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Technical aspects of fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia☆

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Abstract In isolated congenital diaphragmatic hernia, prenatal prediction is made based on measurements of lung size and the presence of liver herniation into the thorax. A subset of fetuses likely to die in the postnatal period is eligible for fetal intervention that can promote lung growth. Rather than anatomical repair, this is now attempted by temporary fetal endoscopic tracheal occlusion (FETO). Herein we describe purpose-designed instruments that were developed thanks to a grant from the European Commission. The feasibility and safety of FETO have now been demonstrated in several active fetal surgery programs. The most frequent complication of the procedure is preterm premature rupture of the membranes, which is probably iatrogenic in nature. It does have an impact on gestational age at delivery and complicates balloon removal. FETO is associated with an apparent increase in survival compared with same severity controls, although this needs to be evaluated in a formal trial. The time has come to do so.

Congenital diaphragmatic hernia (CDH) occurs sporadically, with an incidence of 1/2500 to 1/5000 of newborns, depending on whether stillbirths are included. The vast majority of cases are left-sided CDHs, whereas 13% are right-sided CDHs; bilateral lesions, complete agenesis, and other rarities comprise less than 2%. In approximately 40% of cases, there are associated anomalies. Their presence is an independent predictor of neonatal death, with less than 15% of babies surviving in this group. The majority are thus

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apparently *isolated*. Although CDH is a surgically correctable defect, it is the developmental arrest of both airway and vessels that causes problems in the postnatal period. Depending on the degree of pulmonary hypoplasia, neonates will experience severe respiratory insufficiency and develop pulmonary hypertension. Currently, 2 of 3 cases are diagnosed prenatally; the parents of an affected fetus should be referred to a tertiary care center experienced in assessing this anomaly and managing CDH in the perinatal period [1]. Based on a comprehensive diagnostic and prognostic assessment, parents will make their decisions [2]. There is still controversy regarding the natural history of this disease, which today may be difficult to define given that parents may request termination of the pregnancy. In utero referral to centers that offer highly specialized neonatal care may impact the survival rate [3-5]. The current mortality for prenatally diagnosed, isolated left-sided CDH is probably under or around 30% at tertiary care centers (Table 1).

1. Prediction methods

Prediction of mortality is crucial for attempting fetal intervention. Roughly speaking, this is based on estimation of lung size, the degree of liver herniation, and, increasingly, evaluation of the pulmonary circulation. We refer to recent reviews of the imaging methods used for this purpose [12,13]. These novel methods are still being validated, and currently fetal treatment programs still rely on the widest validated method for patient selection: the lung-to-head ratio, first described by Metkus et al [14]. It involves a 2-dimensional measurement of the lung area contralateral to the lesion, in proportion to the head circumference in the standard biparietal view. Because lung and head sizes do not increase equally during pregnancy, lung size measurement of the index case is better expressed as a function of what is expected in a gestational age control using a formula specific for the measuring technique and the side of the lesion [15-17]. This method has been validated in 354 fetuses with unilateral isolated CDH evaluated between 18 and 38 weeks' gestation, both in terms of mortality and morbidity (Fig. 1) [18]. Volumetry of both lungs should intuitively increase accuracy. Three-dimensional ultrasound is now widely available, but accurate imaging of the smallest, ipsilateral lung is not possible in more than 40% of fetuses [19]. Fetal magnetic resonance imaging (MRI) does not have this limitation and hence will probably become the method of choice for anatomical lung assessment [20]. Several studies have demonstrated a correlation between total lung volume and survival, as well as the need for extracorporeal membrane oxygenation [21,22]. Liver herniation, which in several studies has been shown to be an independent predictor, is another marker. Although it is identifiable by ultrasound, the degree of liver herniation can be quantified by fetal MRI [23]. Interestingly, the amount of herniated liver may be independent of lung volume. Lung vascularization can be assessed by looking at the number of branches, vessel diameters, flow velocimetry or volume, and reactivity to maternal oxygen inhalation, as recently reviewed by Claus et al [13]. Several studies have shown that the latter techniques may improve predictive accuracy [24-26]. At this time, most studies come from centers where severe cases are overrepresented, with some undergoing fetal intervention. Future studies by other groups will enable a more thorough validation. In summary, there is increasing evidence that the prognosis of an individual fetus with isolated CDH can now be made in a timely manner, which raises the question about use of fetal therapy in the most severe cases.

Table 1 Recent series on postnatal outcome of isolated CDH

	No. of cases	TOP rate	Survival rate
Stege et al [6]	185	N.R.	70%
Gallot et al [3]	314	7%	63%
Hedrick et al [7]	89	N.R.	66%
Datin-Dorrière et al [8]	99	20%	63%
Postnatal series			
Sartoris et al [9]	244	N.R.	70%
Mettauer et al [10]	147	N.R.	77%
Grushka et al [5]	121	N.R.	81%

Some units report survival rates after transfer of the neonate. These series therefore do not include the hidden mortality. TOP indicates termination of pregnancy; N.R., not reported. This table was adapted from Deprest et al [11].

2. Fetal surgery for CDH

The initial approach to CDH was anatomical repair, as demonstrated experimentally [27]. Clinical application of anatomical fetal CDH repair was abandoned once it became clear that it was not possible in fetuses with liver herniation and that those without did not benefit from the intervention [28,29]. Lung growth can also be triggered by tracheal occlusion (TO), as evidenced by several experimental studies. In brief, lung fluid production and fetal breathing movements stimulate lung growth and maturation. Occlusion prevents egress of lung fluid, increasing airway pressure, causing proliferation, increased alveolar air space, and maturation of pulmonary vasculature [30]. When TO is sustained, it reduces the number of type II pneumocytes and hence surfactant expression, which can be alleviated by in utero release ("plug-unplug sequence") [31]. TO was first clinically achieved by maternal laparotomy, hysterotomy, and fetal neck dissection and tracheal clipping [32]. The Philadelphia group with Flake et al [32] described a variable, at times explosive lung response, even prompting earlier delivery. The survival rate in that study was 33%, with the majority having serious neurological morbidity. The San Francisco team of Harrison et al [33] moved to endoscopic