowledge about the factor liver herniation will be reviewed [12].

Briefly, the best-studied prognostic method in use today is the lung-to-head ratio (LHR), which involves standardized 2-dimensional ultrasound measurement of the contralateral lung at the level of the four-chamber view of the heart, as demonstrated by the antenatal CDH registry [84, 85]. When expressed as a proportion of what can be expected in a normal fetus (observed/expected LHR), this measuring method is independent of gestational age

(fig. 1) [86]. This is also the sole method tested for prediction of (early neonatal) morbidity [87].

Bilateral lung volumetry, as compared to 2-dimensional measurement of the contralateral lung area, certainly has the potential to improve prediction, but this remains to be demonstrated [88–90]. Again, here volumes also need to be expressed as a function of what is expected in a normal control. The most accurate method is to match cases with normal lung development and with equal estimated fetal weight, though gestational age also works fairly well [91]. There is a debate on whether lung volumetry should be done by 3-dimensional ultrasound or fetal magnetic resonance. In our own experience, the latter seemed superior because of its higher resolution allowing more often a reliable measurement of the ipsilateral (smaller) lung [92]. 'Liver-up' has already early on been recognized as a poor prognostic factor, and this has been confirmed in two meta-analyses [93, 94]. Herniation of the liver into the thorax is observed in about 50% of left-sided cases, whereas it is nearly a constant in the right-sided cases. Logically, the predictive value could be improved if the amount of liver herniation is quantified more precisely. This was already done by several groups, but standardization is lacking [95]. Also, it remains to be demonstrated whether lung volume and (amount of) liver hernation are independent predictors, as suggested in our recent study [96]. From a pragmatic viewpoint, in Europe we currently use a combination of both variables for prenatal counselling.

Another tool is the assessment of the pulmonary circulation, which one might hope may be predictive of PHT. This is the second most important cause of death in CDH. Over the course of time, measurements of the number of branches, vessel diameters, flow velocimetry or volume, and reactivity to maternal oxygen inhalation have been made. This is described in detail in the contribution of Cruz-Martinez et al. [97]. Vascular and airway development are interconnected so that there is certainly a relationship between vascular assessment and measurements of lung size [98–100]. However, several studies have already pointed to the independent nature of these measurements.

Early Clinical Experience with TO

The tale of clinical TO started, as for most fetal surgical procedures, at the University of California, San Francisco (UCSF). Following the failure of foam plugs to occlude the trachea, TO was achieved by laparotomy, hysterotomy, neck dissection and tracheal clipping (fig. 2) [44]. Soon, a clinical series was published by the group of the Children's Hospital of Philadelphia. All fetuses had severe pulmonary hypoplasia prior to TO. The lung response was variable and overall survival rate was 33%. Four out of the 5 survivors had serious neurological morbidity [101]. The UCSF later reported a 75% survival rate, which they related to the use of endoscopic uterine access (fig. 3). For clarity, this meant initially uterine exposure by laparotomy, multiple cannulation and endoscopic tracheal dissection and clipping [49, 102]. The use of TO also made it possible to operate on fetuses with liver herniation. Later, the UCSF group moved to a single 4.5-mm port inserted into the uterus following laparotomy and use of a balloon [102, 103]. The first percutaneous endoluminal occlusion was reported by Quintero et al. [104]. 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' proposed an operation through a 3.3-mm percutaneous access with the use of an endoluminal balloon (fig. 3) [14]. This programme had barely started when the results of the single-centre NIH-sponsored randomized controlled trial (RCT) became available [105]. The survival rate after FETO was over 75% as was hoped. But as in the previous RCT, there was an unexpectedly high survival rate in the expectantly managed group. Given that there was no apparent benefit from fetal surgery, the European FETO consortium considered stopping their trial. However, at a closer look, the patients in American RCT did not meet the severity criteria the FETO task force used, i.e. fetuses with an LHR <1.0 (around 26–29 weeks: observed/expected LHR 25–27%) and liver herniation (severe pulmonary hypoplasia).

Current Percutaneous FETO Technique

Ideally, we strived to perform FETO at 26–28 weeks. FETO was done under general anaesthesia at first, but we soon moved to regional and local anaesthesia with fetal sedation and immobilization. The first balloons were removed via an ex utero intrapartum treatment procedure, but we soon tried to establish whenever it is clinically possible to reverse the occlusion in utero, either by ultrasound-guided puncture or fetoscopy. This allowed for vaginal delivery and early return of the patient to the referring unit, but the most important argument was that in sheep it improved pulmonary maturation [63].

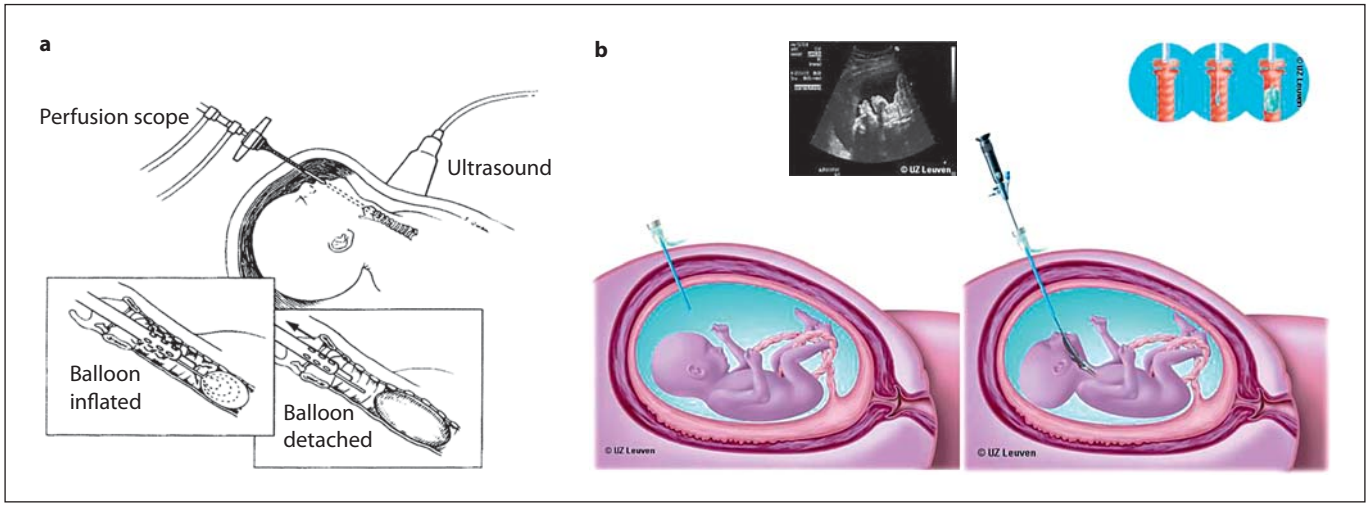

Fig. 3. Clinical TO techniques using a balloon. **a** Via laparotomy and hysterostomy [49]. **b** Percutaneous [122]. Reproduced with permission.

Additionally, it was hoped that the lesser invasiveness, as a result of the use of locoregional or local anaesthesia, the percutaneous approach and the smaller diameter of instruments, would reduce the membrane rupture rate observed by the UCSF group (table 1). After an initial report in 2004 [14], we recently came up with data on our entire experience of 210 consecutive cases [15].

In the European setting, the majority of patients are not staying at the FETO centre after occlusion or for delivery. Our data, therefore, report on the outcomes irrespective of the location of management of the fetus or neonate. The most frequently used technique for reversal of occlusion was fetoscopy (50%). Ultrasound-guided puncture accounted for 19% of cases. Hence, in a third of cases, the airways were managed around the time of delivery. In 21%, this was done while the fetus was still on the umbilical cord, and in 7% it was done postnatally. There were difficulties with balloon removal in 10 cases, when this happened in unprepared circumstances. This may have led or contributed to neonatal death [14, 106] and is the reason why we want to avoid at all cost an unplanned balloon removal. Therefore, we now plan elective removal at 34 weeks and insist that patients stay close to the FETO centre in the occlusion phase, since it is the only place that has sufficient experience and can organize a 24/7 service for the management of fetal airways.

In 210 consecutive cases, preterm prelabour rupture of membranes within 3 weeks of FETO occurred in 16.7% cases. The rupture rate prior to 34 weeks was 25%. When amniorrhexis occurred, labour did not necessarily start so that an expectant management was possible. Delivery took place at a median of 35.3 weeks, but it was before 34 weeks in 30.9% cases. On the basis of data from the antenatal CDH registry, FETO would increase survival rate in severe cases with left-sided CDH from 24.1 to 49.1% and in right-sided CDH from 0 to 35.3% ($p < 0.001$) [84]. Short-term morbidity in survivors is also better than expected: it is close to that of cases with moderate pulmonary hypoplasia, who are managed expectantly during pregnancy [107]. Most newborns require surgical patching of the diaphragm, indicating the rather large size of the defect in this selected group.

A number of predictors of survival were identified, but many of these are interconnected. One is the observed/expected LHR prior to the procedure [15, 108]. This would suggest that smaller lungs, having a smaller airway epithelial surface, might have a reduced ability to produce lung liquid, hence rising airway pressure to a lesser extent. A second predictor is the gestational age at delivery. Logically this follows the high occurrence of preterm prelabour rupture of membranes, which itself is also a predictor, in turn related to operation time. The second intervention (balloon removal) might also increase the risk for early delivery. However, we observed at the same time a higher survival rate in fetuses in whom the balloon was removed more than 24 h prior to birth [8]. Therefore, a balance has to be made between the advantages of elective and timely balloon removal and the risk of early delivery by the second intervention or letting the pregnancy progress and be confronted with an acute

Table 1. Fetal surgery for CDH – trends in clinical experience

	Harrison et al. (2003) [105] n = 11	FETO consortium (2009) n = 210	South American series (2010) n = 16 [16], n = 12 [123]
Criteria for surgery (left)	LHR <1.4 and liver 'up'	LHR <1.0 and liver 'up'	LHR <1.0 and liver 'up'
Anaesthesia	general	locoregional or local	locoregional
Access through abdominal wall	laparotomy	percutaneous	percutaneous
Access diameter	5-mm cannula	3.3-mm cannula	2.7-mm trocar 3.3-mm trocar
Occlusive device	clip or balloon	balloon	balloon
Operation time, min	NR	10 (3–93)	27.6 ± 8.3 NR[2]
Reversal of occlusion	–	deflation rate: 17/209 (8%)	deflation rate: 10/16 (62%) deflation rate: 1/10
	EXIT delivery	in utero reversal	EXIT delivery in utero reversal
PPROM <34 weeks, %	100	25	NR
PPROM <37 weeks, %	100	47	35 60[3]
Mean gestational age at birth, weeks	30.8 (28–34)	35.3 (25.7–41.0)	35.6 (28–38) 37 (35–37)
Survival till discharge (LHR <1.4), %	73 (8/11) (controls: 77%)	not eligible	not eligible
Survival till discharge (LHR <1.0)	1/3 (33%)	86/175 (49%)	left: 7/12 (58%)[1] left: 5/12 (42%)
Survival till discharge Right CDH	–	12/34 (35%)	2/5 (40%) 1/1

The data in the last column are deducted from the original studies in this issue and take into account all described cases. The upper line is from Ruano et al. and the lower line is from Peralta et al. NR = Not rated; EXIT = ex utero intrapartum treatment; PPROM = preterm prelabour rupture of membranes.

[1] A contemporary control group was reported with a survival rate of 5.6%.

[2] Median of 11 min is quoted, but excludes 12 patients, including 2 failures. Preterm delivery <34 weeks: 35.7%.

[3] Preterm PROM rate 35.3%, but exact definition not quoted.

need for balloon removal. One could also move FETO to later in gestation, which would reduce the risk of preterm birth, but clinical data show that this yields a lesser lung response [109]. For this reason, we offer late TO only to moderate cases in the setting of a trial [10, 11].

There are few demonstrable clinical side effects of the balloon on the developing trachea, except in very early occlusions and when complications arise at the time of balloon removal [110]. Neonates and infants do however have larger tracheal dimensions referred to as 'tracheomegaly'. This does not seem to have an obvious clinical impact, except for a barking cough on effort [111]. Over time, the widening seems to become less important [112]. This is in line with the observations from animal experiments, but serious side effects can obviously not be excluded [113].

We are aware of other experience [114, 115], and also US-based programmes at UCSF [116] (NIH trial identifier: NCT00768703), St. Lukes at Denver, Colo. (NCT00881660) and the Hasbro Hospital in Providence, R.I. (NCT00966823). In this issue of *Fetal Diagnosis and Therapy*, two larger case series from Brazil are also published. The reported outcomes of the study by Ruano et al. [16] and Peralta et al. [117] are quasi duplicates of what we reported (table 1).

The Tracheal Occlusion to Accelerate Lung Growth (TOTAL) Trial and FETO in the Future

The fact that the FETO procedure, just as laser photocoagulation for transfusion syndrome is increasingly being used, underscores the acceptability of a minimally invasive fetal surgical procedure, both by physicians and patients. This success may also become the Achilles heel of the procedure. The above history of fetal surgery for this condition has demonstrated that things are not always what they seem. Therefore, it is more than time to conduct, in controlled circumstances, this randomized trial comparing expectant management during pregnancy and fetal intervention, followed by standardized neonatal care. 'Controlled' means that there is rigorous adherence to selection criteria, surgical technique and skills, availability of emergency airway management, postnatal management, follow-up of patients and precise as well as comprehensive reporting. We may be the first to be blamed for not having started a randomized trial earlier, which was for a variety of reasons [19]. Meanwhile, in Europe, we finally moved to a randomized trial comparing expectant management during pregnancy to late (30–32 weeks) FETO in cases of moderate hypoplasia (NCT00763737), and more recently, FETO at 27–30 weeks for severe cases (NCT01240057).

Soon we will be joining centres in London, Paris and Toronto which have a considerable fetoscopic turnover as well as a case load of CDH fetuses, and also have training for the FETO procedure. Though difficult, it is hoped that other North American centres will also join the list of several European centres endorsing this trial. We decided to adopt a pragmatic approach, with few centres doing FETO, yet with more tertiary care centres offering standardized postnatal care, either in expectantly managed cases or after balloon removal. The balloon is removed at 34 weeks. Postnatal management of this multicentre trial is standardized by a consensus protocol made up by leading European neonatal centres directed by Tibboel and Schaible [118, 119]. The same neonatal experts report in this issue on their outcomes using a nearly identical protocol [120]. Given different background survival rates (in expectantly managed cases) in some areas, there might be room for additional trials. We would, however, plead for agreement between investigators to have at least comparable study designs and outcome measures to allow future comparison.

Conclusion

Currently, the diagnosis of CDH should prompt referral of the patient to a tertiary care centre used to manage this condition. There a comprehensive evaluation, including imaging and (high-resolution) genetic studies, should be carried out. The primary purpose of this evaluation is to rule out associated anomalies and to assess the severity of pulmonary hypoplasia in order to offer parents an individualized prognosis. The latter can be done on the basis of the dimensions of the lung, its vascularization and liver position. Further multidisciplinary consultation should address the neonatal issues as well as later morbidities. Based on this complete evaluation and after extensive counselling, patients should make an informed choice out of the available management options which also include fetal therapy for more severe cases and in a number of centres spread over the world. In Europe, all elements are available to formally evaluate FETO for severe and moderate CDH. Over the last 5 years, we have built up sufficient experience to consider FETO as a safe and clinically acceptable procedure. What needs to be done now is to assess whether the procedure is truly beneficial, and therefore we have designed 2 randomized trials. Fetal medicine specialists have earlier shown (in twin-to-twin transfusion syndrome) that RCTs can work in fetal surgery [121]. These trials are the only way to control the history of FETO, which in the absence of level I evidence of superiority will start to live its own life with ever-ongoing debates between advocates and opponents. We, therefore, strongly urge that patients who are open to trial participation should be referred to FETO centres for additional evaluation and counselling about the logistics of fetal surgery and eventually trial participation.

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