Clinically relevant discordances identified after tertiary reassessment of fetuses with isolated congenital diaphragmatic hernia

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Bulleted statements:

What is already known about this topic?

- Primary diagnosis of Congenital Diaphragmatic Hernia (CDH) is based on ultrasound evaluation.
- Postnatal prognosis is strongly related to the presence of associated anomalies
- CDH severity criteria are fetal lung size measurements and liver herniation. These parameters are used for parental counselling as well as to select cases eligible for prenatal intervention.

What does this study add?

- We documented relevant discrepancies regarding the diagnostic accuracy and the assessment of severity between initial evaluation prior to referral and final evaluation at the fetal surgery centre.
- Identification of a low termination of pregnancy rate in patients who were specifically referred for fetal surgery.

Abstract:

OBJECTIVE: Fetoscopic Endoluminal Tracheal Occlusion (FETO) may improve outcome of severe isolated Congenital Diaphragmatic Hernia (iCDH). We aimed to identify any discrepancy between initial assessment at the referring hospital and the evaluation at the fetal surgery center, and to document parental decisions following counseling for fetal surgery.

DESIGN: Single centre retrospective study on patients with presumed iCDH either referred for assessment and counseling or referred for fetal surgery. Discordant findings were defined as either a >10% difference in lung size, discordant liver position or associated anomalies.

RESULTS: Outcomes from 129 consecutive assessments over 24 months were analyzed. Amongst fetal surgery referrals 2 % did not have CDH and 10% had undiagnosed associated anomalies. Liver position was discordant in 7%. Thirty-three % had discordant lung size. 94% of patients eligible for surgery underwent FETO. In patients referred because suspicion of CDH, associated anomalies were found in 14%. Fetal liver and lung assessments were discordant in 50% resp. 38%. Of those patients eligible for FETO, 26% requested termination. For 3 patients, the postnatal course was marked by a genetic or syndromic additional diagnosis.

CONCLUSION: Discordances between initial assessment before referral and evaluation in our institution were frequent, some of them clinically relevant.

Introduction:

About 30% of live born infants with congenital diaphragmatic hernia (CDH) without associated structural or chromosomal defects (i.e. 'isolated CDH') die in the neonatal period due to lung hypoplasia or pulmonary hypertension[1]. Neonatal mortality can be predicted based on prenatal ultrasound estimation of fetal lung size and liver position[2]. The best validated technique to measure the fetal lungs with ultrasound is the lung-to-head ratio (LHR), which can be expressed as a function of what is expected in a gestational age matched control fetus (obtained / expected or O/E LHR)[3,4]

In fetuses with a predicted poor prognosis, fetoscopic endoluminal tracheal occlusion (FETO) can be offered to accelerate lung growth, thereby possibly improving survival. Observational studies have shown that FETO can increase neonatal survival in fetuses with severe lung hypoplasia (i.e. an O/E LHR smaller than 25% and liver herniation). This is now tested in a randomized controlled TOTAL-trial (www.clinicaltrials.gov; NCT01240057) [5].

One of the questions arising during the design of the study protocol was whether assessment of patients should be done in a few centralized 'FETO-units', similar to what was done for the Management Of Myelomeningocele Study on spina bifida[6] or whether decentralized randomization, as in the Eurofoetus trial for twin-to-twin transfusion[7], would be an option. The latter reduces patient travelling and facilitates patient recruitment. That is only acceptable if the referring centers could reliably (1) diagnose CDH, (2) exclude associated anomalies, (3) assess the O/E LHR and liver position and (4) adequately counsel patients.

We therefore set out for this retrospective study in which we compare diagnostic performance in terms of associated anomalies and severity of CDH by referral hospitals to that of a fetal surgery unit. Moreover, we also assessed whether eventual diagnostic differences would have an impact on clinical management and uptake of fetal therapy.

Material and methods:

This is a single centre, retrospective study including all pregnant women who were referred to the University Hospitals Leuven over a 24 months period, with a prenatal diagnosis of isolated CDH (i.e. CDH without associated structural or chromosomal

anomalies). For all cases, we retrieved the O/E LHR and liver position as measured at the referring center. In our unit, all women underwent a detailed fetal ultrasound to exclude additional anomalies, to measure lung size and to assess liver position. O/E LHR was obtained either using the longest perpendicular diameter technique or the tracing method[3]. All ultrasounds assessments were performed using Voluson 730 or E8 ultrasound device (GE Medical Systems, Milwaukee, WI, USA) by 3 fetal medicine fellows (ED, LG, TVM), experienced in the assessment of fetuses with CDH and with a track record of at least 80 fetal lung assessments each. All ultrasounds were supervised by an experienced fetal medicine consultant. Subsequently, eligible patients were counseled about the different management options, including expectant management, termination of pregnancy (TOP) and FETO, as described in detail elsewhere[8]. For FETO, we explicitly discussed the experimental nature of the procedure as well as the logistic implications of a fetus with an occluded trachea as described in the patient information section of the TOTAL-trial website (www.eurocdh.org)[9]. Fetuses eligible for FETO had an O/E LHR <25% or ≤45% for left or right sided CDH respectively, liver herniation, a normal karyotype and no associated anomalies. However, fetuses with hydrops, an associated congenital pulmonary airways malformation (CPAM) or a bronchopulmonary sequestration (BPS) were still considered for FETO as these anomalies do not necessarily impact on outcome[10]. For all cases, we also retrieved whether the infant survived until discharge from the neonatal intensive care unit and whether associated anomalies were diagnosed after birth.

For this study, patients were divided in two groups: (1) '*assessment referrals*' including women who were sent for advanced prenatal assessment and in whom the referring physician had not yet decided on the eligibility for fetal intervention; (2) '*Fetal surgery referrals*' were patients in whom the referring physician concluded the CDH to be isolated and the lung hypoplasia to be severe, hence suggested fetal therapy.

Analysis

We classified findings from the referring center and observations made in our fetal surgery unit as being either dis- or concordant for the presence of CDH associated anomalies, the lung size, and liver herniation expressed as either overestimated (=liver reported up while being down) or underestimated (=liver reported down while being up). The lung size assessment was based on a measurement of the O/E LHR. Discordant measures were empirically defined as a difference between the two O/E LHR exceeding 10% (in either direction). We also retrieved the concordance of prenatal and postnatal associated anomalies. The FETO program and studies on CDH severity assessment and outcome prediction were approved by the Ethics Committee of the University Hospitals Leuven.

Statistics

Statistical analysis was made using JMP Version 7.0 (SAS Institute Inc, Cary NC USA, 2007) looking for significant relationships between variables. Chi-square test was used to compare outcomes for cases where variables were categorical. One-way ANOVA was used when the outcome variable was continuous and the predictor variable was categorical. A P value < 0.05 was considered statistically significant.

Results:

During the study period, 129 fetuses referred with isolated CDH were evaluated in our fetal surgery unit. Forty-three patients (33%) were considered as assessment referrals and 86 (67%) as fetal surgery referrals. Seventeen cases with right CDH were registered (5 in the referral group and 12 in the fetal surgery group). The mean gestational age at first assessment was 26 weeks gestation.

Structural fetal evaluation and additional postnatal findings

Discordances between fetal structural anomalies documented by the referring center and results of the fetal assessment at the referral center were identified in 16 fetuses. Two fetuses from the fetal surgery referral group did not have diaphragmatic hernia, one had no anomalies at all, the other had an isolated macrocystic CPAM. Those findings were confirmed after birth in both cases. Additional fetal anomalies were documented in 14 of the 127 cases with confirmed CDH (11%). The nature of these anomalies is displayed in Table 1. Nine fetuses (64%) had extra-thoracic anomalies and 5 had intra-thoracic anomalies (4 CPAM, 1 BPS). All these defects were confirmed after birth.

Additionally, 3 infants were diagnosed after birth, with a genetic anomaly or syndrome, that were not prenatally diagnosed either in the referring center or in our unit. One case of Denys Drash syndrome and one newborn with a Matthew-Wood syndrome were recorded. Both infants died during the early neonatal period from ventilatory insufficiency. The third child was found to have a deletion on chromosome 8 that was missed on prenatal karyotype done elsewhere. The parents of this newborn were counselled and a decision for palliative management was taken. The neonate died at 12 days of life.

Severity assessment

Predictors of pulmonary development were documented within the written referral letter in around one third of referred patients. Lung size was assessed in 32 patients (24.8%) and liver position in 47 (36.4%) (Table 2). The O/E LHR was reported in 8 fetuses (18.6%) within the assessment group and in 24 patients (27.9%) within the

fetal surgery group. Liver position was reported in 18 patients (41.8%) within the assessment group compared to 29 (33.7%) within the surgery group.

Within the group of patients specifically referred for fetal surgery and already counselled about severity indicators measured by the referring doctors, 2 cases of discordance for liver herniation (7%) and 8 cases of discrepant O/E LHR(33%) were reported (Table 2).

Severity of CDH based on liver position was generally underestimated by the referring center as comparet to our evaluation, whereas severity of pulmonary hypoplasia based on lung size was in most cases overestimated. Only 56 (72%) of patients referred for fetal surgery ultimately met the criteria for fetal surgery.

Uptake of FETO in patients with a fetus with severe pulmonary hypoplasia.

Overall, 79 fetuses met the criteria for fetal surgery (69%) with no significant difference between the referral (n=23; 62%) and fetal surgery group (n=56; 72%). The outcomes of these 79 fetuses are displayed in Table 3. Seventy underwent fetal surgery after counseling, 2 declined surgery and chose for expectant management and 7 pregnancies were terminated.

The uptake of fetal surgery was 21% higher in patients referred specifically for FETO (94%) as compared to the group of patients referred only for assessment (74%) (not significant; 95% Confidence Interval 4% - 41%). Conversely, the difference in termination rate was 24% with significantly more terminations in the group of patients referred for assessment (26%) than those specifically for fetal surgery (2%) (95% Confidence Interval 9% - 45%; p 0.002).

Pregnancy outcomes of patients with CDH without extra-thoracic associated malformations.

In total, 118 patients had either isolated CDH (n=113), or CDH with an additional intra-thoracic pulmonary anomaly (n=5). Of those, 7 opted for TOP, for 6 patients out of these a severe fetal pulmonary hypoplasia was diagnosed, and in one patient the fetus had moderate fetal lung hypoplasia (27.5%) was terminated. One-hundred and eleven patients continued the pregnancy and two were lost for follow-up. Three intra-uterine fetal demises were registered (IUFD; 2.7%), one case in the expectantly managed group, at term, without an identified obvious cause, the 2 other IUFD happened after fetal surgery, one remotely after balloon insertion and one remotely

after balloon removal, however both happened before labour. The total survival rate in the 106 live born infants was 55.7% (n=59), i.e. 42.8% after FETO (all theses cases had severe lung hypoplasia). This was significantly different for patients expectantly managed. Their survival rate was 70.7%. In those, there were no cases of severe fetal lung hypoplasia, 22 patients with moderate fetal pulmonary hypoplasia, and 8 patients with mild hypoplasia) (p=0.002)).

Discussion

This study identified important discrepancies between fetal assessments made prior to referal and fetal evaluations in a FETO unit. Amongst a population of patients referred for an isolated CDH, signficant differences were demonstrated at a qualitative (the nature and extent of the fetal anomaly) and quantitative level (quantified severity of fetal lung hypoplasia).

Our study confirms that physicians in referring centers can reliably diagnose CDH, as evidenced by a 98% accuracy of diagnosis. However, associated anomalies were missed in 11% of cases. Although not all of these missed associated lesions impact on pulmonary prognosis, some may certainly affect the patients perception of the disease hence influence the decision parents make about the different management options. Indeed, as shown in Table 1, 3 out of 6 women referred for fetal surgery, finally decided to terminate the pregnancy after identification of associated extrathoracic anomalies. We see two reasons why associated lesions went more often undiagnosed in the referring centers: first, in CDH, the fetal pulmonary anatomy is strongly distorted and mediastinal shift is present. As a consequence, lung lesions are more difficult to diagnose and might not strike the eye of a sonographer less familiar with CDH. Second, the ultrasounds performed in a FETO-center are primarily directed at excluding additional anomalies, rather than at making the diagnosis of CDH (as this has already been done by the referring physician). As such, sonographers in a referral center have a different mindset and will be more focussed on smaller details. Despite high skills, the ability for fetal surgery units to exclude additional fetal anomalies remains limitated as illustrated by the reported 2% of postnatal diagnosis of genetic syndromes that were not suspected during prenatal fetal evaluations.

This study also showed that over 60% of patients were referred to our center without a formal quantitative assessment of the fetal pulmonary hypoplasia, despite the diffusion and promotion of lung size and liver position assessment tools in the scientific literature. [3,4,7]

Moreover, of patients referred with a quantification of the severity of CDH, discrepancy with our findings remained frequent. Though this is speculative, yet it

seems to indicate that many fetal medicine specialists are unfamiliar or feel uncomfortable with prenatal lung measurement on ultrasound. This is easy to understand given the rarity of the condition, the difficulty to discriminate between lung and liver, which have comparable echogenicity, and the distorded anatomy. It has been shown that accurate measurement of the LHR requires time and experience (the learning curve includes more than 70 cases) [11]. Besides unfamiliarity with the severity measurement method, time constraints may also play a role. Measurement of the O/E LHR implies a few calculations which are at that time not automated in the current ultrasound reporting softwares. To facilitate this we have created a website which provides an automatic calculator (www.totaltrial.eu).

Given the discrepant findings between referring centers and FETO centers, it seems cautious as a referring physician not to make a severity statement prior to referral of a patient. Indeed, both under- and overestimation of lung size is confusing and upsetting for the patient. That has been shown for other fetal pulmonary conditions, and can lead to premature decisions and suboptimal management[12]. Based on our findings, we recommend for a clinical trial to centralize the assessment of CDH severity in high volume centers with sufficient case-load to validate specific clinical and prenatal ultrasound skills. This also led us to require referral of potential candidates for the TOTAL-trial to a FETO-center to perform an accurate fetal assessment before randomization of the patient. This is a major hurdle for patient recruitment and could potentially cause a referral bias.

Finally, our findings show that the counseling done by referring physicians around FETO is likely to be realistic and correctly perceived by patients. This is illustrated by the percentage (6%) of women referred for FETO with a fetus fulfilling the surgical criteria, who finally opted out of the procedure after counseling at the FETO center. This contrasts with the much lower uptake (74%) of surgery in the ‘assessment group’.

This study has certainly a number of drawbacks. First, during the recruiting period, we did not have an independent gold standard reference for the measurement of lung size or liver position. As such it is unclear whether the LHR measurement performed in the referring center or the one recorded at the FETO-unit was the gold

standard. A gold standard for assessing lung hypoplasia would be lung-to-body weight ratio, but this is only available on postmortem examination. Fetal magnetic resonance assessment has been proposed as an alternative to ultrasound evaluation, though this has not been shown to be more accurate for prediction of postnatal outcomes[13].

Prenatal assessment of liver position is another important severity criteria used to decide if a FETO procedure is indicated. Fetal liver herniation is difficult to assess and even more difficult to quantify with fetal imaging techniques[2,14,15]. Observations made during postnatal diaphragmatic repair surgerical procedure could serve as another standard, but unfortunately, we could not obtain surgical reports for all patients, neither would they probably have been standardized.

Another weak point of this study needs to be mentioned. No scientifically validated explanation could be provided to explain the cause of the observed discrepancies between centers. As such, we could only speculate on this in the discussion. Finally, the CDH population in this study is certainly affected by a referral bias. Indeed, severe fetal pulmonary hypoplasia was identified in over 35% of the referred population (n=16/43) – which is an overrepresentation when compared to the numbers published in the antenatal CDH registry (15%)[3].

In conclusion, this study suggests that severity assessment for cases with isolated CDH, is not yet widely practiced and, when done, it may significant differ from what was obtained in a high volume center. Based on these observations, we conclude that the counselling as well as decisions about prenatal management options would be probably more efficient if patients with CDH were directly referred to dedicated centers, where volume and experience are higher.

The possibility to use new technologies for remote consults could be considered, such as sending two-dimensional image or 3D volumes. The impact of tele-consulting using primarily obtained images for this condition has not yet been studied to our knowledge. This practice may also have its limitations, as this presumes a proper ability to aquire the shots and volumes appropriately and in a standardized fashion.

Future studies aiming to evaluate postnatal outcomes and correlations with fetal indicators used to stratify the severity of the identified pulmonary hypoplasia should include a centralized assessment prior to randomization.

Table 1. Cases with discordant structural findings in fetuses referred as isolated CDH.

n.	Group	Anomaly identified prenatally	Management
CDH with additional extrathoracic malformations			
1	Assessment	SUA, VSD	TOP
2	Assessment	Pectus excavatum, esophageal atresia, hypospadias	TOP
3	Assessment	Mega cisterna magna, malposition gallbladder[1]	TOP
4	Surgery	Limb anomaly: agenesis of lower part of the leg and club foot	Expectant, neonatal death
5	Surgery	Severe scoliosis	Expectant, neonatal death
6	Surgery	Asymmetric posterior ventricles, SUA, limb anomaly	TOP
7	Surgery	Severe IUGR, SUA, renal malformation[3]	Expectant, neonatal death
8	Surgery	Agenesis corpus callosum	TOP
9	Surgery	Pterigium colli, profile[2] - PPROM at 29 weeks	TOP
CDH with additional intrathoracic malformations			
10	Assessment	CPAM	FETO
11	Assessment	CPAM	FETO
12	Assessment	BronchoPulmonary Sequestration (BPS)	Expectant
13	Surgery	CPAM	FETO
14	Surgery	CPAM	FETO

[1] Mosaicism Trisomy 1 ; [2] Turner mosaicism and [3] microdeletion chromosome 8 were identified later on.

Abbreviations: *SUA: Single Umbilical Artery; VSD: ventricular septal defect; TOP: termination of pregnancy; IUGR: intrauterine growth restriction; CPAM: congenital pulmonary airway malformation; FETO: Fetal Endoscopic Tracheal Occlusion. PPROM: preterm premature rupture of membranes*

Table 2. Descriptive statistics and comparison between "Assessment referrals" and the "Fetal surgery referrrals".

	Assessment referrals	Fetal surgery referrals	Entire population over 2 year period	*p*-value
N (%)	43 (33%)	86 (67%)	129	
Descriptive statistics (based on assessment at FETO-unit)				
No CDH		2		
Right CDH	5/43 (12%)	13/84 (15%)	18/127 (14%)	ns
Liver up	5/5 (100%)	12/13 (92%)	17/18 (94%)	ns
O/E LHR	32.13%	25.8%	31.4%	ns
Left CDH	38/43 (88%)	71/84 (85%)	109/127 (86%)	ns
Liver up	29/38 (76%)	59/71 (83%)	88/109 (81%)	ns
O/E-LHR	30,9%	23%	24%	ns
% with severe lung hypoplasia*	13/38 (34%)	43/71 (61%)	56/109 (51%)	<0.005
Discordance between referring center and FETO-unit				
Absence of DH	0	2/86 (2%)	2 (2%)	
Presence of associated anomalies	6/43 (14%)	8/86 (10%)	14/129 (11%)	ns
Liver discordance	9/18 (50%)	2/29 (7%)	11/47 (23%)	<0.005
Overestimated severity	1/18 (5%)	1/29(3%)	2/47 (4%)	ns
Underestimated severity	8/18 (44%)	1/29(3%)	9/47 (19%)	<0.005
O/E LHR	3/8 (38%)	8/24 (33%)	11/32 (34%)	ns
overestimated lung size >10%	0/8 (0%)	0/8 (0%)	0/16 (0%)	ns
underestimated lung size >10%	3/8 (38%)	8/24 (33%)	11/32 (34%)	ns

* O/E LHR < 25% and liver herniation

Table 3: In utero outcomes of patients eligible for FETO (n=79), broken down by group, which were significantly different for populations. (p=0.003).

	TOP	Expectant management	FETO	Total
Referral population	6/23 (26%)	0 (0%)	17/23 (74%)	23
Fetal surgery population	1/56 (2%)	2/56 (4%)	53/56 (94%)	56
Entire population	7/79 (9%)	2/79 (3%)	70/79 (89%)	79

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