DEBATE

Current controversies in prenatal diagnosis 4: Should fetal surgery be done in all cases of severe diaphragmatic hernia?[†]

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INTRODUCTION

There have been several significant developments in prenatal care over the last 20 years that allow us to consider whether all severe cases of congenital diaphragmatic hernia (CDH) should have fetal surgical intervention. First, the introduction of routine fetal morphology ultrasound allows prenatal detection in approximately 60% of cases (Garne *et al.*, 2002). Second, the recognition of associated structural anomalies, chromosomal abnormalities, and genetic syndromes has improved and the centralization of the management to high-volume (<seven admissions/year) centers using consistent neonatal protocols has been shown to improve infant survival (Javid *et al.*, 2004). This has also given tertiary prenatal centers the opportunity to develop more reliable methods for determining high risk of pulmonary hypoplasia and predicting pregnancy outcome. Finally, surgical techniques have been pioneered that allow intervention through a fetoscopic approach, which involves less maternal morbidity, and these techniques have been successfully demonstrated. As we now have the ability to offer prenatal therapy, we debate whether it is appropriate to do this in all cases.

THE CASE FOR FETAL SURGERY, THE FETO-CONSORTIUM
J. A. Deprest

Whereas CDH with associated anomalies has a poor prognosis (mortality exceeds 80%), in cases with an isolated defect, neonatal survival is around 60–70%. Another way of interpreting this is that even in the best circumstances, 30% of the fetuses will not survive and are therefore candidates for prenatal intervention. The debate on fetal surgery can be summarized on three issues of controversy:

- The accurate determination of postnatal prognosis for fetuses with isolated CDH.
- The potential to improve outcome through fetal intervention without adverse effects.
- The validation of this 'experimental' fetal therapy.

Prognosis for infants with isolated CDH

The most common cause of death for neonates is ventilatory insufficiency and pulmonary hypertension caused by abnormal lung development. Several prenatal methods have been proposed to measure lung size and perfusion in order to predict neonatal outcome (Doné *et al.*, 2008). The best validated method so far uses the lung area to head circumference ratio (LHR) (Jani *et al.*, 2006a). It is the most reproducible and accurate when tracing the lung contours (Peralta *et al.*, 2005) and can be made independent of gestational age by expressing the ratio of observed/expected LHR (O/E LHR) (compared to gestational age matched controls) (Jani *et al.*, 2007b). There is also a correlation between O/E LHR and short-term neonatal morbidity (Jani *et al.*, 2008). An additional prognostic factor is the presence of liver herniation, which reduces survival by 25% (Jani *et al.*, 2006a). Although initial reports from the prenatal CDH registry suggested that liver position was an independent predictor of outcome, this was not substantiated in a second and larger study of 354 cases (Jani *et al.*, 2006a, 2007b). We as well as others continue to search for improved methods for the prediction of survival and serious morbidity (Gucciardo *et al.*, 2008).

Although some clinicians maintain that survival at large tertiary centers is higher, hence outcome cannot be predicted *in utero*, data from apparently unsuspected sources continue to describe survival rates around 70%, which in turn is related to either LHR and/or liver position (Sartoris *et al.*, 2006; Hedrick *et al.*, 2007; Yang *et al.*, 2007; Datin-Dorriere *et al.*, 2008). In the absence of convincing contradictory evidence, we continue to counsel patients about the expected outcome based on prenatal measurements (Figure 1). Based on those, fetuses with either extreme (lethal) or severe (survival <30%) lung hypoplasia are offered fetal surgery.

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Experimental rationale for prenatal intervention and early clinical experience

The aim of prenatal surgical intervention for CDH is to stimulate fetal lung growth. At present this is achieved through tracheal occlusion (TO) rather than *in utero* anatomical correction and closure of the diaphragm. The pathophysiology behind this concept is beyond the scope of this debate, but has been excellently summarized by Nelson *et al.* (2006) and Khan *et al.* (2007). Briefly, TO prevents egress of airway fluid, causing tissue stretch, which acts as a signal for lung growth. It increases lung-to-body-weight ratio, total lung DNA-content, and distal airway proliferation and matures pulmonary vasculature. Sustained occlusion reduces the number of alveolar type-2 cells, which can be alleviated by cyclical TO (Nelson *et al.*, 2005), but this is not technically feasible at present. The current prenatal strategy therefore involves a 'plug–unplug' sequence of TO followed by removal of the tracheal obstruction (Flageole *et al.*, 1998).

TO was initially performed by maternal laparotomy and fetal neck dissection but can now be safely done using percutaneous access under local or regional anesthesia (Flake *et al.*, 2000; Harrison *et al.*, 2003; Deprest *et al.*, 2004) (Table 1). It is a single 3.3 mm port procedure using a balloon to occlude the trachea. This avoids neck dissection, it will expand to accommodate tracheal growth and also makes reversal easier, either by fetoscopy or puncture. We insert the balloon at 26–28 weeks (the cannalicular phase of lung development) and remove it at 34 weeks (the saccular-alveolar phase of lung development). Patients delivering prior to this require emergency peripartum balloon removal, which necessitates availability of skilled clinicians around the clock. The fetoscopic endotracheal occlusion (FETO) task force (Deprest *et al.*, 2004) continued its program despite publication of the randomized controlled trial by Harrison *et al.* (2003), which did not show any benefit from prenatal TO. In that study, however, only three cases with O/E LHR < 27% (LHR < 1.0) and liver herniation were included, so the trial was inconclusive for this group. In our experience, involving now >150 cases, the survival rate associated with TO has been 50–57%, which is significantly better than that seen in controls matched for disease severity

(Jani *et al.*, 2005, 2006a, 2007b). No maternal complications have been reported but iatrogenic preterm rupture of the membranes occurs in approximately 20% of the cases; hence, early delivery remains a major obstacle. Despite this, ≥75% of patients deliver ≥34 weeks, comparing favorably to the earlier experience of Harrison *et al.* (2003). The best preoperative predictor of survival is the lung size prior to TO, suggesting that the larger the lung, the more vigorous the fetal response (Jani *et al.*, 2006b; Peralta *et al.*, 2008). Whereas the patch rate in survivors is high (indicative of the severity of the defect), short-term morbidity is better than expected (Jani *et al.*, 2007a). Long-term evaluation, including follow-up of neurodevelopment and tracheal function continues but overall morbidity appears to compare favorably with that reported using traditional postnatal management strategies.

Clinical validation of FETO

We recognize that FETO should be the subject of a proper clinical trial. A randomized trial in a single center would allow optimal standardization of both surgical and neonatal management but in the absence of a proper funding authority this is simply impossible in Europe. Several logistic, financial, medico-legal, and ethical obstacles have also stood in the way to date. We have now designed a more pragmatic trial to evaluate whether the addition of FETO to current neonatal management at European tertiary centers improves the outcome in selected cases. FETO will be offered at the task force centers and women will be requested to stay on campus while occlusion continues so that optimal facilities are available for balloon removal in an emergency. Following removal, patients will return to their referring tertiary centers where neonatal management will be standardized via a consensus protocol.

We have received unexpected resistance to the randomization of cases considered to have severe pulmonary hypoplasia (<30% chance of survival without prenatal intervention) both from parents and physicians. As an alternative, fetuses from this group will therefore all be offered FETO, but will be randomized to two different gestational ages for TO. The principal outcome measure of this trial will be survival at discharge. A second group of fetuses, that has moderate pulmonary

Table 1—Fetal surgery for CDH—trends in clinical experience

	Harrison *et al.* (2003)	FETO consortium (to 2008)
Criteria for surgery	LHR < 1.4 and liver 'up'	LHR < 1.0 and liver 'up'
Anaesthesia	General	Loco-regional or local
Access	Laparotomy 5 mm cannula	Percutaneous 3.3 mm cannula
Occlusive device	Clip most endoluminal balloon	Endoluminal balloon
Reversal of occlusion	EXIT delivery	*In utero* reversal
PPROM <34 weeks	100%	20%
Mean gestational age at birth	30.8 (28–34)	35 weeks (27–38)
Survival (overall)	77% (control: 76%)	50–55% (uncontrolled)[a]
Survival (LHR < 1.0)	33% (n = 3)	50–55%

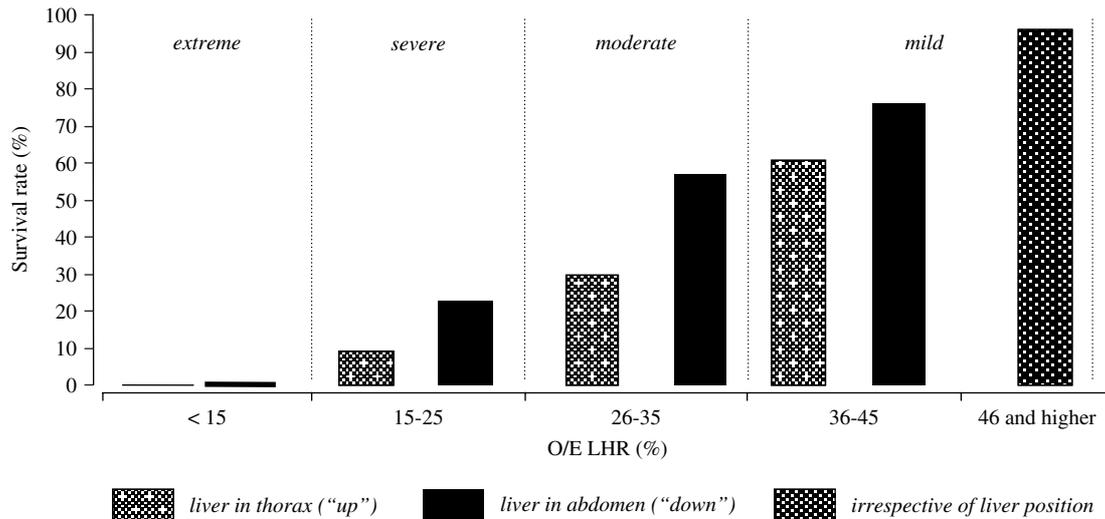[a] In the prenatal CDH registry, survival in this group is under 15%.

Figure 1—Survival rates depending on the observed/expected LHR and liver position based on data in the prenatal CDH registry. (From: Deprest *et al*., 2008; reprinted, with permission from Elsevier)

hypoplasia (predicted survival 30–60% without prenatal intervention) (Figure 1) will be randomized to either FETO or expectant management. The main outcome measures will include assessment of neonatal morbidity as we hypothesize that fetal intervention decreases bronchopulmonary dysplasia (the need for O_2 supplementation at 28 days) by 20%. FETO has indeed been shown to have several beneficial effects for pulmonary function including an improvement in alveolar-arterial oxygen difference and lung compliance in moderate hypoplasia and a reduction in bronchopulmonary dysplasia in severe hypoplasia (despite earlier gestational age at birth) (Keller *et al*., 2004; Jani *et al*., 2007a). The latter proposed trial will allay fears that studies have focused on mortality to date, whereas the morbidity in survivors is at least as relevant. Power calculations have demonstrated that these are realistic goals for assessment, and all now depends on the disciplined attitude of the fetal medical community not to offer FETO outside this or other trials to allow sufficient patient recruitment.

The so called 'Tracheal Occlusion To Accelerate Lunggrowth-trial (TOTAL trial) has now been approved and will start recruiting October 2008 (www.totaltrial.eu).

THE CASE AGAINST FETAL SURGERY
A. W. Flake

Justification for fetal intervention for severe CDH revolves around the following three areas of controversy:

What is the natural history of CDH?

The 'natural history' of CDH can be defined as 'The outcome that can be expected for *a population* of newborns treated by whatever is considered *contemporaneous optimal care* in the *environment* in which they are born'. From the perspective of the fetal surgeon, the population consists of fetuses diagnosed with isolated CDH that are referred for consideration of fetal surgery and are stratified by prenatal prognostic criteria to be 'severe'. Differences in population, contemporaneous optimal care, and birth environment make the natural history both variable and dynamic. Thus, the natural history is an evolving entity that needs to be updated continuously on an institutional basis (Flake, 1996). The impact that perceived natural history can have on evaluating CDH treatment was recently highlighted by the randomized, controlled trial performed at University of California, San Francisco (UCSF) for TO *versus* postnatal treatment (Harrison *et al*., 2003). In this trial, selection criteria that historically predicted 63% mortality were chosen. In the trial, 75% of the control group survived. In the intervening period, the 'natural history' had improved! Institution of parenchymal sparing management strategies such as permissive hypercapnia has improved CDH survival (Wilson *et al*., 1997; Boloker *et al*., 2002; Downard *et al*., 2003). Whereas in the 1980s and early 1990s, it was believed that up to 40% of CDH infants were destined to die from severe fixed pulmonary hypoplasia (Harrison *et al*., 1994), the current reality is that only approximately 10% of CDH infants have inadequate parenchyma to support survival and that the majority of mortality arises from 'reversible' pulmonary hypertension and iatrogenic barotrauma. In institutions achieving improved survival for CDH, the design of fetal intervention trials based on mortality endpoints has become increasingly difficult.

Can we identify those fetuses most likely to benefit from fetal intervention?

Prenatal prognostic parameters that have proven helpful in predicting severity of fetal CDH include liver position and lung volume measurements. Liver position is the most significant and reproducible independent determinant of outcome with liver herniation predictive of poor outcome (Albanese *et al*., 1998; Jani *et al*.,

2006a; Hedrick *et al.*, 2007). Lung volume measurements, whether indirect (LHR) or direct (MRI or 3D US) do not provide additional independent predictive value for mortality over liver herniation, but do provide confirmatory evidence of severity. In our most recent series, fetuses with liver up have a mortality of approximately 55% (Hedrick *et al.*, 2007). Thus our ability to predict mortality for an individual fetus with CDH, even with our best prognostic test is little better than 50/50, hardly adequate for selection of fetuses for fetal intervention. The ability to predict morbidity for an individual fetus is even less well defined. So at the present time, we cannot predict a 'most severe subset' of fetuses with CDH that are destined to die or have quality of life impacting morbidity without fetal intervention.

Can fetal intervention improve upon the natural history of severe CDH?

There have been waves of investigator enthusiasm in the prenatal treatment of CDH, spurred by encouraging results in animal models and early nonrandomized clinical results. In the late 1980s, there was enthusiasm for open repair of CDH until a prospective trial was performed demonstrating no efficacy for fetal intervention, particularly in severe patients with liver up (Harrison *et al.*, 1997). In the early 1990s, there was enthusiasm for TO as a prenatal approach to CDH. Once again, a prospective clinical trial of open TO performed at Children's Hospital of Philadelphia (CHOP) (Flake *et al.*, 2000) and a randomized trial of fetoscopic TO performed at UCSF (Harrison *et al.*, 2003) demonstrated no efficacy for TO. Particularly discouraging was the observation that even when excellent lung growth was achieved, the lungs functioned poorly. Subsequent follow up on survivors of TO in the UCSF randomized trial have shown no clinically significant difference in pulmonary function over control CDH patients treated conventionally (Keller *et al.*, 2004). In the CHOP study, detailed histological assessment of the lungs of nonsurvivors demonstrated no differences in lung morphology compared to control patients that died with severe CDH. Now in the early 2000s, there has been a series of optimistic publications from the Eurofetus group describing improved survival in nonrandomized series of CDH patients using single port balloon TO with and without release (Deprest, 2002; Deprest *et al.*, 2004, 2005, 2006a,b). The investigators have demonstrated that they can perform the technical maneuvers with remarkable finesse. They have demonstrated that an approximately 50% survival rate can be achieved in CDH patients selected by historical criteria to have a less than 10% survival. While these results appear impressive, the studies have cited control LHR data accrued from multiple institutions, including UCSF, many years ago (Jani *et al.*, 2008). More recently, they have stated results for contemporaneous controls but provide no data describing their control group. In summary, they have not defined the contemporaneous natural history for the population of patients that they are treating and they have not tested their approach by a randomized controlled clinical trial.

Until these basic standards are met, it is critical that the community at large maintain a healthy skepticism regarding TO for CDH. It is critical that European and US centers maintain their equipoise and cooperate to combine data and perform well-designed, randomized, controlled studies examining both morbidity and mortality endpoints before application of TO in severe CDH patients can be condoned.

SUMMARY

Several groups involved in fetal surgery now have the requisite skills for FETO but the widespread development of this intervention remains controversial. There are several fundamental areas of disagreement. Some of the American literature suggests that improvements in neonatal care have led to a fundamental shift in survival without fetal intervention. Despite the fact that some of these observations were made in 1997 (Wilson *et al.*, 1997), they do not seem to have affected more recent outcomes (Hedrick *et al.*, 2007; Datin-Dorriere *et al.*, 2008). Prospective datasets representing both regions are needed to establish whether these differences are real or related to local study bias. To some extent, this first area of disagreement is irrelevant if a subgroup of cases with severe disease and extremely poor prognosis can be confidently identified. Once again, there is considerable disagreement over this. Although both liver herniation and LHR seem to be prognostic, there is disagreement on whether they are independent predictors and for that reason the European trial will take both variables into account. It is expected that other methods, assessing volume of the lung or herniated liver as well as vasculature, may further refine prediction of outcome.

Although clinicians representing both sides of this debate call for a randomized controlled trial to resolve some of these issues, it is important to recognize that, due to the differences discussed earlier, they are not aiming to examine the same hypothesis. The European FETO study will not examine the issue of whether fetal intervention improves survival in the most severe group of cases. This may be left to American clinicians to examine. In the meantime, the European trial will answer important questions regarding the timing of the FETO procedure and will begin to address the issue of more widespread use of this technique with the aim of improving long-term morbidity as well as survival for affected infants. Both sides of the debate agree that in order to resolve these controversies, TO should currently not be performed outside of well-designed clinical trials.

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