

REVIEW

Prenatal diagnosis, prediction of outcome and *in utero* therapy of isolated congenital diaphragmatic hernia

Elisa Doné^{1,3}, Leonardo Gucciardo¹, Tim Van Mieghem¹, Jacques Jani², Mieke Cannie⁴, Dominique Van Schoubroeck¹, Roland Devlieger¹, Luc De Catte¹, Philipp Klaritsch³, Steffi Mayer³, Veronika Beck³, Anne Debeer^{3,6}, Eduardo Gratacos⁵, Kypros Nicolaides² and Jan Deprest^{1,3*}

¹Fetal Medicine Unit of University Hospitals Leuven, Leuven, Belgium

²Fetal Medicine Unit of King's College Hospital, London, United Kingdom, UK

³Interdepartmental Centre for Surgical Technologies, Faculty of Medicine, KU Leuven, Leuven, Belgium

⁴Department of Radiology, University Hospitals Leuven, Leuven, Belgium

⁵Fetal Medicine Unit of Hospital Clinic, Barcelona, Spain

⁶Department of Neonatology, University Hospitals Leuven, Leuven, Belgium

Congenital diaphragmatic hernia (CDH) can be associated with genetic or structural anomalies with poor prognosis. In isolated cases, survival is dependent on the degree of lung hypoplasia and liver position. Cases should be referred *in utero* to tertiary care centers familiar with this condition both for prediction of outcome as well as timed delivery. The best validated prognostic indicator is the lung area to head circumference ratio. Ultrasound is used to measure the lung area of the index case, which is then expressed as a proportion of what is expected normally (observed/expected LHR). When O/E LHR is <25% survival chances are <15%. Prenatal intervention, aiming to stimulate lung growth, can be achieved by temporary fetal endoscopic tracheal occlusion (FETO). A balloon is percutaneously inserted into the trachea at 26–28 weeks, and reversal of occlusion is planned at 34 weeks. Growing experience has demonstrated the feasibility and safety of the technique with a survival rate of about 50%. The lung response to, and outcome after FETO, is dependent on pre-existing lung size as well gestational age at birth. Early data show that FETO does not increase morbidity in survivors, when compared to historical controls. Several trials are currently under design. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS: congenital diaphragmatic hernia; pulmonary hypoplasia; lung-to-head ratio; fetal tracheal occlusion

INTRODUCTION

Congenital diaphragmatic hernia (CDH) occurs sporadically with an incidence of 1–2/5000 of newborns, depending on whether stillbirths are included or not. CDH does not designate one single clinical entity and outcomes are diverse (Ackerman and Pober, 2007). The embryology, molecular and genetic mechanisms behind this anomaly are beyond the scope of this article (Rottier and Tibboel, 2005; Ackerman and Pober, 2007; Bielinska *et al.*, 2007). Eighty-four percent of lesions are left-sided (LCDH), 13% right-sided (RCDH) and 2% bilateral. Complete agenesis, herniation of the central tendinous part and eventration are other rare manifestations. In around 40% of cases, there are associated anomalies, an independent predictor of neonatal death, with less than 15% of babies surviving in this group (Skari *et al.*, 2000; Rottier and Tibboel, 2005). The majority, however, has an isolated defect. While the name essentially points to a defect in the diaphragm, it is the abnormal lung development that accompanies the condition that

gives it its clinical relevance. The changes in the lung are usually seen as a direct consequence of compression by herniating viscera during pregnancy, although this is probably only partly true. Some even argue the condition actually arises in the lung. In essence, lungs in fetuses with CDH have a reduced number of conducting airways as well as vessels. There are fewer alveoli, thickened alveolar walls, increased interstitial tissue, markedly diminished alveolar air space and gas-exchange surface area. There is a reduced number of vessels, adventitial thickening, medial hyperplasia and peripheral extension of the muscle layer into the smaller intra-acinary arterioles. Both lungs are affected, the ipsilateral one more than the contralateral one. There may be other anatomic aberrations present in the diaphragm and in the upper gastrointestinal tract such as the position of the liver, lower esophagus and stomach.

PRENATAL DIAGNOSIS

In the last 20 years, prenatal detection rates significantly improved, from 15% in the mid-1980s to almost 60% in the late nineties (Dillon *et al.*, 2000). In countries with ultrasound screening programs the diagnosis of CDH is often made in the prenatal period. The diaphragm

*Correspondence to: Jan Deprest, Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Division Woman and Child University Hospitals Leuven, Leuven 3000, Belgium.
E-mail: jan.deprest@uzleuven.be



Figure 1—(A) Fetus with CDH on ultrasound, the contralateral lung area has been traced along the longest axes at a level coinciding with the four chamber view. (B) Ultrasound section of the thorax the day of surgery in a severe case, (C) one day after balloon insertion, with changed echogenicity of the lungs. (D) Same view several weeks later and the ipsilateral lung has become visible as well. [(B-D) longest axis method]. (Reproduced with permission from UZ Leuven)

can be visualized with high-resolution equipment even in the first trimester. In its absence, abdominal organs are visualized in the chest while examining the cross-sectional view of the thorax to obtain a four-chamber view (Figure 1). Left-sided CDH is most common and is typically characterized by shift of the heart and mediastinum to the right, caused by herniation of the stomach and intestines. The stomach is easily recognized because of its fluid contents. Viscera may show peristalsis and contrast with the more echogenic fetal lung. The liver may also be herniated, but being echogenic as well, it may be more difficult to differentiate it from the lung (Figure 1). Right sided cases are more difficult to detect, because the herniating liver may be confused with lung, and because the stomach is in its normal position. Even though the right lobe of the liver may shift the mediastinum to the left, the heart remains on the left, however it is usually compressed. Doppler interrogation of the umbilical vein and hepatic vessels, or location of the gall bladder may be used as additional landmarks to

define the position of the liver. Cardiac compression and polyhydramnios are indirect signs of CDH.

The main differential diagnoses are other pulmonary pathologies, such as cystic pathology (cystic adenomatoid malformation, bronchogenic, enteric and neuroenteric cysts), mediastinal teratoma and thymic cysts) or bronchopulmonary sequestration or bronchial atresia. In these conditions intra-abdominal organs are not displaced. In CDH one should always look for associated anomalies. These include, in descending order of frequency, cardiac, renal, central nervous system and gastrointestinal anomalies (Graham and Devine, 2005). In the presence of multiple anomalies CDH may be associated with chromosomal anomalies but it can also be part of a monogenic and syndromal condition (see Hurst *et al.* in this issue). Amniocentesis and genetic consultation are therefore mandatory.

In cases of suspected CDH, parents should be referred to a tertiary center where serious congenital anomalies like this one both in the prenatal and postnatal period are

managed. The most important reason being that they are able to make a comprehensive diagnostic and prognostic assessment, upon which parents can further base their decisions. Prior to that point, physicians should refrain from making generic comments based on their own overall perception of this condition. When dealing with congenital anomalies, parents usually base their opinions and decisions on the initial counseling, which may, after more comprehensive review, prove to be wrong. The kind of work up required consists of advanced structural ultrasound evaluation, including assessment of the heart, as well as fetal karyotyping. In our experience, we consider that prenatal MRI is justified, not just because its use in measuring lung volumes is validated (Rypens *et al.*, 2001; Cannie *et al.*, 2008) moreover it may help in excluding other anomalies. Once the assessment is complete, a multidisciplinary counseling process starts, which should be done by the various specialists who will be involved in postnatal care.

NEONATAL MANAGEMENT AND THE DIFFICULTY OF ASSESSING EXACT SURVIVAL RATES FOR CDH

The *morphologic* changes become obvious only when the lung becomes *functional* at birth. These lead to variable degrees of respiratory insufficiency and pulmonary arterial hypertension (PAH). Reduced air space and vascular bed leads to hypoxia, hypercarbia as well as PAH. The aberrant vasculature is also more sensitive to vasoconstriction, which worsens PAH, further increasing the

right-to-left shunt. This leads to a vicious cycle preventing gas exchange of the shunted blood, increasing acidosis and hypoxia (Figure 2). Before the 1990s the cornerstone of neonatal management was aggressive hyper-ventilation and hyperoxygenation, together with other measures for controlling PAH, and *emergency* repair of the defect (Moya and Lally, 2005). These two tenets have been questioned and today ‘gentle ventilation’ followed by delayed surgery has improved results. Gentle ventilation protocols or spontaneous breathing, with permissive hypercapnea and minimal sedation reduce baro- and volutrauma (Böloker *et al.*, 2002; Vitali, 2005). High frequency oscillatory ventilation (HFOV) has been suggested as a *primary* ventilation mode in cases of lung hypoplasia, but most centers consider it as *rescue* therapy prior to the eventual use of extra corporeal membrane oxygenation (ECMO) (Okuyama *et al.*, 2002; Smith *et al.*, 2005). PAH is increasingly treated by early administration of inhaled nitric oxide (iNO) (Kinsella *et al.*, 2003). Recently it has been suggested that keeping the ductus arteriosus patent by administration of prostaglandins PGE₁ in case of severe secondary left ventricular cardiac dysfunction may be beneficial (Inamura *et al.*, 2005; Kinsella *et al.*, 2005). Some centers are proponents of a liberal use of ECMO (Khan and Lally, 2005), but its role has been criticized because of unproven benefits, its inherent complications and because it is not widely available. *Surfactant* use has so far no proven benefit when treating CDH, not even in selected subgroups (Van Meurs and Congenital Diaphragmatic Hernia Study Group, 2004). Data from the CDH study group registry also failed to show any benefit of surfactant on the clinical course of infants on ECMO (Colby *et al.*, 2004). In a retrospective analysis

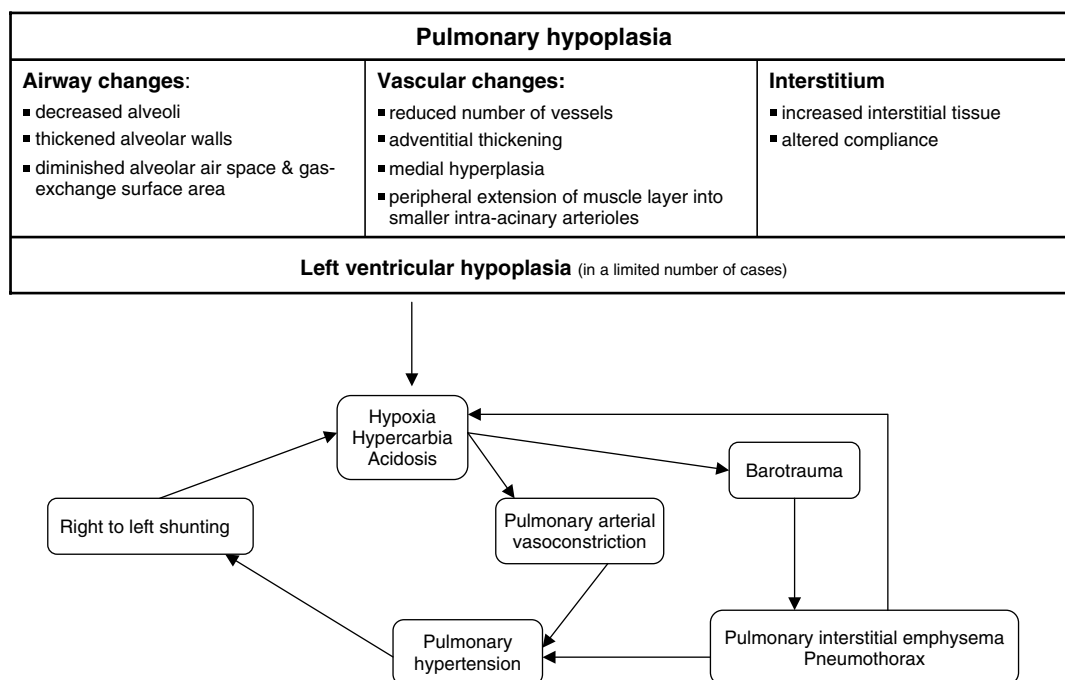


Figure 2—Pathophysiology of neonatal lung function in congenital diaphragmatic hernia. (Modified from: Laberge & Flageole, 2007; with permission from the authors)

of term infants treated with surfactant, no improved survival rate or decreased use of ECMO or occurrence of chronic lung disease were documented (Khan and Lally, 2005). The same applied to preterm infants.

With advances in neonatal therapy, one would expect to continue seeing increasing survival rates. However, reported survival rates actually continue to vary widely for a number of reasons. Series might include isolated cases as well as those with additional problems. Further consideration needs to be given to termination of pregnancy. In the United Kingdom, termination rates range from 9% for isolated CDH to 51% in case of associated anomalies (Tonks *et al.*, 2004). Some studies only consider cases from birth (inborn) or after transfer to the tertiary unit (outborn). The mismatch between numbers reported by postnatal as opposed to fetal medicine specialists, who use different denominators, is referred to as 'hidden mortality' (Harrison *et al.*, 1978). Also included in the prenatal losses are the 1–2% cases where spontaneous demise occurs (Gallot *et al.*, 2007). The simple practice of termination of pregnancy, particularly its increased use in cases that are considered to have poor prognostic indicators, may lead to an *apparent* increase in survival in postnatally reported series.

On the other hand, prenatal diagnosis may prompt *in utero* referral to a tertiary center, which in turn can increase survival. For example, in France this policy significantly increased survival from 41 to 66% ($p = 0.03$) (Gallot *et al.*, 2007). Centralized management, with increased case load and using consistent neonatal protocols leads to increased survival rates. This was demonstrated by the Canadian Neonatal Network that showed that high volume centers (>12 CDH admissions over the 22 months period) had 13% higher survival rate than low volume centers (Javid *et al.*, 2004).

For these reasons, it has become difficult to define the natural history of CDH. Population-based statistics remain our best source of information (Ontario Congenital Anomalies Study Group, 2004). Studies from France, Australia and the United Kingdom report survival rates of between 50 and 70% for isolated CDH (Stegé *et al.*, 2003; Colvin *et al.*, 2005; Gallot *et al.*, 2005). That this is a realistic estimate is confirmed by a comparable 60–70% survival rate reported by the CDH study group (Moya and Lally, 2005). Certain centers quote rates in excess of 80–90% and claim this is a result of their local neonatal management protocol, using one or the other particular ventilation strategy or ECMO, etc. It is however impossible to rule out bias in their statistics by prenatal selection or perinatal loss prior to referral (Downard *et al.*, 2003; Bagolan *et al.*, 2004). In Europe, the most optimistic survival rates published by one large referral center, which have a case load of more than 25 cases/year and offer ECMO, are 70–75% (Sartoris *et al.*, 2006). Last but not least, fetal medicine specialist should not forget that survivors may have morbidity, including pulmonary, gastrointestinal (gastroesophageal reflux and feeding problems), orthopedic, hearing and neurodevelopmental problems (Muratore *et al.*, 2001). For this reason, survivors should remain in long-term, possibly for life, specialized multidisciplinary follow up programs (West and Wilson, 2005).

PREDICTION OF OUTCOME

Prediction of outcome has been attempted by using various combinations of *indirect* features that might indicate the severity of the condition, such as relative size of the ventricles of the heart (ventricular disproportion), amniotic fluid volume, degree of mediastinal shift and the position of the stomach. These are all poorly validated prognostic indicators at this moment and so are not discussed further here. The most critical problem of the neonate with CDH is lung hypoplasia and it is therefore logical to assess that problem directly using a variety of imaging techniques (Deprest *et al.*, 2005).

Contralateral lung area

The basic aim of imaging is to measure lung size and/or resistance to flow in the pulmonary circulation as a proxy for pulmonary hypoplasia and hypertension, which are the two leading causes of death and morbidity. Lung size can be assessed by 2D-ultrasound in different ways but best validated is the use of the contralateral lung area to head circumference ratio (LHR) (Metkus *et al.*, 1996). First, the contralateral lung area is measured in the plane used to examine the four chamber view. That measure is related to a biometric index, i.e. the head circumference measured at the standard biparietal view. Different methods for lung measurement have been described, but the most reproducible and accurate one is by tracing the long contours (Figure 1) (Peralta *et al.*, 2005). Alternative methods use the longest axis or the anterior-posterior diameter at the mid-clavicular line. These methodological differences have caused confusion and have also potentially partly discredited its use. However, we were able to validate the predictive value of LHR in a multicenter study conducted by the prenatal CDH registry. This involved 184 consecutive cases of isolated left-sided CDH examined at 22–28 weeks of gestation who were live born beyond 30 weeks at 10 centers (Table 1) (Jani *et al.*, 2006b). Both LHR and intra-thoracic position of the liver were independent predictors of outcome. Year of management, gestational age at assessment or birth were not predictive factors. As some people questioned whether conclusions could be extrapolated to both sides of the Atlantic, we also looked at location of management and that was also not predictive.

Earlier it seemed that outcome could be better predicted when using a combination of markers. Herniation of the liver is in itself related to survival and therefore remains a logical candidate (Hedrick *et al.*, 2007). Liver has comparable echogenicity to the lung, and Doppler interrogation of the umbilical vein and hepatic vessels help in determining its position. The hepatic vessels may be shown above the diaphragmatic ridge or the intra-hepatic portion of the umbilical segment of the portal vein can be seen displaced to the left from midline. In doubt fetal MRI can be used (Cannie *et al.*, 2006b).

Between 12 and 32 weeks, normal lung area increases four times more than the head circumference. Thus the LHR increases during gestation as clearly shown by

Table 1—Neonatal outcome as a function of LHR in fetuses with left-sided isolated CDH and liver herniation, expectantly managed (left) or after FETO (right) (From Jani *et al.*, 2006a,b)

Degree of pulmonary hypoplasia	LHR	O/E LHR ^a	N	Expectant management (Jani <i>et al.</i> , 2006b)	N	TO (Jani <i>et al.</i> , 2006a)
Extreme	0.4–0.5	15–19	2	0 (0%)	6	1 (16.7%)
Severe	0.6–0.7	20–23	6	0 (0%)	13	8 (61.5%)
	0.8–0.9	24–27	19	3 (15.8%)	9	7 (77.8%)
	<i>LHR < 1.0</i>	15–27	27	3 (11.1%)	28	16 (57.1%)
Moderate	1.0–1.1	28–31	23	14 (60.9%)		n a
	1.2–1.3	32–35	19	13 (68.4%)		n a
Mild	1.4–1.5	36–39	11	8 (72.7%)		n a
	≥1.6	≥41	6	5 (83.3%)		n a
	<i>Total</i>		86	43 (50%)		

n.a., not applicable since these fetuses were not eligible for FETO in current protocols.

^a % and conversion rounded up to 0.55 of LHR.

Peralta in the nomograms for LHR for both lungs in 650 fetuses (Figure 3) (Jani *et al.*, 2006b). The effect of gestational age on lung size measurement can be taken into account by expressing the measured LHR of the index case (*observed*) over the appropriate normal mean (*expected*) for gestation of the same side lung. In a second report from the prenatal CDH registry, now including 354 fetuses with unilateral (left and right) isolated CDH evaluated between 18 and 38 weeks (Jani *et al.*, 2007d in press), we could show that the O/E LHR in CDH was on average 39% (Figure 3). In more than 90% of cases it was below the 5th percentile of the normal. In a regression analysis O/E LHR measured at any time in gestation and gestational age at delivery, but not position of the liver, were shown to be independent predictors of survival. There was a trend for better prediction when O/E LHR was determined at 32–33 rather than 22–23 weeks but this did not reach significance. In a preliminary report from the CDH-prenatal registry O/E LHR also seems to correlate with short term morbidity indicators. These data are currently being prepared for publication (Jani *et al.*, 2006a).

Briefly one can say that survival chances go up as the O/E LHR increases. Previous publications have suggested that the degree of lung hypoplasia can be used to predict survival rate using an empirical four step differential classification based on lung size (Deprest *et al.*, 2006; Gucciardo *et al.*, 2008). Given below is the degree of pulmonary hypoplasia using this classification and chances of survival predicted by the LHR, when cases with isolated left-sided CDH and liver herniation are managed at tertiary care centers with similar expertise to those participating in the prenatal registry (Figure 3C).

- fetuses with an O/E LHR <15% have *extreme pulmonary hypoplasia* and (virtually) no survivors are currently reported.
- fetuses with an O/E LHR between 15 and 25% have *severe pulmonary hypoplasia* and their predicted survival is around 15%.
- fetuses with an O/E LHR between 26 and 45% have *moderate hypoplasia*. They have an expected survival rate of 30–60%, depending on the size of the lung.

- fetuses with an O/E LHR over 45% have *mild hypoplasia* and are very likely to survive.

There is an ongoing debate on whether the position of the liver is an independent predictor but one can certainly take that factor into account when refining the algorithm above (Cannie *et al.*, 2006b). For each category of severity there could be further subdivisions according to position of the liver, those with a liver up having a worse prognosis.

The prenatal CDH registry study is one of the few prenatal studies reporting on *right*-sided lesions. Side of the defect is an independent predictor of poor outcome (Jani *et al.*, 2007b). When measuring LHR in right-sided CDH, one measures the left lung, which is anyway smaller than the right. However data from Peralta provided reference values so O/E LHR can be determined. Our observations confirmed an overall worse prognosis (survival rate 44%; *n* = 25). There were no survivors in cases with an O/E LHR <45%. It would be interesting to obtain total lung volumes to determine whether there is a true biological difference behind this apparent difference in right-sided CDH.

3D ultrasound

Other methods may also predict lung size adequately but because they have only been used recently, they lack robust validation. Rather than measurement of a cross-section of *one* lung in a *single* plane, current three-dimensional ultrasound technology potentially allows measurement of bilateral or *total* lung volume in *three* dimensions. As with 2D methods, lung volume measured using volumetric methods should be expressed as an observed/expected ratio. Several groups have published nomograms for multiplanar or rotational volume 3D acquisitions in normal fetuses. Initial experience in fetuses with CDH is becoming available. We were not able to measure the ipsilateral lung in about 40% of cases, which limits the potential of 3D to measure the total lung volume (Jani *et al.*, 2007a). Others may debate this, but its superiority over 2D measurements needs to be demonstrated (Ruano *et al.*, 2004).

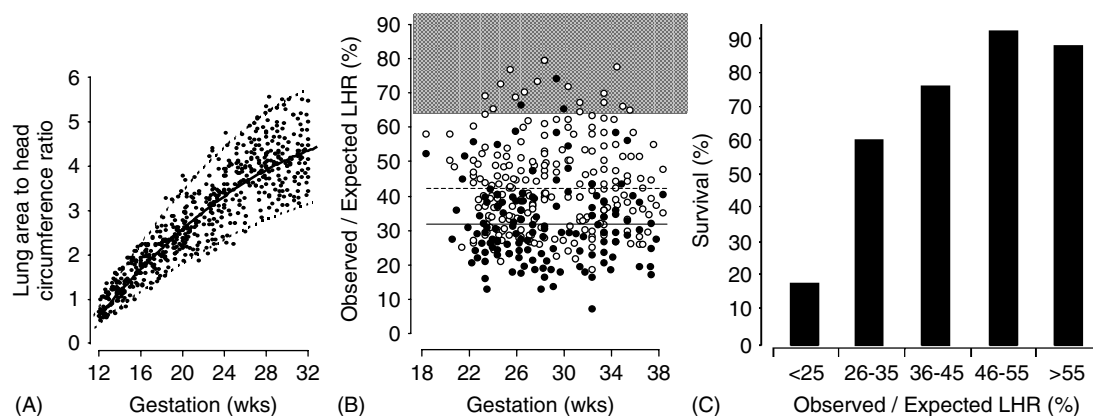


Figure 3—(A) Measurements of right lung-to-head ratio in normal fetuses throughout pregnancy, showing it is function of gestational age. (B) Observations in cases with right O/E LHR of fetuses with isolated left-sided CDH. Closed circles, full line relate to nonsurvivors; open circles, dotted line are from survivors. The gray shaded area depicts the lower part of the normal range (mean = 100%; interquartile range:). The mean O/E LHR of survivors is higher than in nonsurvivors. (C) Survival rates according to the O/E LHR in fetuses with isolated left-sided diaphragmatic hernia and liver herniation ($n = 161$) (Reworked from Peralta *et al.*, 2005; Jani *et al.*, 2007d)

Fetal MRI

The fetal lung is primarily composed of water, therefore has high signal intensity on MRI, allowing morphological and volumetric evaluation. The use of fetal MRI for volumetry has been reported by several groups and several nomograms are available (Coakley *et al.*, 2000; Rypens *et al.*, 2001; Williams *et al.*, 2004; Cannie *et al.*, 2006a; Cannie *et al.*, 2008). Lung volume can be predicted on the basis of gestational age or liver volume, but is more accurate when based on fetal body volume, which discounts the effect of gestational age, as well as differences in growth. Fetal MRI has a high-spatial resolution, can be applied in obese patients and, more importantly in fetuses with CDH, both the contralateral and ipsilateral lung can be accurately measured, which contrasts with our experience with 3D ultrasound (Jani *et al.*, 2007b). There is an impressive amount of work going on in this field at this moment, both in validating reliability of volumetric assessment and as a predictive tool in the target population.

Prediction of pulmonary arterial hypertension (PAH)

Another major clinical problem in the neonatal period is the occurrence of pulmonary arterial hypertension, believed to find its origins in structural vessel changes. *In utero* assessment of lung vasculature seems therefore another logical approach. One can measure number of branches, vessel diameters, flow velocimetry or flow volume with 2D or 3D techniques. The Toronto group demonstrated that the ipsilateral main branch pulmonary vessel diameter relates to the severity of hypoplasia both in the prenatal and postnatal period, when it is a significant predictor of morbidity (Suda *et al.*, 2000; Sokol *et al.*, 2002, 2006). Recently Ruano established nomograms for main branch pulmonary artery (PA) diameters, which will allow proper validation of this concept (Ruano *et al.*, 2007). He and the team from

Necker (Paris) also proposed the use of 3D power Doppler to assess the entire lung vasculature, and predict neonatal survival as well as the occurrence of PAH (Ruano *et al.*, 2006).

In our practice, we focus on measurement of the PA reactivity with maternal hyperoxygenation. This mimics changes in fetal hemodynamics as they occur after birth (Broth *et al.*, 2002). This hyperoxygenation test involves Doppler measurements of the pulsatility index (PI) in the first branch of the contralateral PA, before and after maternal administration of 60% O₂ by mask. A decrease of $\geq 20\%$ of the PI-value after O₂ exposure is considered reactive. In an initial study on 22 fetuses with severe CDH evaluated after 30 weeks, a reactive test was predictive of survival, whereas a negative test predicted an increased risk for severe PAH and neonatal death (Doné *et al.*, 2006). Unfortunately, this test can only be done late in gestation.

The methods described above, along with others still need proper validation in larger numbers, and at some stage may allow more precise prediction, in particular by using composite measures.

CONSEQUENCES OF PRENATAL ASSESSMENT AND INTERVENTIONS IMPROVING FETAL LUNG DEVELOPMENT

Modern counseling consists of describing the typical postnatal course of a newborn with CDH, and the known morbidity of the disease. But given the above, it should also include individualized information on the expected outcome. In *mild* cases with for instance a predicted survival rate of $>60\%$, arrangements for planned delivery at a referral center must be made in a timely fashion. In more severe cases (O/E LHR $<25\%$), as with fetuses with associated anomalies, other options should be discussed. In view of the overall poor prognosis, termination of pregnancy is one option. In between there is a gray area with a predicted survival rate of 30 to 60%.

For decades researchers have tried to offer the severe group an alternative that would enable reversal of the (nearly) lethal pulmonary hypoplasia prior to birth. First attempts consisted of *in utero* anatomical repair but this was abandoned because of poor results in a trial and because it could not be performed in fetuses with liver herniation. Di Fiore and Wilson put the concept of triggering lung growth by tracheal occlusion back on the table (Di Fiore *et al.*, 1997). The idea was inspired by an experiment of nature occurring in fetuses with congenital high airway obstruction syndrome (CHAOS), who display impressive lung growth. During pregnancy, fetal lungs secrete fluid into the airways, creating a positive pressure under the glottis. Fetal breathing movements allow the fluid to exit the airways, leveling that pressure. This results in periods of tissue stretch, its cyclical nature being important for an appropriate balance between growth and differentiation (Nelson *et al.*, 2005). Surgical tracheal occlusion (TO) takes advantage of this principle, its effects being a function of the timing and duration. In brief, when sustained until birth, despite lung growth, airway epithelial maturation is compromised. *In utero* reversal of occlusion (clinically translated as a plug–unplug sequence) experimentally achieved morphologically better lung maturation (Flageole *et al.*, 1998). Nelson later demonstrated that best results were obtained with a protocol of 47 h of occlusion alternated with 1 h of release. He did this between 110 (canalicular phase) and 138 days of ovine gestation (saccular; term = 145 days; Figure 4) (Nelson *et al.*, 2005).

This ‘ideal’ scenario of cyclical TO is at present not achievable in humans and therefore one has to adhere to a less than perfect scenario. We use a balloon, which is inserted and then removed during these phases of lung development, i.e. TO at 26–28 weeks and its reversal at 34 weeks. Whether this is the optimal scenario is a debate in itself (Deprest *et al.*, 2006; Kohl *et al.*, 2006).

CLINICAL INTERVENTION

To cut the clinical ‘plug’ odyssey short, tracheal occlusion was initially performed by laparotomy, hysterotomy, fetal neck dissection and tracheal clipping (Flake *et al.*, 2000) but later moved to multiple uterine cannulation to allow fetoscopic tracheal dissection and clipping (Harrison *et al.*, 2003b). The use of an endotracheal balloon, as we first described in sheep, made it possible to occlude the trachea through a single 3.3 mm port (Flageole *et al.*, 1997; Deprest *et al.*, 1998)(Figure 5). The balloon accommodates and follows tracheal growth without inducing tracheomalacia (Chiba *et al.*, 2000; Deprest *et al.*, 2000). *In utero* removal can be done either by fetoscopy or ultrasound-guided puncture; however the center must be ready at all times to offer emergency peripartum removal by laryngo-tracheoscopy if required. Initially procedures were done under general anesthesia, but we quickly moved to local regional or even local anesthesia with fetal sedation and immobilization (Deprest *et al.*, 2004).

In the first years TO was offered to a wider range of fetuses. In the NIH sponsored randomized controlled trial (RCT) cases with lung size up to lung area = 36% (LHR = 1.4) were offered fetal therapy. In this single center setting, TO did not improve survival compared to optimal neonatal care. However nearly all cases had moderate hypoplasia (lung area >25%) and were therefore expected to have reasonable outcomes without intervention. In that study there were virtually no cases with extreme or severe hypoplasia and these were subsequently the criteria for fetal therapy used by the fetal endoscopic tracheal occlusion (FETO)-task force.

The initial results of the FETO procedure were reported in some overlapping reports (Jani *et al.*, 2005). In brief there were no maternal complications but iatrogenic preterm rupture of the membrane (iPPROM), typically presenting as amniorrhexis without immediate onset of labour, remained a major obstacle. Ideally, we admit or host such patients for surveillance so that

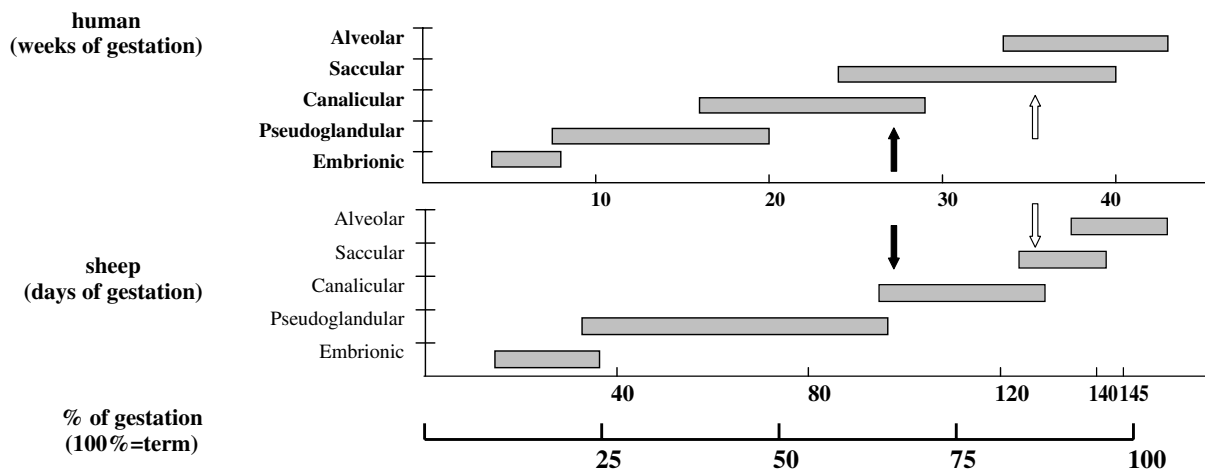


Figure 4—Comparison of lung developmental stages and their length in humans, fetal lambs and rabbits, which were among the species used in the experimental studies on tracheal occlusion. Reference is human lung development (top) and bottom line is the percentage (%) of gestation. The black arrows point to the time point of occlusion, the open arrows its reversal. (Courtesy of Xenia Roubliova)

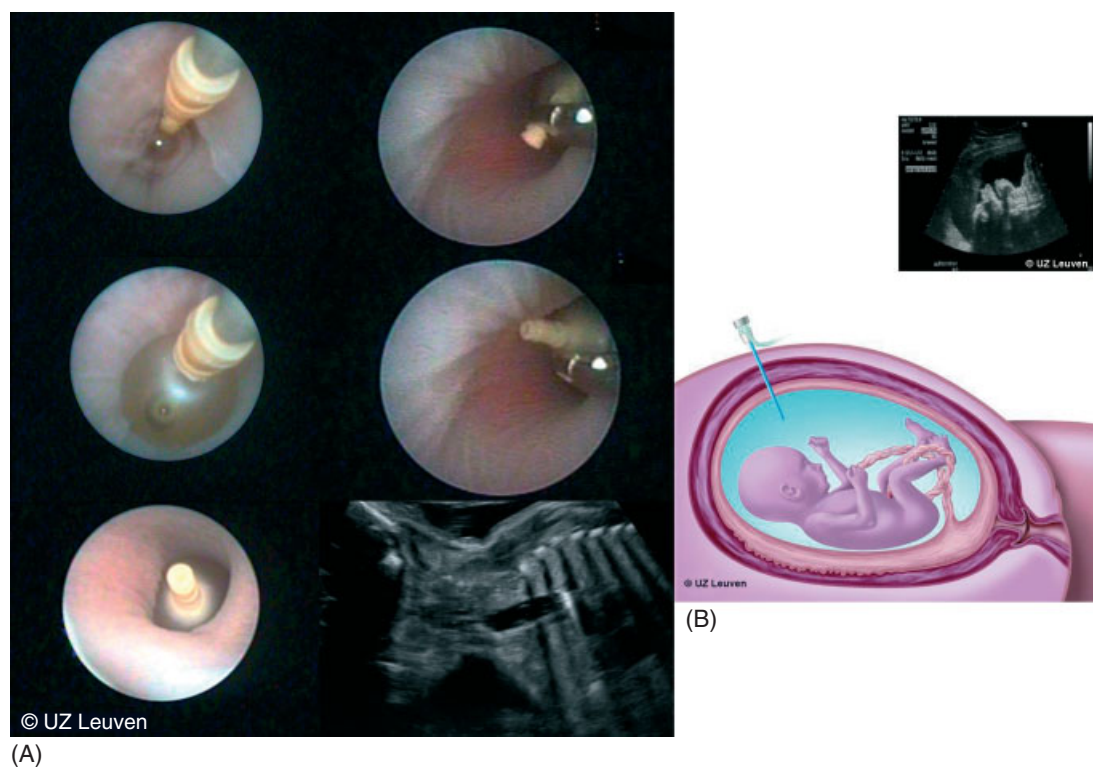


Figure 5—(A) Fetoscopic images of balloon insertion. The catheter, loaded with the balloon is inserted, the balloon is inflated between carina and vocal cords and then detached. Last one is ultrasound image of the balloon in place. (B) Schematic drawing of cannula insertion towards the mouth with in upper corner the ultrasound image of the direction of the cannula. (Reprinted from Gucciardo *et al.*, 2008, with permission of the authors and Elsevier)

the balloon can be removed safely but also as late as possible. This occurs in one out of four patients, with the majority of those with ruptured membranes eventually delivering prior to 34 weeks. This is a serious limitation of FETO and also has logistic consequences for FETO treatment centers. They need to be permanently prepared to accept patients needing urgent removal of the balloon since occasional problematic balloon removals have been reported.

More than 75% of patients deliver beyond 34 weeks (mean GA at birth = 36 weeks), which is significantly more than the 31 weeks observed by Harrison *et al.* (2003a). This has an impact on survival, which is in the early period can be as high as 75%. Survival till discharge continues to be between 50 to 57% (Jani *et al.*, 2006c). Neonatal survival was higher with prenatal *versus* perinatal balloon retrieval (83.3% vs 33.3%; $p = 0.013$), a trend persisting till discharge (67% vs 33%; NS). Major predictors of survival are gestational age at delivery and lung size prior to FETO (Table 1) (Jani *et al.*, 2006c) In other words, fetuses with the smallest lungs are less likely to respond to fetal therapy than those with larger lungs. Apart from that, the individual increase in lung area or volume after FETO is an independent predictor of survival (Cannie *et al.*, 2008; Peralta *et al.*, 2008). Furthermore, the pulmonary vascular reactivity changes following FETO. Measurement of the reactivity to maternal hyperoxygenation following FETO shows the same trend (Doné *et al.*, 2006). Conversely, the inability

of the lung to respond to TO indicates that the neonate is likely to die from (persisting) pulmonary hypoplasia, which remains the leading cause of death. Most babies require patch repair, indicating the size of the defect in this selected group. Short term morbidity in survivors is actually better than expected from the severity of lung hypoplasia. We showed that it is comparable to that of cases with moderate pulmonary hypoplasia, who were expectantly managed (Jani *et al.*, 2007c). Data on longer term morbidities are being collected but it will be difficult to compare our observations, given the scarce survivors in the same severity group. To date we are only aware of one baby with severe developmental delay following TO.

DISCUSSION

Today most cases of CDH will be prenatally diagnosed during ultrasound screening. This should prompt referral to a tertiary care center familiar with this condition. There the fetal medicine specialists will not only rule out associated anomalies but also for isolated cases give an individual prognosis. This information should then be used in the multidisciplinary counseling process of the expectant parents. The modern techniques described here allow for an accurate prognosis in most cases, whereas in the past we were forced to use rather imprecise risk estimations, which often deprived the fetus the benefit

of the doubt. In contrast, today fetuses with a moderate lung hypoplasia can now rightfully be given a good prognosis when born in optimal conditions. At the other end of the spectrum the situation is more complicated, but at least several options are possible today. For cases with severe or extreme hypoplasia, minimally invasive fetal therapy can now be offered as an alternative to termination of pregnancy.

There are several unresolved issues with the current status of FETO. The procedure has proven its safety and reproducibility but the logistic consequences cannot be underestimated. The mother will have to travel (often internationally) to a center offering fetal surgery. She also must be willing to accept the risk and the consequences of rupture of the fetal membranes. We now strongly recommend that patients are in that case monitored close to or on campus, to constantly balance the advantages of keeping the airways occluded *versus* the need for acute removal of the balloon. For a number of reasons the balloon is ideally removed prior to birth, and this requires experienced hands until a novel, more reversible, occlusion device is designed.

The procedure certainly remains investigational, and we hope to establish appropriately designed and realistic trials. However, in the absence of standardized neonatal therapy, it would be methodologically ideal to manage patients on one or a few selected sites but patients and referring centers may be reluctant to agree to this, should be it would be possible to achieve funding. Medicolegal and ethical issues are also obstacles. One of these is that the prediction methods have become strongly validated and that fetuses which are currently eligible for FETO have very low predicted survival chances when expectantly managed. These may seem unacceptably low to parents. With growing experience, we are able to predict lung response and survival chances based on lung measurements *prior* to FETO. For extreme hypoplasia, FETO at 26–29 weeks, increases survival to 15% which certainly does not meet parent's expectations. The potential of earlier, mid-gestational TO or medical adjuncts, to yield a better lung response is currently being studied. What is even more challenging is that we have the potential of measuring the response *after* FETO. We have so far not introduced such information into our clinical algorithm, raising an even more thought provoking and ethical dilemma. Then there is also the debate on whether FETO should not be deferred to the saccular phase of lung development (>30 wks), which seems clinically to yield a lesser lung response, but reduces the consequences of iPPROM (Jani *et al.*, 2005; Deprest *et al.*, 2006; Kohl *et al.*, 2006). Furthermore, newer postnatal strategies are emerging to keep this disease a 'moving target' (Kunisaki *et al.*, 2007). Needless to say, we are at the crossroads where there are multiple options for trial design, and where conclusions may vary from continent to continent, or center to center.

ACKNOWLEDGEMENTS

The European Commission supports this work in its 6th Framework and the Marie Curie Fellowship Programme

(MEST CT2005 019707; EuroSTEC; LSHC-CT-2006-037409). J.J., L.G., T.V.M., E.D., P.K., V.B. and S.M. are recipients of a grant from the European Commission. A.D. is the recipient of a grant of the 'Klinisch Onderzoeksfonds UZ Leuven'. J.D. is the recipient of a 'Fundamental Clinical Researcher' grant of the Fonds Wetenschappelijk Onderzoek-Vlaanderen (1.8.012.07.N.02). The collaborating centers from the prenatal CDH registry group and our colleagues from the FETO-task force or referring doctors are acknowledged for their contribution.

REFERENCES

Ackerman KG, Pober BR. 2007. Congenital diaphragmatic hernia and pulmonary hypoplasia: new insights from developmental biology and genetics. *Am J Med Genet Part C Semin Med Genet* **145C**: 105–108.

Bagolan P, Casaccia G, Crescenzi, *et al.* 2004. Impact of a current treatment protocol on outcome of high-risk congenital diaphragmatic hernia. *J Pediatr Surg* **39**: 13–318.

Bielinska M, Jay P, Erlich J, *et al.* 2007. Molecular genetics of diaphragmatic defects. *Ann Med* **39**: 261–274.

Boloker J, Bateman D, Wung J, Stolar C. 2002. Congenital diaphragmatic hernia in 120 infants treated consecutively with permissive hypercapnea/spontaneous respiration/elective repair. *J Pediatr Surg* **37**: 357–366.

Broth RE, Wood DC, Rasanen J, *et al.* 2002. Prediction of lethal pulmonary hypoplasia: the hyperoxygenation test for pulmonary artery reactivity. *Am J Obstet Gynecol* **187**: 940–945.

Cannie M, Jani J, De Keyzer F, *et al.* 2006a. The use of Fetal Body Volume at Magnetic Resonance Imaging to accurately quantify fetal relative lung volume in fetuses with suspected pulmonary hypoplasia. *Radiology* **241**: 847–853.

Cannie M, Jani J, Dymarkowski S, Deprest J. 2006b. Fetal MRI: luxury or necessity? *Ultrasound Obstet Gynecol* **27**: 471–476.

Cannie M, Jani J, Dekeyzer F, *et al.* 2007. Lung response to fetal tracheal occlusion is better prior to 29 weeks than after. *Am J Obstet Gynecol* **197**: S161, (abstract 554 SMFM 2008).

Cannie M, Jani J, Van Kerkhove F, *et al.* 2008. Fetal body volume at MR imaging to quantify total fetal lung volume—normal ranges. *Radiology* **247**(1): 197–203.

Chiba T, Albanese CT, Farmer DL, *et al.* 2000. Balloon tracheal occlusion for congenital diaphragmatic hernia: experimental studies. *J Pediatr Surg* **35**: 1566–1570.

Coakley FV, Lopoo JB, Lu Y, *et al.* 2000. Normal and hypoplastic fetal lungs: volumetric assessment with prenatal single-shot rapid acquisition with relaxation enhancement MR imaging. *Radiology* **216**: 107–111.

Colby C, Lally K, Hintz S, *et al.* 2004. Surfactant replacement therapy on ECMO does not improve outcome in neonates with congenital diaphragmatic hernia. *J Pediatr Surg* **39**: 1632–1637.

Colvin J, Bower C, Dickinson J, Sokol J. 2005. Outcomes of congenital diaphragmatic hernia: a population-based study in Western Australia. *Pediatrics* **116**: 356–363.

Deprest JA, Evrard VA, Van Ballaer PP, *et al.* 1998. Tracheoscopic endoluminal plugging using an inflatable device in the fetal lamb model. *Eur J Obstet Gynecol Reprod Biol* **81**: 165–169.

Deprest J, Evrard V, Verbeken E, *et al.* 2000. Tracheal side effects of endoscopic balloon tracheal occlusion in the fetal lamb model. *Eur J Obstet Gynecol Reprod Biol* **92**: 119–126.

Deprest J, Gratacos E, Nicolaides KH. 2004. Fetoscopic tracheal occlusion (FETO) for severe congenital diaphragmatic hernia: evolution of a technique and preliminary results. *Ultrasound Obstet Gynecol* **24**: 121–126.

Deprest J, Jani J, Cannie M, *et al.* 2005. Progress in intra-uterine assessment of the fetal lung and prediction of neonatal function. *Ultrasound Obstet Gynaecol* **25**: 108–111.

Deprest J, Jani J, Gratacos E, Nicolaides K, The FETO Task Group, Nelson S. 2006. Deliberately delayed and shortened fetoscopic tracheal occlusion—a different strategy after prenatal diagnosis of

- life-threatening congenital diaphragmatic hernias. *J Pediatr Surg* **41**: 1345–1346.
- Di Fiore JW, Fauza DO, Slavin R, *et al.* 1997. Experimental fetal tracheal ligation reverses the structural and physiological effects of pulmonary hypoplasia in CDH. *J Pediatr Surg* **29**: 248–256.
- Dillon E, Renwick M, Wright C. 2000. Congenital diaphragmatic herniation: antenatal detection and outcome. *Br J Radiol* **73**: 360–365.
- Doné E, Jani J, Van Schoubroeck D, Debeer A, Deprest J. 2006. Maternal hyperoxygenation test in fetuses with prenatally treated severe diaphragmatic hernia: longitudinal observation study. *Am J Obstet Gynecol* **195**: (suppl. s21): 45.
- Downard CD, Jaksic T, Garza JJ, *et al.* 2003. Analysis of an improved survival rate for congenital diaphragmatic hernia. *J Pediatr Surg* **38**: 729–732.
- Flageole H, Evrard V, Piedboeuf B, *et al.* 1998. The plug-unplug sequence: an important step to achieve type II pneumocyte maturation in the fetal lamb model. *J Pediatr Surg* **33**: 299–303.
- Flageole H, Evrard V, Vandenberghe K, *et al.* 1997. Tracheoscopic tracheal occlusion in the ovine model: possible application in congenital diaphragmatic hernia. *J Pediatr Surg* **32**: 1328–1332.
- Flake A, Crombleholme T, Johnson M, Howell L, Adzick NS. 2000. Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: clinical experience with fifteen cases. *Am J Obstet Gynecol* **183**: 1059–1066.
- Gallot D, Coste K, Francannet C, *et al.* 2005. Antenatal detection and impact on outcome of congenital diaphragmatic hernia: a 12-year experience in Auvergne (France). *Eur J Obstet Gynecol Reprod Biol* **125**: 202–205.
- Gallot D, Boda C, Ughetto S, *et al.* 2007. Prenatal detection and outcome of congenital diaphragmatic hernia: a French registry-based study. *Ultrasound Obstet Gynecol* **29**: 276–283.
- Graham G, Devine PC. 2005. Antenatal diagnosis of Congenital Diaphragmatic Hernia. *Semin Perinatol* **29**: 69–76.
- Gucciardo L, Deprest J, Doné E, *et al.* 2008. Prediction of outcome in isolated congenital diaphragmatic hernia and its consequences for fetal therapy. *Best Pract Obstet Gynaecol* **12**(1): 123–138.
- Harrison MR, Bjordal RI, Langmark F, Knutrud O. 1978. Congenital diaphragmatic hernia: the hidden mortality. *J Pediatr Surg* **13**: 227–230.
- Harrison MR, Keller RL, Hawgood SB, *et al.* 2003a. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. *N Engl J Med* **349**: 1916–1924.
- Harrison MR, Sydorak RM, Farrell JA, Kitterman JA, Filly RA, Albanese CT. 2003b. Fetoscopic temporary tracheal occlusion for Congenital Diaphragmatic Hernia: prelude to a randomized controlled trial. *J Pediatr Surg* **38**: 1012–1020.
- Hedrick HL, Danzer E, Merchant A, *et al.* 2007. Liver position and lung-to-head ratio for prediction of extracorporeal membrane oxygenation and survival in isolated left congenital diaphragmatic hernia. *Am J Obstet Gynecol* **197**: 422.e1–4.
- Inamura N, Kubota A, Nakajima T, *et al.* 2005. A proposal of new therapeutic strategy for antenatally diagnosed congenital diaphragmatic hernia. *J Pediatr Surg* **40**: 1315–1319.
- Jani J, Gratacos E, Greenough A, *et al.*, The FETO Task Group. 2005. Percutaneous Fetal Endoscopic Tracheal Occlusion (FETO) for severe left sided congenital diaphragmatic hernia. *Clin Obstet Gynecol N Am* **48**: 910–922.
- Jani J, Benachi A, Mitanchez D, *et al.* 2006a. Lung-to-head ratio and liver position to predict neonatal morbidity in fetuses with isolated congenital diaphragmatic hernia: a multicenter study. *Am J Obstet Gynecol* **195**: (suppl. (S60)): 164.
- Jani J, Keller RL, Benachi A, *et al.* 2006b. Prenatal prediction of survival in isolated left-sided diaphragmatic hernia. *Ultrasound Obstet Gynecol* **27**: 18–22.
- Jani J, Nicolaides KH, Gratacos E, Vandecruys H, Deprest J, The FETO Task Group. 2006c. Fetal lung-to-head ratio in the prediction of survival in severe left-sided diaphragmatic hernia treated by fetal endoscopic tracheal occlusion (FETO). *Am J Obstet Gynecol* **195**: 1646–1650.
- Jani J, Cannie M, Peralta CFA, Deprest J, Nicolaides KH, Dymarkowski S. 2007a. Comparison of 3D ultrasound and Magnetic Resonance Imaging in assessing lung volumes in fetuses with congenital diaphragmatic hernia. *Radiology* **244**: 575–582.
- Jani J, Nicolaides KH, Benachi A, *et al.* 2007b. Timing of lung size assessment using the observed to expected lung area to head circumference ratio in the prediction of postnatal survival in fetuses with isolated diaphragmatic hernia. *Ultrasound Obstet Gynecol* **31**: 37–40.
- Jani J, Nicolaides K, Gratacos E, *et al.* 2007c. Short term neonatal morbidity in severe left sided diaphragmatic hernia treated by tracheal occlusion before 30 weeks. *Am J Obstet Gynecol* **197**: S162, (Abstract 558 SMFM 2008).
- Jani J, Nicolaides KH, Keller RL, *et al.*, On Behalf of the Antenatal-CDH-Registry Group. 2007d. Observed to expected lung area to head circumference ratio in the prediction of survival in fetuses with isolated diaphragmatic hernia. *Ultrasound Obstet Gynecol* **30**: 67–71.
- Javid P, Jaksic T, Skarsgard E, Lee S. 2004. Canadian Neonatal Network. Survival rate in congenital diaphragmatic hernia: the experience of the Canadian Neonatal Network. *J Pediatr Surg* **39**: 657–660.
- Khan A, Lally K. 2005. The role of extracorporeal membrane oxygenation in the management of infants with congenital diaphragmatic hernia. *Semin Perinatol* **29**: 118–122.
- Kinsella J, Dunbar I, Abman S. 2005. Pulmonary vasodilator therapy in congenital diaphragmatic hernia: acute, late, and chronic pulmonary hypertension. *Semin Perinatol* **29**: 123–128.
- Kinsella J, Parker T, Dunbar I, Abman S. 2003. Noninvasive delivery of inhaled nitric oxide therapy for late pulmonary hypertension in newborn infants with congenital diaphragmatic hernia. *J Pediatr* **142**: 397–401.
- Kohl T, Gembruch U, Tchatcheva K, Schaible T. 2006. Deliberately delayed and shortened fetoscopic tracheal occlusion—a different strategy after prenatal diagnosis of life-threatening congenital diaphragmatic hernias. *J Pediatr Surg* **41**: 1344–1345, (Letter).
- Kunisaki SM, Barnewolt CE, Estroff JA, *et al.* 2007. Ex utero intrapartum treatment with extracorporeal membrane oxygenation for severe congenital diaphragmatic hernia. *J Pediatr Surg* **42**: 98–104, discussion 104–6.
- Laberge JM, Flageole H. 2007. Fetal tracheal occlusion for the treatment of congenital diaphragmatic hernia. *World J Surg* **31**(8): 1577–1586.
- Metkus AP, Filly RA, Stringer MD, Harrison MR, Adzick NS. 1996. Sonographic predictors of survival in fetal diaphragmatic hernia. *J Pediatr Surg* **31**: 148–152.
- Moya FR, Lally KP. 2005. Evidence based management of infants with Congenital Diaphragmatic Hernia. *Semin Perinatol* **29**: 112–117.
- Muratore C, Kharasch V, Lund D, *et al.* 2001. Pulmonary morbidity in 100 survivors of congenital diaphragmatic hernia monitored in a multidisciplinary clinic. *J Pediatr Surg* **36**: 133–140.
- Nelson SM, Hajivassiliou CA, Haddock G, *et al.* 2005. Rescue of the hypoplastic lung by prenatal cyclical strain. *Am J Respir Crit Care Med* **171**: 1395–1402.
- Okuyama H, Kubota A, Oue T, *et al.* 2002. Inhaled nitric oxide with early surgery improves the outcome of antenatally diagnosed congenital diaphragmatic hernia. *J Pediatr Surg* **37**: 1188–1190.
- Ontario Congenital Anomalies Study Group. 2004. Apparent truth about congenital diaphragmatic hernia: a population-based database is needed to establish benchmarking for clinical outcomes for CDH. *J Pediatr Surg* **39**: 661–665.
- Peralta CF, Cavoretto P, Csapo B, Vandecruys H, Nicolaides KH. 2005. Assessment of lung area in normal fetuses at 12–32 weeks. *Ultrasound Obstet Gynecol* **26**: 718–724.
- Peralta CF, Jani J, Van Schoubroeck D, Nicolaides KH, Deprest JA. 2008. Fetal lung volume after endoscopic tracheal occlusion in the prediction of postnatal outcome. *Am J Obstet Gynecol* **198**(1): 60.e1–5.
- Rottier R, Tibboel D. 2005. Fetal lung and diaphragm development in Congenital Diaphragmatic Hernia. *Semin Perinatol* **29**: 86–93.
- Ruano R, Aubry MC, Barthe B, Mitanchez D, Dumez Y, Benachi A. 2006. Quantitative analysis of pulmonary vasculature by 3D- power Doppler ultrasonography in isolated congenital diaphragmatic hernia. *Am J Obstet Gynecol* **195**: 1720–1728.
- Ruano R, Benachi A, Joubin L, *et al.* 2004. Three-dimensional ultrasonographic assessment of fetal lung volume as prognostic factor in isolated congenital diaphragmatic hernia. *Br J Obstet Gynaecol* **111**: 423–429.
- Ruano R, de Fatima Yukie Maeda M, Ikeda Niigaki J, Zugaib M. 2007. Pulmonary artery diameters in healthy fetuses from 19–40 weeks gestation. *J Ultrasound Med* **26**: 309–316.

- Rypens F, Metens T, Rocourt N, *et al.* 2001. Fetal lung volume: estimation at MR imaging—initial results. *Radiology* **219**: 236–241.
- Sartoris J, Varnholt V, Dahlheim D, Schaible T. 2006. CDH in Mannheim—algorithm and results. *Monatsschr Kinderheilkd* **153**: 717.
- Skari H, Bjornland K, Haugen G, *et al.* 2000. Congenital Diaphragmatic Hernia: a meta-analysis of mortality factors. *J Pediatr Surg* **35**: 1187–1197.
- Smith N, Jesudason E, Featherstone N, *et al.* 2005. Recent advances in congenital diaphragmatic hernia. *Arch Dis Child* **90**: 426–428.
- Sokol J, Bohn D, Lacro RV, *et al.* 2002. Fetal pulmonary artery diameters and their association with lung hypoplasia and postnatal outcome in congenital diaphragmatic hernia. *Am J Obstet Gynecol* **186**: 1085–1090.
- Sokol J, Shimizu N, Bohn D, Dohert D, Ryan G, Hornberger LK. 2006. Fetal pulmonary artery diameter measurements as a predictor of morbidity in antenatally diagnosed congenital diaphragmatic hernia: a prospective study. *Am J Obstet Gynecol* **195**: 470–477.
- Stege G, Fenton A, Jaffray B. 2003. Nihilism in the 1990s. The true mortality of CDH. *Pediatrics* **112**: 532–535.
- Suda K, Bigras JL, Bohn D, Hornberger LK, McCrindle BW. 2000. Echocardiographic predictors of outcome in newborns with CDH. *Pediatrics* **105**: 1106–1109.
- Tonks A, Wyldes M, Somerset DA, *et al.* 2004. Congenital malformations of the diaphragm: findings of the West Midlands Congenital Anomaly Register 1995 to 2000. *Prenat Diagn* **24**: 596–604.
- Van Meurs and Congenital Diaphragmatic Hernia Study Group. 2004. Is surfactant therapy beneficial in the treatment of the term newborn infant with congenital diaphragmatic hernia? *J Pediatr* **145**: 312–316.
- Vitali Arnold. 2005. Bench-to-bedside review: Ventilator strategies to reduce lung injury—lessons from pediatric and neonatal intensive care. *Crit Care* **9**: 177–183.
- West S, Wilson J. 2005. Follow up of infants with congenital diaphragmatic hernia. *Semin Perinatol* **29**: 129–133.
- Williams G, Coakley FV, Qayyum A, Farmer DL, Joe BN, Filly RA. 2004. Fetal relative lung volume: quantification by using prenatal MR imaging lung volumetry. *Radiology* **233**: 457–462.