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Prenatal diagnosis and management of congenital diaphragmatic hernia

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A B S T R A C T

Congenital diaphragmatic hernia is characterized by failed closure of the diaphragm, thereby allowing abdominal viscera to herniate into the thoracic cavity and subsequently interfering with normal lung development. At birth, pulmonary hypoplasia leads to respiratory insufficiency and persistent pulmonary hypertension (PHT), that is lethal in up to 32% of patients. In isolated cases, the outcome may be predicted prenatally by medical imaging and advanced genetic testing. In those fetuses with a predicted poor outcome, fetoscopic endoluminal tracheal occlusion may be offered. This procedure is currently being evaluated in a global randomized clinical trial (www.TOTALtrial.eu). We are currently investigating alternative strategies

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including transplacental sildenafil administration to reduce the occurrence of persistent PHT.

Introduction

Congenital diaphragmatic hernia (CDH) is a rare condition (prevalence: 1–4/10,000 pregnancies; ORPHA: 2140) [1]. The defect typically is posterolateral (Bochdalek; ~70%); rarer forms are anterior (Morgagni; ~27%) or central (~2%). Bochdalek hernia is usually left sided CDH (LCDH; 85%), whereas right-sided CDH (RCDH; 13%) or bilateral (2%) are rare [2]. From embryonic life, abdominal organs herniate into the thorax, interfering with lung development. This leads to pulmonary hypoplasia characterized by fewer and less mature airway branches and pulmonary vessels with small cross-

Table 1
Prenatal predictors of survival and/or morbidity in CDH.

Prenatal Predictors of survival/morbidity		
Center	Predictor	Imaging method
Lung		
Osaka (Japan), 1990 [15]	Lung to Thorax Transverse Area Ratio	Ultrasound
San Francisco (USA), 1996 [12]	Lung to Head Ratio (LHR)	
Mainz (Germany), 1999 [81]	Lung Diameter tothoracic Circumference ratio	
Paris (France), 2004 [18]	Lung Volume	
Leuven (Belgium); London (UK); San Francisco (USA); Paris, Lille, Strasbourg (France); Barcelona (Spain); Rotterdam, Nijmegen (The Netherlands); Tel Has homer (Israel), 2007 [14]	Observed to Expected LHR (O/E LHR)	
Miami (USA), 2013 [16]	Quantitative Lung Index	
Philadelphia (USA), 2000 [82]	Total Fetal Lung Volume (TFLV)	MRI
Brussels (Belgium); Lille, Paris, Nantes, Lyon, Bordeaux, Grenoble, Rouen (France), 2001 [21]	O/E TFLV	
Liver		
San Francisco (USA), 1998 [28]	Liver Herniation	Ultrasound
Houston (USA), 2015 [30]	Liver to Thorax Ratio (LiTR)	
Tochigi-Ken (Japan), 2001 [83]	Lung to Liver Signal Intensity Ratio	MRI
Leuven (Belgium); Lille (France), 2008 [31]	LiTR	
Houston (USA), 2012 [29]	Percentage Liver Herniation (-%LH)	
Stomach		
Seattle (USA), 1992 [32],	Stomach Position	Ultrasound
Osaka, Kyushu (Japan), 2011 [34]	Stomach Herniation	
Leuven (Belgium), 2015 [84]	Stomach Volume	MRI
Vascular		
Rotterdam (The Netherlands), 1997 [85]	Flow Velocity Waveform	Ultrasound
Auckland (New Zeeland), 1998 [86]	Pulmonary Artery (PA) Resistance Index (RI)	
Nagasaki (Japan), 1998 [87]	PA Pulsatility Index (PI)	
Osaka (Japan) 2003 [43]	PA Acceleration Time/Ejection Time Ratio	
Paris (France), 2004 [88]	PA Power Doppler (PD) Mapping	
Toronto, Canada, 2006 [45]	PA Diameter (⌀)	
Paris (France), 2006 [46]	3D PD Vascularization Flow Index (VFI)	
Barcelona (Spain); Leuven (Belgium), 2010 [89]	Fractional Moving Blood Volume	
Cincinnati (USA), 2010 [90]	⌀ PA/Aorta	MRI
	Mc Goon Index	

sectional area, structural remodeling and altered vasoreactivity [3]. At birth, this results in ventilatory insufficiency and pulmonary hypertension (PHT), which leads to neonatal death in approximately 30% of cases despite neonatal care in specialized high-volume tertiary centers with standardized protocols [4]. Survivors may suffer from chronic lung disease, persistent PHT, gastroesophageal reflux, feeding and growth problems, neurocognitive delay, hearing loss, thoracic deformations, and hernia recurrence [5]. In two thirds, the diagnosis is made by the second trimester during prenatal screening ultrasound (US) [6]. This should initiate referral to a tertiary center with experience in the perinatal management of CDH. The purpose is to rule out associated anomalies (up to 40%) and individualize prognosis [1] by genetic testing and advanced imaging. Only after having had that information, parents can choose between expectant management with prenatal referral for elective delivery, termination of pregnancy, or, in selected patients, fetal intervention. Before that, no severity statements should be made because of potential discrepancy between initial and eventual assessment [7].

Genetic testing

Genetic testing is mandatory for accurate counseling, future pregnancies, and eligibility for prenatal therapy. A genetic etiology is found in $\leq$35% by conventional karyotyping [8]; an additional 9% of them have clinically relevant copy number variants identifiable by array comparative genomic hybridization [9], and more recently, we identified a genetic cause by targeted resequencing in 10% of archived samples. In case of associated structural defects, the search for recognized syndromes is recommended [10]. A detailed list of genetic findings associated with CDH can be found elsewhere [11].

Prenatal imaging

Imaging is dedicated to characterize associated anomalies and making a personalized prognosis (Table 1). For details on how imaging can be best done in a standardized way, we refer to a paper from the European Reference Network "ERNICA" [11].

Predicting outcome by lung size

The measurement of pulmonary size is the most logical approach to assess hypoplasia and subsequently to predict neonatal outcome. The lung-to-head ratio (LHR) is the contralateral lung size measured at the level of the 4-chamber view and divided by the head circumference [12]. The lung area is most accurately and reproducible measured by tracing [13]. However, the lungs and head do not grow at the same pace. To correct for this, LHR is better expressed as a percentage of what is expected in a normal gestational age match (O/E-LHR; calculator available at www.totaltrial.eu) [14] (Fig. 1). Other 2D methods to assess lung size are less validated and hence will not be further discussed [15–17] (Table 1).

Lung volume estimated by 3-dimensional US also correlates with neonatal outcome, yet no better than O/E-LHR [18,19]. The contralateral lung size may also not be measurable, and there is operator and hardware variability [20]. Magnetic resonance imaging (MRI) is the reference technique for (lung) volume estimation [21]. Further, MRI is not limited by maternal habitus, fetal position, or amniotic fluid volume [22]. In analogy to the O/E-LHR, absolute bilateral volumes are converted to a percentage of what is expected in a normal fetus ([observed-to-expected total lung volume]; O/E-TLV). The matched control can be chosen according to gestation age yet matching on body volume increases accuracy, especially when out of the normal range or uncertain dates [21,23,24]. Whether O/E TFLV better predicts outcome than O/E LHR remains controversial [25–27].

Liver position

Liver herniation into the thorax compromises outcome [28]. On US, liver position is usually expressed as a binary variable "up" (intrathoracic) or "down" (intra-abdominal). Quantification of liver herniation may be more sensitive to predict outcome [29–31]. We are aware of three methods for the quantification of liver herniation. With MRI, we [31] proposed to measure the ratio of liver to the total chest volume (liver herniation-to-thoracic volume ratio = MRI-LiTR), whereas Lazar et al. [29]

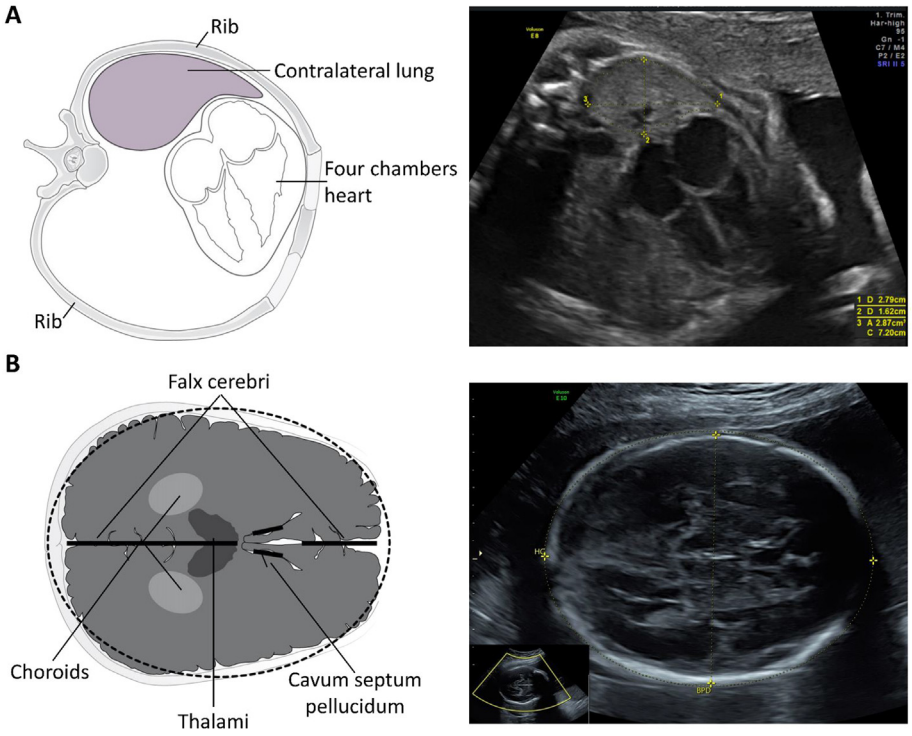

Fig. 1. Schematic drawings (left) and ultrasound images (right) of relevant sections for the calculation of the O/E LHR. A: The area of the contralateral lung is measured on the four-chamber view, with the lung close to the probe; B: Standard plane for the measurement of the head circumference. Drawings: Myrthe Boymans; reproduced with permission of the UZ Leuven.

calculated the percentage of liver that is into the fetal chest (MRI-%Liver herniation). Britto et al. [30] described the liver-to-thoracic area ratio (US-LiTR) by 2D US, measured on the standard 4-chamber view (Table 1).

Stomach position

Stomach position as visible on US was suggested as a prognostic indicator already in 1992 [32]. Although initially a binary variable [33], Kitano suggested to grade the degree of herniation (4 steps) on coronal sections of the thorax [34]. More recently, Cordier et al. introduced a 4-step grading system using rather the standard 4-chamber views, hence facilitating its reproducibility [35]. Stomach position correlates with neonatal mortality; whether it is truly an independent predictor remains unproven, as none of the studies conducted an upfront power analysis [34–38] (Table 2). It is easier to determine the stomach position rather than quantify liver herniation, as the stomach is anechoic and the liver echogenicity is close to or identical to that of the lung [20].

Pulmonary hypertension

PHT is a major contributor to postnatal mortality [39]. PHT is believed to have a morphological and functional basis, which leads to increased pulmonary vascular resistance because of less and smaller pulmonary artery branches along with altered vasoreactivity. Persistent PHT results in right ventricular dysfunction eventually leading to right cardiac failure [40]. Although many prenatal prognostic indicators may correlate to PHT early in neonatal life, we could not demonstrate an adequate correlation with persistent PHT [41], which is the clinically relevant endpoint, as it correlates with mortality and

Table 2
Studies reporting the value of stomach position and prediction of survival in isolated congenital diaphragmatic hernia cases managed expectantly.

Imaging	Study	(n)	Stomach grading system	Significance
Ultrasound	Metkus et al., 1996 [12]	55	Intra-thoracic Intra-abdominal	N.S. – study underpowered
	Dommergues et al., 1996 [33]	76	Intra-thoracic Intra-abdominal	P = .008 ◆
	Laudy et al., 2003 [91]	26	Intra-thoracic Intra-abdominal	N.S. – study underpowered
	Datin-Dorriere et al., 2008 [92]	66	Intra-thoracic Intra-abdominal	P = .043~
	Kitano et al., 2011 [34] +	109	Coronal plane, stomach in relation to the right/left thoracic plane. (0, 1, 2, 3)	P = .014~
	Cordier et al., 2015 [35]	114	4-chamber view, stomach in relation to the heart and AV valves. (1, 2, 3, 4)	P = .010~
	Basta et al., 2016 [38]	90	4-chamber view, stomach in relation to the heart (1, 2, 3, 4)	P=<.001 ◆
	Sananes et al., 2016 [36] ≈	77	Kitano Cordier	P = .002~ P = .018~
MRI	Schaible et al., 2012 [25]	76	Intra-thoracic Intra-abdominal	N.S
	Victoria et al., 2012 [37]	85	Intra-thoracic/Intra-abdominal 4-chamber view, stomach in relation to the heart (1, 2, 3, 4)	P = .002 ◇ N.S~ N.S

Abbreviations: AV, atrio-ventricular.
◇Univariate analysis; ~Multivariate analysis; ◆Bivariate analysis; ≈Survival until 6 months; +Intact discharge: defined as discharge without major morbidities (need for respiratory support, tube feeding, parenteral nutrition or vasodilators).

long-term morbidity [42]. The logical approach to assess lung vascularization is by direct measurement, which has been attempted by a variety of techniques. To the best of our knowledge, these measurements are not easy to reproduce, and their added predictive value remains uncertain as shown in a recent meta-analysis [41,43–49] (Table 1).

Practical severity stratification

The consortium currently conducting a clinical trial on fetal therapy for LCDH stratifies fetuses on the basis of O/E-LHR combined with liver position as documented on US [11]. On the basis of the expected outcome, earlier, we proposed to discriminate extreme, severe, moderate, and mild forms of pulmonary hypoplasia [14]. In LCDH, an O/E-LHR under 25% is defined as severe and an O/E-LHR 25–34.9% (irrespective of the liver position) or 35–44.9% with liver up as moderate. Conversely, when the latter occurs without liver herniation, or when O/E-LHR >45%, CHD is considered mild. In retrospect, referring to a condition with 40–50% mortality and 50–60% morbidity as “moderate” is semantically misleading [14]. We also acknowledge that the current prediction algorithm can be improved by using other (combinations of) parameters, yet before implementing that widely, appropriately powered studies with standardized neonatal management need to be conducted.

Right-sided congenital diaphragmatic hernia

Whether RCDH is a more severe condition and a separate entity with different outcomes and treatment response than LCDH remains a matter of controversy [50–53]. From a prenatal perspective, we documented an overall survival of 53%, which is lower than that for LCDH [54]. In that study, the O/E-LHR correlated with survival: when under 45%, survival was 17% in expectantly managed cases [54], a finding in line with that reported in our earlier multicenter study [14]. Because a >80% mortality in LCDH correlates with an O/E-LHR <25%, and in RCDH with <45%, it is tempting to assume RCDH is a more severe

condition. However, the anatomy of the right and left lungs is different, and on 2D ultrasound, one may not be truly measuring the same in case of LCDH or RCDH. As RCDH is rare, it will be very difficult to demonstrate with sufficient power correlations between O/E-LHR or other types of lung size measurements with mortality, let be morbidity. Additionally, liver herniation is not discriminative in RCDH, as it is nearly always present. Eventually, one may need different algorithms for this condition [50].

Fetal therapy for CDH

The ability to prenatally identify a future nonsurvivor prompts the question for an intervention that can reverse this natural course. The current clinical strategy to promote lung growth in severe cases is by percutaneous fetoscopic endoluminal tracheal occlusion (FETO) [55]. Clinical observations that fetuses with laryngeal atresia have larger lungs inspired animal experiments, which demonstrated that TO reverses experimental pulmonary hypoplasia [56,57]. Airway obstruction prevents egress of lung fluid, thereby increasing airway pressure, activating stretch receptors, and inducing proliferation. Under experimental conditions, sustained TO markedly reduced type II-pneumocyte counts and subsequently surfactant expression. This was prevented by in utero release of the occlusion ("plug-unplug sequence") and, to some extent, prenatal steroid administration [58,59]. The plug–unplug strategy was clinically translated into a percutaneous procedure with a low risk for serious maternal morbidity [60].

Fetoscopic balloon insertion

FETO is performed under sono-endoscopic guidance and local anesthesia (Fig. 2). We earlier described the technique in detail [61]. Immobilization and pain relief are obtained by fetal drug

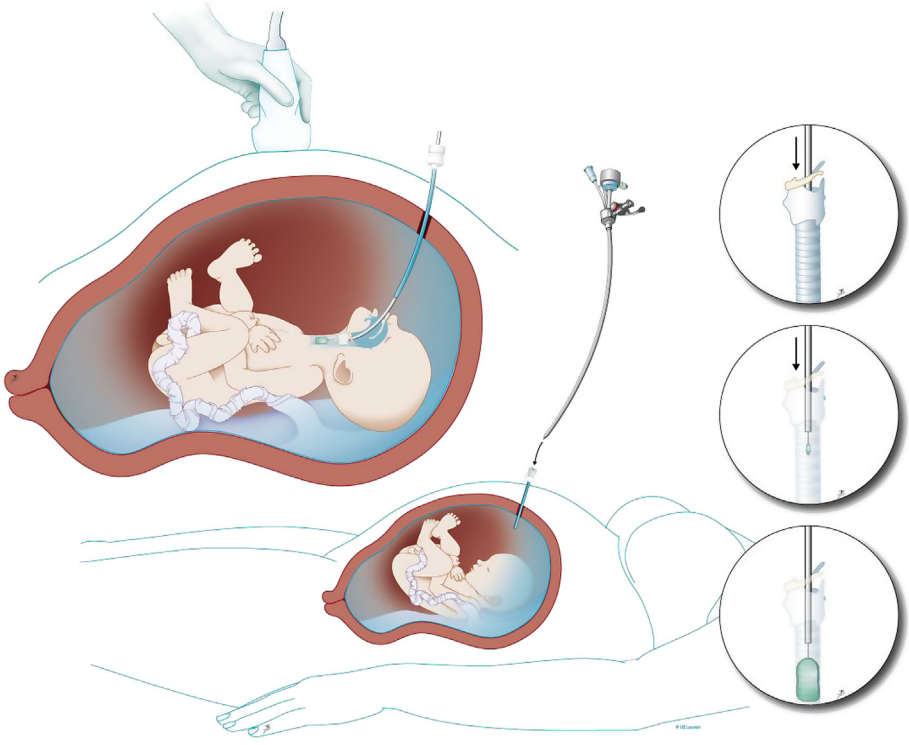

Fig. 2. Schematic drawing of percutaneous fetoscopic endoluminal tracheal occlusion. Inset: a detachable balloon, normally used for endovascular occlusion, is positioned in the trachea. Reproduced with permission from UZ Leuven, Leuven, Belgium. Drawing Myrthe Boymans.

administration. A thin-walled flexible cannula is inserted avoiding the placenta and aiming to or above the fetal nose tip. A 1.3 mm fetoscope housed within a slightly curved 3.3 mm sheath (Karl Storz, Tuttlingen, Germany) is advanced into the trachea until the carina is visualized. A detachable balloon (Goldbal2, Balt, Montmorency, France) is positioned between the vocal cords and carina with a purpose-designed delivery catheter (Baltacci-BDPE-100; Balt). The balloon can be visualized on US as an anechoic structure. The median duration of FETO is 10 min; longer operation times are associated with higher premature rupture of membrane (PROM) rates [62].

Reestablishment of airway patency

Clinical data suggest that prenatal balloon removal increases survival and reduces morbidity [63,64]. Leaving the balloon in place until delivery also creates the challenge of emergency removal at birth [65]. Prenatal removal also allows the patient to return to the institution where she would normally deliver. On the basis of animal experiments, we schedule reversal at 34 weeks, which can be done by fetoscopy, ultrasound-guided puncture, tracheoscopic removal on placental circulation, or postnatal puncture. With regard to 302 balloon removals, two thirds were by fetoscopy, 21% by puncture, 10% on placental circulation, and 1% ex utero. The modality chosen is probably a matter of surgeon preference. After puncture, the balloon is typically expelled, probably because of the spontaneous outflow of fluid from the lungs during fetal breathing. In our experience, balloon removal was done nonelective in 28%. The only neonatal deaths due to balloon removal difficulties occurred when delivery took place in an unprepared setting or inexperienced center [65].

Outcomes of FETO

We already reported outcomes of more than 200 interventions. In comparison to historical controls of similar severity, FETO increased survival from 24% to 49% in severe LCDH (O/E-LHR <25%) and seemed to improve early respiratory morbidity [64,66]. In RCDH with an O/E-LHR <45%, FETO increased survival from 17% to 42% [54]. In survivors, fetal tracheomegaly has been documented but does not seem to have a clinical impact apart from a barking cough, which decreases with time [67,68]. Adverse tracheal side effects from FETO are rare and typically occur in case of a very early occlusion and at the time of emergency balloon removal (Table 3). Our initial experience and that of others suggest benefit, as shown in a meta-analysis. Because most think that there is still equipoise, we designed a randomized clinical trial (RCT) “Tracheal-Occlusion-To-Accelerate-Lung-growth” (www.TOTALtrial.eu) in fetuses with LCDH and severe yet also moderate lung hypoplasia (NCT01240057/NCT00763737) [69]. In severe cases, balloon insertion is at 27–30 weeks. That is slightly later than initially because we aimed to decrease delivery <32 weeks, which adversely impacts survival [66]. In moderate cases not earlier considered eligible for fetal therapy [55], we occlude at 30–32 weeks, which still induces some lung growth [70]. In that study, we choose oxygen dependency as an additional outcome parameter. Postnatal management is standardized along the EuroCDH-consortium guidelines [71]. Recruitment in the moderate TOTAL-trial exceeds already more than 85% of the sample size. The trial arm for severe CDH started later, yet the first interim analysis was done in October 2017. We acknowledge that both trials started far too late because of several reasons [72,73] and that the path toward the TOTAL-trial has been particularly difficult as demonstrated in the timeline (Fig. 3).

Future experimental solutions

Whatever the outcome of the TOTAL-trial, FETO is an invasive procedure with increased risk for preterm delivery and preterm rupture of membranes [66]. In addition, because of its technical complexity, FETO cannot be universally implemented. Finally, maximum post-FETO survival in severe cases is ~50% and does not seem to solve persistent PHT [64]. For these reasons, alternative, less invasive, preferentially medical therapies are part of the current agenda of many research groups. For the sake of space, we highlight only one that is closest to clinical application. Sildenafil is a selective inhibitor of phosphodiesterase-5 (PDE5), which degrades cyclic guanosine monophosphate (cGMP). PDE5 acts as a key regulator of the perinatal pulmonary circulation [74]. Sildenafil is already used

Table 3
Experience with FETO and reported complications.

Summary of FETO series complications								
Study	N	GA at FETO wk (range)		Maternal Fetal Complications	Mean GA at delivery	Preterm birth <32 wk	PPROM <34 wk	Emergency balloon removal
Deprest et al., 2004 [60]	21	26 (25–33)	M F	No 1(4.7) Right bronchus laceration, reinsertion one week later	34	5(23.8)	9(42.8)	11(52.3)
Kohl et al., 2006 [93]	8	30.6 (29–32.4)	M F	No No	33.9	0(0)	NA	2(25)
Jani et al., 2009 [66]	210	27.1 (23–33.3)	M F	No 4(1.9) Tracheal lacerations, 4(1.9) IUFD (1 bradycardia/ 3 unknown), 2(0.9) TOP, 10(4.7) deaths due to balloon removal difficulties elsewhere	35.3	36(17.4)	NA	109(51.9)
Peralta et al., 2011 [63]	8	26.8 (26–29)	M F	No No	37	0(0)	5(62.5)	No
Ruano et al., 2011 [94]	17	NA	M F	1(5.8) Hemoperitoneum managed expectantly 1 (5.8) Placental abruption; 1(5.8) balloon was in the right bronchus could not be retrieved and the fetus died	35.6	3(17.6)	6(35.2)	4(25)
Ruano et al., 2012 [95]	20	NA	M F	1(5) Chorioamnionitis No	35.6	3(15)	NA	5(25)
Cannie et al., 2013 [96]	31	28.6 (25.3–30.7)	M F	1(3.2) Hemoperitoneum No	34.7	NA	NA	NA
Ruano et al., 2013 [97]	8	23.7 (NA)	M F	No 2(25) tracheomegaly 1 trachea not accessible, and the fetus died	33.5	2(25)	3(37.5)	NA
Persico et al., 2017 [98]	21	28.1 (26–31.1)	M F	No NA	34.7	2(9.5)	10(47.6)	10(47.6)
Belfort et al., 2017 [99]	11	27.9 (25.7–29)	M F	No 1(9.1) Chorioamniotic separation	35.3	1(9.1)	2(18.8)	2(18.8)

Abbreviations: N, number of cases; GA, gestational age; wk, weeks; PPROM, preterm pre-labour rupture of membranes; M, maternal; F, fetal.

clinically and well tolerated by babies with CDH affected by PHT [75]. In addition to having a vasodilatory effect, sildenafil promotes pulmonary angiogenesis and inhibits pulmonary artery remodeling [76]. This was first demonstrated by Thebaud [77]. We later confirmed in a rabbit model that transplacental sildenafil leads to normal vascular wall thickness, peripheral muscularization, normal number of fifth or higher order generation of vessels, and normal Doppler flow. Sildenafil also improved airway morphology and postnatal lung mechanics. We applied and received orphan designation for this drug for the prevention of PHT in CDH from the European Medical Agency. Sildenafil has already been clinically administered in randomized controlled trials in women with preeclampsia and oligohydramnios [78,79]. Both trials could not identify any safety issues. In the STRIDER trial, sildenafil was given for fetal growth restriction. This trial is currently suspended because of potential harm by an increased incidence of persistent PHT and a nonsignificant trend for increased neonatal death in one out of three centers [80]. These findings still need to be confirmed because they are in contrast with those of the other two STRIDER studies (including more than 120 patients treated with sildenafil) and of other studies on antenatal sildenafil administration. Even if this would be confirmed for growth restriction, such association with PHT may not persist when the drug is given to fetuses with pulmonary hypoplasia, as in CDH. Sildenafil has been shown in animal models to have a different effect on lung development in normal and hypoplastic lungs; in normally developed lungs, it was associated with impaired vascular branching. This suggests that the effects of sildenafil on fetal lungs are dependent on the fetal condition. Additionally, in CDH, the drug would be given to prevent a condition

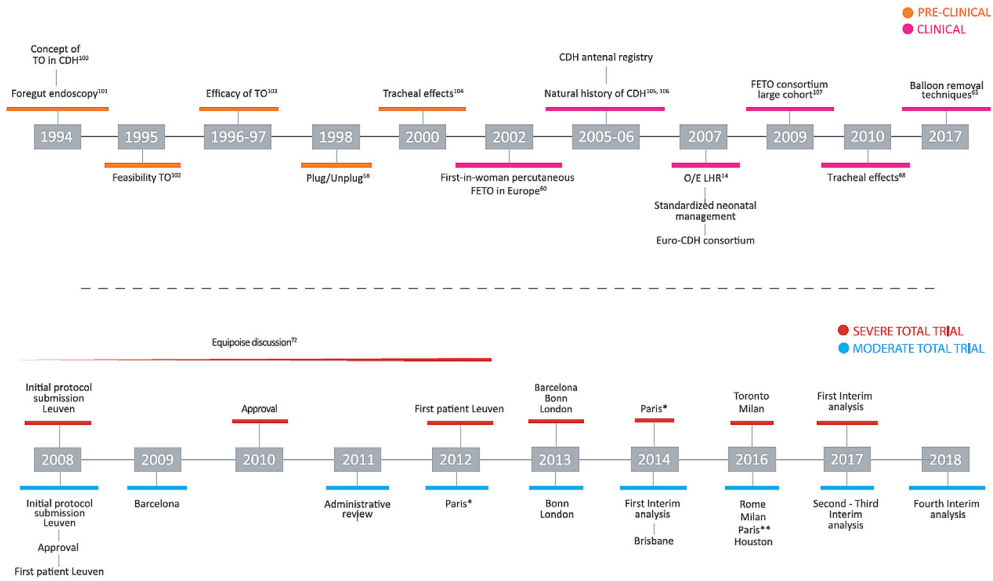

Fig. 3. Timeline of events of the making of FETO (top) and the road of the TOTAL trial (bottom); the names of the cities refer to the first patient recruited in each center. CDH, congenital diaphragmatic hernia; *, Béclère; **, Necker. [Numbers] indicate references. Copyright UZ Leuven, Leuven, Belgium. [14,58,60,65,68,72,100–107].

for which the drug is already used postnatally. This is why we believe that the recent findings of the STRIDER trial should not be withholding us to further clinically investigate maternal sildenafil administration for CDH. Conversely, confirmation of fetal safety becomes even more relevant and that is why we think the phase I/IIB study investigating placental transfer, maternal, and fetal safety of short-lasting sildenafil administration should be continued (EUDRACT number 2016-002619-17).

Summary

Mothers who carry a fetus with CDH should receive personalized counseling on the expected outcome. We recommend standardized prenatal imaging and genetic testing with microarrays. Lung size and liver herniation are good predictors of survival in LCDH; morbidity is more difficult to predict. Neonates should be managed by standardized protocols in high-volume centers. Prenatal therapy for LCDH should, according to us, only be offered within the context of the TOTAL trial; for severe RCDH, we offer the procedure clinically. Currently, medical prenatal interventions are also being investigated, which may be added to FETO or be offered as a stand-alone intervention, both improving outcome in comparison to expectant management in selected patients.

Practice points

- Prenatal diagnosis and individualized counseling should be at a tertiary center familiar with managing this condition and include advanced genetic testing and imaging.
- Standardized prenatal assessment and postnatal management are recommended.
- In isolated cases, prognosis is based on the side of the lesion and lung size.
- Whether liver herniation and/or position of the stomach is an independent predictor remains uncertain.
- FETO for LCDH is an investigational procedure offered within the TOTAL trial; we offer the procedure clinically for RCDH.

Research directions

- Design sufficiently powered studies to develop more accurate prediction algorithms
- Investigating alternative therapies to reduce the burden or improve the outcomes of FETO.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2018.12.010.

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