Commentary

Antenatal Management of Congenital Diaphragmatic Hernia: what's next ?

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What is already known about this topic ?

- Congenital Diaphragmatic Hernia can be diagnosed and its severity assessed in the prenatal period.
- In fetuses with severe or moderate pulmonary hypoplasia, fetal surgery can be offered.
- In selected cases, Fetoscopic Endoluminal Tracheal Occlusion improves survival but increases the risk for prematurity.

What does this study add?

- Further research into accurate prenatal prediction of outcome is needed and the best biomarkers should be identified.
- We propose prospective registration of cases treated with FETO, to increase our understanding of the effect of the duration of occlusion and the potential impact of preterm delivery.
- Outcomes of fetal surgery should improve further, both by technical innovation in the current technique as well as the introduction of additional and more effective e therapies.

Abstract

Congenital diaphragmatic hernia (CDH) can be diagnosed in the prenatal period and its severity can be measured by fetal imaging. There is now level I evidence that, in selected cases, Fetoscopic Endoluminal Tracheal Occlusion (FETO) increases survival to discharge from the neonatal unit as well as the risk for prematurity. Both effects are dependent on the time point of tracheal occlusion. FETO may also lead to iatrogenic death when done in unexperienced centres. The implementation of the findings from our clinical studies, may also vary based on local conditions. These may be different in terms of available skill set, access to fetal therapy, as well as outcome based on local neonatal management. We encourage prior benchmarking of local outcomes with optimal postnatal management, based on large enough numbers and using identical criteria as in the recent trials. We propose to work further on prenatal prediction methods, and the improvement of fetal intervention. In this manuscript, we describe a research agenda from a fetal medicine perspective. This research should be in parallel with innovation in neonatal and pediatric (surgical) management of this condition.

Introduction

Congenital diaphragmatic hernia (CDH) is a good target condition for fetal therapy, as it originates prenatally and results in severe postnatal mortality and morbidity which have not improved significantly over the last decade despite advances in neonatal care. Neonatal survival rates have stalled at around 70% [1]. Many research teams have explored strategies to stimulate growth and maturation of airways and pulmonary vessels, initially by prenatal anatomical repair of the diaphragmatic defect through hysterotomy, and later by fetal tracheal occlusion[2]. In the early 21st century, the concept of tracheal occlusion moved from the *animal* experimental laboratory towards early *clinical* application, and from *external* tracheal clipping by hysterotomy[3] to *endoluminal* occlusion (FETO) with a detachable balloon[4]. The latter allowed this procedure to be done percutaneously under local anesthesia, and facilitated its *in utero* reversal[5]. Table 1 summarizes some of that Odyssey, illustrating the steps our group has taken to eventually tick all the boxes of the *fetal surgery check-list* defined by the International Fetal Medicine and Surgery Society[6].

However, many questions persist around the management of CDH today, and practice may need to vary depending on pre- and postnatal facilities as well as on the scientific evidence becoming available over time. Here, we highlight some of these issues and describe how we plan to address some of these using current technology. We also highlight emerging technologies and new therapeutic approaches that may help improve both prediction of outcome and outcome itself. We are aware that, as fetal medicine specialists and being deeply involved in the development of fetoscopy, we may be biased in our views. We also acknowledge the major contributions of other research teams and innovations in pediatric surgery and neonatal and pediatric care.

Table 1: Scorecard for fetal therapy for Congenital Diaphragmatic Hernia. Criteria for fetal surgery as defined by the International Fetal Medicine and Surgery Society (first column), contributions by FETO-consortium towards the clinical introduction of FETO (second column) and future research into the antenatal management of isolated CDH. (displayed at bottom of document)

What are outcomes with FETO today ?

Two decades of research involving FETO culminated in the publication of the results of two parallel randomized controlled trials in isolated left-sided CDH with severe and moderate pulmonary hypoplasia, respectively (Table 2)[7,8]. In severe hypoplasia the balloon was inserted *early* (27^{+0} to 29^{+6} weeks' gestation) and FETO improved survival from 15% to 40%[8]. A very similar improvement in survival (20% to 42%) was achieved in a non-randomized study of severe *right*-sided CDH treated with FETO at a comparable gestational age, by comparison to a parallel cohort of fetuses managed postnatally[9]. In *moderate* hypoplasia the balloon was inserted *late* (30^{+0} to 31^{+6} weeks' gestation) in an effort to reduce the risks of very preterm birth. In that study FETO improved survival from 50% to 63%, but this difference was not statistically significant[7]. Analysis of the pooled data from the severe and moderate hypoplasia trials suggest that FETO increases survival in both severe and moderate disease (Table 2; Figure 1a en 1b), but the observed lesser effect in the moderate group was a mere consequence of the delayed insertion of the balloon[10].

An adverse consequence of FETO in both trials, which was also observed in other clinical studies was the increased risk for iatrogenic preterm membrane rupture and preterm birth[11,12]. In the TOTAL trials this risk was inversely related to the gestational age at insertion of the balloon (Figure 1c) [10]. Although the trials did not demonstrate any significant differences between the FETO and control groups in prematurity related complications, they were not powered for these secondary outcomes. Furthermore, we have not yet reported long term outcome as we are in the process of collecting such data.

Table 2: Outcomes of fetuses diagnosed with isolated CDH in the prenatal period, either left or right sided, expectantly managed during pregnancy or having tracheal occlusion with the TOTAL trial and a large study on right sided CDH under the same management protocol.

Practical implementation FETO

Completion of the TOTAL trials was considered to be a major achievement, but immediately concerns were raised as to the possible widespread implementation of FETO.[13,14] This is part of the debate elsewhere in this issue of Prenatal Diagnosis[14]. An important concern with widespread implementation is the risk of perinatal death because of problems with timely removal of the tracheal balloon[15]. Consequently, FETO should only be undertaken in specialist centers, which, according to our criteria, should have extensive experience in fetoscopy, have a sufficient volume of CDH cases, be familiar with assessment of severity of pulmonary hypoplasia[16-18], and be trained with balloon insertion and removal, with the latter service being available 24 hours a day[15]. To our knowledge there is no other fetal procedure posing such extensive demands on the treatment team.

The natural history of CDH is questioned

A criticism of the TOTAL trials is that the mortality in the expected management group was higher than what was reported "in other environments such as North America, where major advances in post-natal care involving respiratory care strategies based on permissive hypercapnia/spontaneous ventilation and extracorporeal life support have generated significantly improved outcomes in prenatally stratified, severe CDH patients" [13]. The authors of this statement refer to studies from 1995 and 1997, a time when a validated model for prenatal severity stratification was not available. Furthermore, the authors refer in their letter to the benefits of postnatal management approaches, such as specific ventilation strategies, extra-corporeal membrane oxygenation and others, for which to our knowledge there is no robust and unbiased controlled data to support such statements. We are sure these strategies have had and will continue to have their place in the further search to improve survival, but it is difficult to use these in an argument against a study where a standardized postnatal management was applied for both arms of the randomized controlled trial. However, we hear the

argument that some postnatal management studies do indeed report higher survival rates than those observed in our trial, hence these patients may not benefit as much from FETO. It must be remembered that the numbers reported in the TOTAL trial included cases with additional anomalies diagnosed postnatally, terminations and in utero fetal deaths. It is therefore indeed possible (and perhaps to be recommended) that when counselling patients, centers that expect high survival rates with postnatal management, "validate" the prediction algorithm and adjust to that accordingly. It is important to remember that prediction algorithms are only meaningful on large numbers and consecutive cases, all selected the same way as in the prediction studies (i.e. prenatal diagnosis, standardized severity assessment in the second or early third trimester, live born after 30 weeks and all managed with a standardized postnatal protocol) and reporting all core outcomes[19]. For example, fetal surgeons from Queretaro[20,21], Mexico concluded that in their setting with suboptimal neonatal management, the postnatal outcome of CDH is less favourable than that observed elsewhere. The same was earlier reported in a study from Brazil[22]. Whether these very low postnatal survival rates could indeed be improved by an antenatal intervention is another discussion; some reflection on the postnatal management may be useful[23]. Regardless, the TOTAL trial survival rates in expectantly managed cases were consistent with our previous observational data and with the results from one randomized clinical trial among neonatal management centers throughout Europe [24-26]. For instance, in fetuses with expectantly managed severe hypoplasia, survival rate was 15% which compares to the 18% anticipated [27]. Given the latter, we feel confident to continue the FETO program with the current selection criteria. We will, sustain the surveillance system with prospective documentation of outcomes, and we will strive to establish long term follow up.

FETO in moderate hypoplasia ?

The conclusion from the analysis of the combined data from the two TOTAL trials is that treatment of the moderate hypoplasia group is most likely to be beneficial, provided the duration of tracheal

occlusion would be extended. The latter can be achieved by either earlier insertion or delayed removal of the balloon[10]. Delay in removal of the balloon *from 34 to 37 weeks* is not currently an option because of the increased risks associated with emergency removal in women with ruptured membranes and/or in labour. Moreover, there is some evidence that survival rates are higher in patients where the balloon is removed more than 24 hours prior to delivery [7,28,29,15]. There is also some evidence that the beneficial effects of FETO are less late in pregnancy, because of limited lung growth[30,31]. Therefore, the alternative option is to carry out FETO in both severe and moderate hypoplasia at *27^{+0} to 29^{+6} weeks.* Although early insertion in moderate hypoplasia would best be evaluated in a randomized controlled trial, in our opinion and based on our experience, this is unrealistic [10 32-38]. As a second best option to evaluate such strategy, we have chosen to prospectively register all consecutive cases undergoing FETO, including all known confounding factors[37]. We will include registration of additional factors that are potentially related to outcome, such as the location, experience and case load of the postnatal management center[39,40]. Because new centers may not apply similar scrutiny as TOTAL-trial fetal surgeons, all local modifications in the protocol should be documented. Nonetheless, we recommend that this type of fetal intervention be not offered outside of the context of this program.

Improvements in fetal surgery

Reduction in FETO-related adverse outcomes could be achieved with technical improvements in endoscopy and occlusion devices. We aim to achieve further miniaturization of the endoscopes, but working on instrumentation has become increasingly difficult due to the (unintended) consequences of the new Medical Device Regulation in Europe. We have successfully completed preclinical studies with the "Smart-TO"-balloon (BS Medical Tech Industry , Niederroedern, France; Figure 2)[41]. This balloon has a magnetic valve that opens by exposure to a strong magnetic field, i.e. the fringe field around an MRI scanner. After deflation, the balloon is either swallowed by the fetus or exits the mouth into the amniotic fluid. Tests in large animal models confirmed that this device has similar occlusive

and tracheal side effects as the currently used "Goldbal" balloon (Balt, Montmorency, France) and that it spontaneously releases after MRI exposure [41-43]. In Leuven and Paris, we have moved to the "first-in-human" trial, aiming to demonstrate the feasibility to deflate the balloon by exposing the fetus to the magnetic field generated by a clinical MRI scanner. This is a step towards obtaining C.E. approval for this medical device. If effective, using this balloon will eliminate the second invasive intervention, lower the burden on patients as well as the team, making FETO safer and thus more acceptable.

Medical strategies to treat pulmonary hypoplasia

Given the suboptimal outcomes and risks of the current surgical technique, alternative strategies to promote airway growth and reverse pulmonary artery changes are needed. We are exploring medical interventions, that would preferentially be administered transplacentally. We moved one of these already from the bench to the bedside. *Sildenafil* is a selective inhibitor of phosphodiesterase type 5 and has vasodilatory and anti-remodelling effects on the pulmonary circulation. It is used for the treatment of neonatal pulmonary hypertension (PHT) including in CDH[44]. Based on its effectiveness in three animal models of CDH [45] we conducted a phase I-IIb trial in pregnant women[46]. Unfortunately, these trials were halted by the authorities because findings in the "Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction" (STRIDER) clinical trial suggested a risk of increased incidence of PHT in neonates who were exposed to sildenafil *in-utero*. This observation was limited to a single regional arm of the larger trial. We have argued that this observation in fetuses with normal lungs should not be extrapolated to CDH fetuses who have pulmonary hypoplasia and abnormal pulmonary vascular development. Several animal studies demonstrated that the vascular effects depend on the degree of lung development, hence can be beneficial or adverse[47 48]. Both fetal rats and rabbits with *pulmonary hypoplasia* show improved lung vasculature when exposed to sildenafil, whereas fetuses with *normal* lungs show abnormal vascular

branching. We have requested permission to carry out further research on the use of sildenafil in pregnant women, but at present this has not been approved[49,50].

An alternative drug for transplacental administration to treat abnormal vascular development is *treprostinil*, which is a synthetic prostacyclin analog. It is clinically approved for the treatment of PHT in adults and children but has only been tested in small patient cohorts[51,52]. It has an anti-remodeling effect on the pulmonary vasculature in addition to causing pulmonary vasodilation. Treprostinil is not teratogenic and we are now trialing it for in utero use for CDH in collaboration with researchers from the Children's Hospital of Philadelphia[53].

Another exciting potentially more comprehensive approach may be the fetal pulmonary administration of amniotic fluid stem cell-derived extracellular vesicles (AFSC-EVs). EVs are biological nanoparticles carrying genetic material and bioactive proteins as cargo. In fact, EVs are mediators of AFSC paracrine signaling and promote lung development and maturation, as shown in multiple models of pulmonary hypoplasia (primary epithelial cells, organoids, explants, and two animal models)[54]. Zani summarizes that journey in this issue of Prenatal Diagnosis[55].

Finally, excitement has been growing on the potential of using non-coding RNAs to improve diagnosis, prognosis and prenatal therapy for CDH. MicroRNAs are small, non-coding RNAs that can regulate the expression of genes. MicroRNA miR-200b has been demonstrated to be more abundantly present in the tracheal fluid of CDH survivors after FETO[56]. Knockout mouse studies showed that miR-200b is required for distal airway development and pulmonary epithelial integrity [57]. And most clinically relevant, prenatal miR-200b therapy reduces the incidence of CDH and improves lung development resulting in better survival in the nitrofen-induced rat model of CDH[58]. MicroRNAs are regulated by circular RNAs (circRNAs) through sequestration. CircRNAs are formed by "back-to-back" splicing and their circular structure protects them from degradation in biological compartments. Because of their biostability they are considered the "perfect disease biomarker". CDH lungs have a unique circRNA profile distinguishing them from control lungs[59]. We have recently discovered that CDH fetuses undergoing FETO with identical prognostic imaging parameters, can be discriminated from future

survivors and non-survivors based on their amniotic fluid circRNA profile before FETO (unpublished data). This suggests that circRNAs can serve as an important prognostic biomarker for pulmonary hypoplasia in CDH and we are currently validating these findings in independent patient cohorts. In contrast to microRNAs, the potential role of circRNAs in the pathogenesis and in prenatal therapy has not been demonstrated and is currently under investigation.

Patient engagement and postnatal trials.

Further to therapeutic innovation, the advent of fetal surgery as an option for parents prompts the question about the needs of these families. We need to investigate whether the current antenatal care pathway is holistic, patient-centered, supports families in all prenatal and postnatal options, and generally meets patient needs [60]. To facilitate this, , we have developed a core set of outcomes to be used in future trials on perinatal interventions for CDH[19] in collaboration with parents and other stakeholders. These will be measured in a standardized manner and reported consistently, thereby improving the quality of research that can be used to guide clinical practice and improve patient care.

All research efforts to improve prenatal management should be paralleled by similar efforts in postnatal management research. Obstetricians may get involved in trials which already start at birth. We are aware of two clinical trials investigating whether delayed cord clamping facilitates neonatal cardiovascular adaptation[61]. This should prevent early hypoxemia, increase circulatory blood volume and avoid loss of venous return and decrease in left ventricle filling, which is caused by immediate cord clamping (CHIC trial, NCT04429750 & Physiological-based Cord Clamping in Congenital Diaphragmatic Hernia, PinC, NCT04373902) [62].

Diagnosis and prediction of outcome in CDH

In order to have treatment options in the prenatal period, the diagnosis of CDH should be made prenatally. Today, screening ultrasound programs fail to diagnose CDH in nearly one out of three cases (32%). This needs to be improved[63]. Once the diagnosis is made, ideally *personalized* prediction is made based on an expert assessment. In Europe, the reference network for rare diseases "ERNICA" has agreed on a standardized method[64]. Prediction of outcome is made by determination of lung size, position of the liver and can also include the position of the stomach as a proxy for liver position. The most used, best validated and widely implemented method for measurement of lung size is based on *two-dimensional ultrasound* measurement of the lung area contralateral to the defect, divided by the head circumference (observed Lung-Head Ratio; LHR), and corrected for gestational age by expressing the observed LHR as a percentage of the LHR *expected* in a normal fetus (*observed*/*expected* lung-to-head ratio or "O/E LHR") [27]. The combination of O/E LHR and liver position is used to categorize fetuses with left sided CDH as having either severe, moderate or mild hypoplasia; this corresponds with survival chances of 18%, ≥60% and ≥85% respectively.[27]. In right-sided CDH, a rarer subtype of CDH with a worse prognosis, liver position is irrelevant. According to a recent large study, an O/E LHR of 50% corresponds with a 20% survival rate[9]. There are several criticisms of the currently used prediction model. One is that it is based on limited and historical data and may therefore benefit from more, contemporary and unbiased data. Even the normative curve can be improved, as it was originally based on cross sectional data, and from a statistical viewpoint it may benefit from more and preferentially longitudinal observations.

A potentially better way of assessing lung size is to use *three-dimensional* ultrasound to determine the volume of both lungs. However, although possible, this approach is difficult to perform and not consistently reliable[65, 66]. Use of magnetic resonance imaging (MRI) can provide reliable measurements of lung volumes and can also report the volume of liver in the chest as a continuous variable, rather than "up" or "down" as with ultrasound, and document stomach position as well[67,68]. A previous study reported that the predictive performance of the ultrasound derived o/eLHR was not significantly different to that of the MRI derived o/e total lung volume, in terms of postnatal survival. This was done

in 76 fetuses with isolated CDH that were all liveborn at 30 weeks' gestation[69]. It is possible that a larger study may demonstrate the superiority on the one technique over the other. Also, 3D-volumetry is time consuming and prone to errors, a problem which can be resolved by using artificial intelligence (AI). AI approaches have solved many previously intractable medical image segmentation problems, but *fetal* MRI still relies on manual segmentations from motion-corrupted stacks of 2D slices. We have used this approach already for the brain and are now implementing it on lung measurements[70,71].

The second most important cause of death in babies with CDH, after pulmonary hypoplasia, is pulmonary hypertension[72] and presently there is no effective method to predict this adverse outcome[29,73]. Other goals for research in CDH fetuses are the study of the fetal heart and brain. Neurodevelopmental delay, hearing, learning and behavioral problems have been reported in up to 16% of children with *isolated CDH*[74] and *postnatal* MRI studies demonstrated abnormalities such as delayed sulcation and white matter injury[75-77]. This may be due to postnatal events but could also originate in utero, as has been observed in fetuses with cardiopathies[78,79], and recently suggested for cerebellar development in CDH fetuses[80].

Rarer and associated forms of CDH

In many studies, reported outcomes still mix those of fetuses with isolated CDH and CDH associated with chromosomal anomalies or other structural malformations. This should be avoided as the prognosis of non-isolated cases is obviously different and difficult to predict. We also suggest that outcomes of fetuses with isolated *left* and *right* diaphragmatic hernia should always be reported separately, and this should also be done for other rarer anatomical forms of CDH as the pathophysiology of all these specific anatomical variations is most likely to be different. For prenatal prediction of prognosis one can therefore not use the same algorithm.

Fetuses that are thought to have isolated CDH, including those who are offered FETO, may later be found to have an associated structural malformation, rare genetic diseases or chromosomal

anomalies. These conditions may be identified prenatally but occasionally the diagnosis may not become apparent until several months after birth. We have observed this both in our earlier experience as well as in the TOTAL trials[7,8,25]. Parents should be informed that this may happen and that it may have severe consequences for their child. As to associated genetic conditions, recent improvements in the accuracy of genetic tests such as exome sequencing should limit the risk of un diagnosed genetic association. When and where that testing will be implemented is another issue, which is out of the scope of this comment. The value of FETO in cases of associated genetic problems is uncertain. The decision to proceed with FETO will depend on the nature of the individual case, the wishes of the parents, even in cases of severe genetic conditions, and the local context.

Conclusion

There is now level I evidence that in utero treatment can improve outcome in selected fetuses with CDH. Inevitably, more fetal centers are likely to now offer this therapy. However, the number of eligible fetuses for such therapy is low and it would be wise to limit the procedure to units with extensive experience in fetal assessment and fetoscopy, as well as high level of neonatal and pediatric surgical care and for further multidisciplinary management of these overall rare cases. Further studies are necessary to first, define the impact of preterm birth on FETO survivors, second, examine the impact of early rather than late tracheal occlusion in fetuses with moderate hypoplasia, third, develop improved models for prenatal prediction of outcome, fourth, improve instrumentation to reduce procedure-related complications, and, finally, explore promotion of lung growth with additional or alternative fetal therapies.

Table 1: Scorecard for fetal therapy for Congenital Diaphragmatic Hernia. Criteria for fetal surgery as defined by the International Fetal Medicine and Surgery Society (first column), contributions by FETO-consortium towards the clinical introduction of FETO (second column) and future research into the antenatal management of isolated CDH.

	Work done within this consortium	Possible future actions
Diagnosis must be made with certainty and additional anomalies excluded	Up to two thirds of cases are picked up in screening programs by the second trimester[63]	Increase awareness, quality control, teaching in early diagnosis, use of advanced genetic testing to rule out underlying problems
Natural history must be predictable **Treatment cannot wait** **Postnatal treatment not effective enough**	Reproducible methods of lung measurement in normal and hernia fetuses using ultrasound and MRI (reviewed in[81]) Other parameters: liver and stomach position Defining severe pulmonary hypoplasia Consensus standardized prenatal assessment[64]	Validating prediction by medical imaging Define novel biomarkers, preferentially usable early in pregnancy and/or correlating with response to fetal therapy Improving prediction mortality by combining biomarkers
Experimental basis of fetal intervention available	Tracheal occlusion in lambs: fetoscopic technique [82-84] and relevance of prenatal reversal (Plug-Unplug Sequence)[85]	More potent intervention: preclinical studies with medical adjuncts and/or novel strategies
Treatment offered within clinical trials by multidisciplinary teams	First in woman study [4] Prospective cohorts [15,25,86] Standardized neonatal management [87,88]and counseling[89] Contemporary controlled cohorts right CDH[9] Randomized controlled trials in left CDH[7,8] Pooled analysis of data[10]	Systematic reviews Prospective registries Controlled trials where that is possible Definition of core outcome set[19] Health Technology Assessment
(Maternal safety)	Documentation of (1) nature and incidence severe complications[90] and (2) of reproductive and psychological outcomes[60]	Defining patient needs in fetal therapy programs, determine acceptability of future alternative therapies

Go to text on Table 1.

Table 2: Outcomes of fetuses diagnosed with isolated CDH in the prenatal period, either left or right sided, expectantly managed during pregnancy or having tracheal occlusion in the TOTAL trial, as well as an analysis and modeling based on the pooled data, as well as a large study on right sided CDH under the same management protocol.

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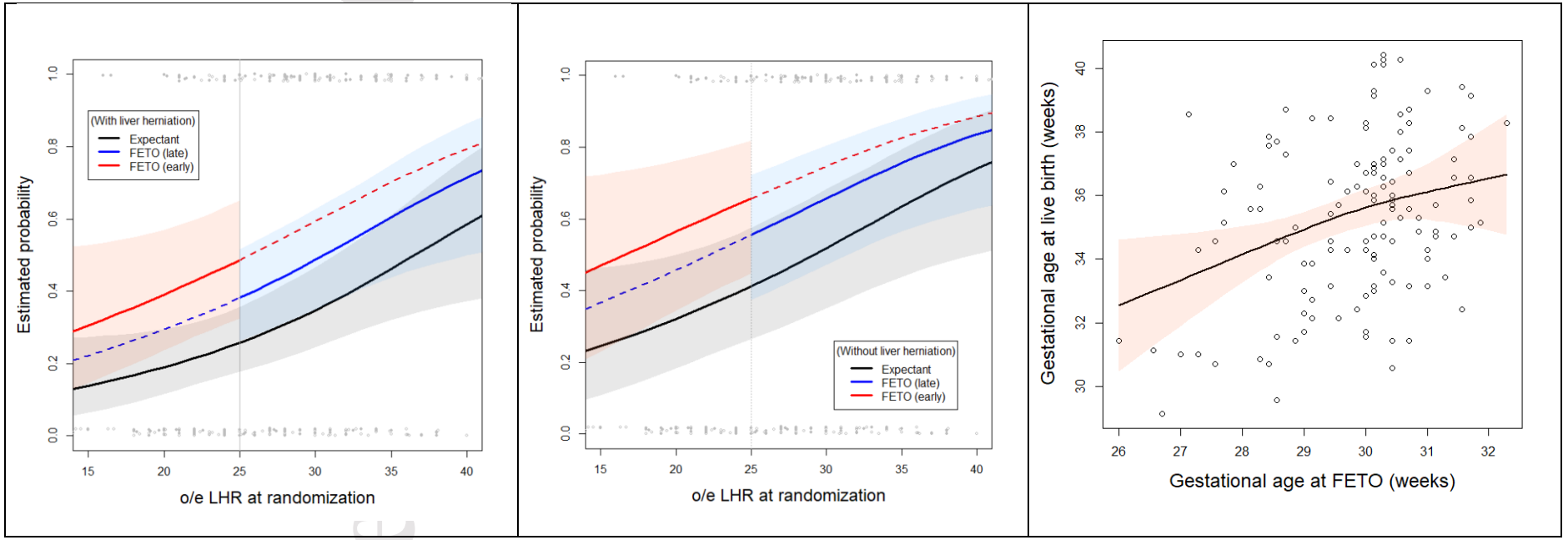
Side, severity	Criteria severity on ultrasound	Survival to discharge		RR (95% CI)
		Expectant	FETO	
Isolated left sided CDH – TOTAL trials				
TOTAL *severe*[8]	O/E LHR <25.0% Irrespective of liver position	6/40 (15%)	16/40 (40%)	**2.67 (1.22-6.11)**
TOTAL *moderate*[7]	O/E LHR 25.0-34.9%, any liver position O/E LHR 35.0-44.9% & liver into chest	49/98 (50%)	62/98 (63%)	**1.27 (0.99-1.63)**
Isolated left sided CDH – Pooled analysis TOTAL data				
Late insertion	O/E LHR 0.0-34.9%, any liver position O/E LHR 35.0-44.9% & liver into chest	55/142 (39%)	79/145 (54%)	**A OR: 1.78 (1.05-3.01)**
Early insertion	O/E LHR 0.0-34.9%, any liver position O/E LHR 35.0-44.9% & liver into chest			**A OR: 2.73 (1.15-6.49)**
Isolated right sided CDH				
Severe[9]	O/E LHR <50% Irrespective of liver position	7/34 (20%)	53/125 (42%)	**2.84 (1.15-7.01)**

To top of document

Figure 1. Estimated probabilities of survival to discharge based on a model, for cases with liver herniation (A) or with the liver confined to the abdomen (B). Dashed red and blue lines indicate situations that are not included in the TOTAL trials: early insertion in moderate hypoplasia and late insertion in severe hypoplasia. C: Estimated gestational age at live birth as a function of gestational age at FETO, with pointwise 95% confidence intervals. Pointwise 95% confidence intervals are added as shaded areas. Raw patient data are indicated on top (survivors) and at the bottom (non-survivors) of the plot. Reproduced, with permission from the authors and the publisher[10].



A B

Figure 2: Smart-TO™ device, uninflated (left) and inflated with 0.7 mL saline (right). This is an experimental tracheal occlusion device with similar dimensions as the device used so far, but with a magnetic valve. This permits non-invasive opening of the valve by exposure to the fringe field of a clinical MRI device[41]. Copyright of and reproduced with permission of the manufacturer.

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