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Results of Fetal Endoscopic Tracheal Occlusion for congenital diaphragmatic hernia and the set up of the randomized controlled TOTAL trial

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ABSTRACT

In isolated congenital diaphragmatic hernia, lung size and/or the position of the liver are predictive of neonatal outcome. Percutaneous Fetal Endoscopic Tracheal Occlusion (FETO) by a balloon can be undertaken to prompt lung growth in the worst cases. The feasibility and safety of FETO is no longer at stake, and it is associated with an apparent increase in neonatal survival. The gestational age at birth, the pre-existing lung size, the ability to remove the balloon prior to birth, and the lung response are predicting outcome. The most frequent complication is preterm premature rupture of the membranes, and as a consequence preterm delivery, which also complicates balloon removal. We have set up a randomized trial for the formal evaluation of FETO in Europe, including criteria for fetoscopy centers. Training of European as well as North American centers is taking place, so that the procedure could be safely and more widely offered.

1. Introduction

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 (LCDH), 13% are right sided (RCDH), and bilateral lesions, complete agenesis and other rarities comprise less than 2%. The presence of associated anomalies, which occurs in around 40%, is an independent predictor of neonatal death. In isolated cases, several tertiairy centers report a rate of survival till discharge of 70% or more (reviewed in [1]). Strategies of delaying surgical repair, for minimizing lung injury ('gentle ventilation'), tolerance of postductal acidosis and hypoxemia and adherence to specific ECMO criteria have a positive impact on survival [2,3]. The leading cause of death remains pulmonary hypoplasia and pulmonary hypertension. Survivors may have significant morbidities, of which the leading ones are pulmonary (including bronchopulmonary dysplasia, asthmatic symptoms and recurrent respiratory tract infections) and gastrointestinal (reflux disease, oral aversion, and growth problems) [4,5].

2. Prenatal assessment of prognosis

Prenatal diagnosis, which occurs in at least two out of three cases, provides the opportunity to refer the patient to a tertiary centre experienced in assessing and managing CDH in the perinatal period. A comprehensive differential diagnostic work up must be followed by an individualized prognostic assessment, so that parents can make decisions. Prediction methods are typically based on estimation of lung size by ultrasound and determination of liver herniation into the thorax. More novel methods (such as Magnetic Resonance Imaging (MRI)-volumetry or signal intensity analysis, the wide range of modalities to study the pulmonary circulation) certainly hold promise for increasingly more accurate prediction but are still being validated. In particular their combination may add to more accurate outcome prediction [6–9]. These methods are beyond the scope of this paper and were reviewed in [10]. We believe that over time fetal MRI will become the method of choice for anatomical lung assessment, but at this point in time there is no proof for superiority over ultrasound yet [11]. In a recent meta-analysis of currently available date we concluded that side of the defect, the position of the liver, and the

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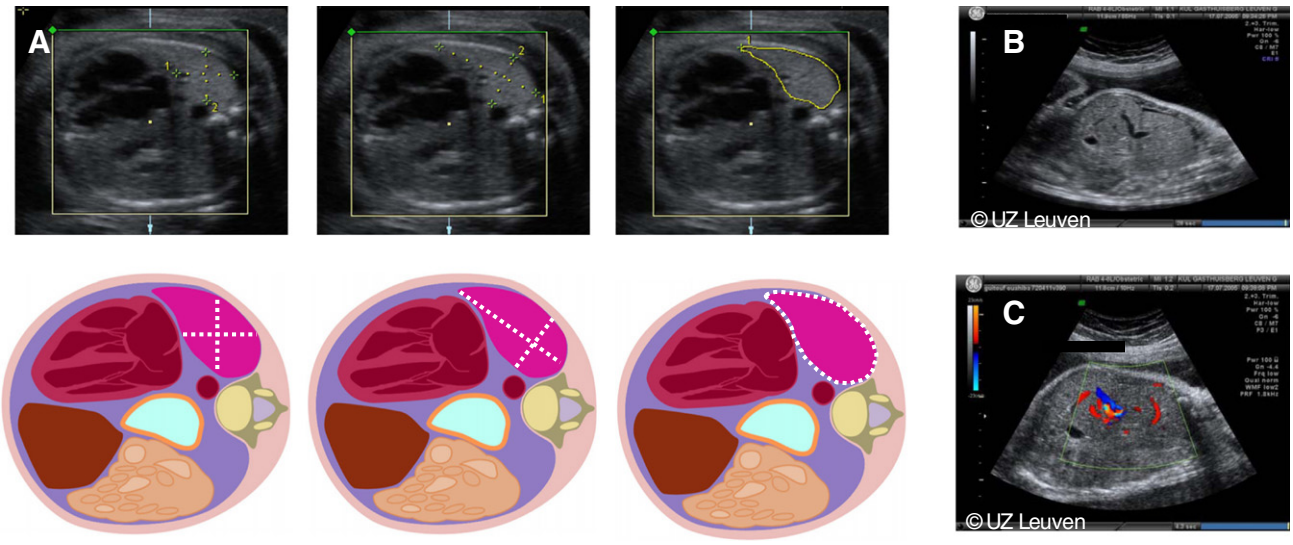

Fig. 1. (A) Schematic and ultrasound images demonstrating how the lung area can be measured. A cross section at the level of the four-chamber view of the heart is made and the contralateral lung is measured. Top row: ultrasound images from a fetus with a left-sided congenital diaphragmatic hernia at 27 weeks of gestation: (left) by multiplication of the anteroposterior (AP) diameter of the lung at the mid-clavicular line by the perpendicular diameter at the midpoint of the AP diameter; (middle) by multiplication of the longest diameter of the lung by its longest perpendicular diameter; and (right) by manual tracing of the limits of the lungs. These are reproduced, with permission from Wileys Publishers, from Jani et al., 2007; DOI: 10.1002/uog.4051 [15]. The far right panels depict how the position of the liver can be determined on a sagittal section (B), using Doppler to interrogate the course of the umbilical vein (C) reproduced from Claus et al. [10] with permission of the authors and Karger.

(observed/expected) total fetal lung volume as determined on MRI was predictive of outcome [12,43].

Again the widest validated prediction method is the use of the so called Lung-to-Head Ratio (LHR), first described by Metkus [13]. At the level of the four chamber view, the area of the lung contralateral to the lesion is measured. In order to assess the impact of pulmonary hypoplasia the lung area is divided by the head circumference measured in the standard biparietal view — which is not affected by the disease. Unfortunately over the years confusion has arisen about the exact method to do so. Peralta meanwhile demonstrated that the most accurate method for measurement of normal lung size is by tracing the lung contours rather than using its transverse or longest diameters [14] (Fig. 1). This was later confirmed by Jani et al. for fetuses with CDH [15]. Measuring the LHR may be difficult in case of CDH, so that a significant learning curve is present, as demonstrated by Cruz-Martinez et al. from Barcelona [16].

Peralta and co-workers from London defined reference ranges for the right and left lung area between 12 and 32 weeks of gestation. In that period the lung area increases 16-fold compared whereas the head circumference only 4-fold, demonstrating that LHR is actually *gestational age dependent*. For that reason, the LHR measurement of an actual index case is better expressed as a function of what is expected in a gestational aged control (observed [O]/expected [E] LHR). For that purpose, formulas are used, which are specific for the measuring technique, and the side of the lesion [10,14]. Also about these formulas there has been some confusion, as the sentinel paper of Peralta did actually not specify all the formulas for calculating the *expected* LHR (which was not the purpose of the paper), neither how gestational age was rounded up. Therefore we publish these formulas with permission of these authors in Table 1, as they are used now by the official calculator for the TOTAL trial available to all (access www.totaltrial.eu).

Anyway, the prognostic value of the O/E LHR later was validated in 354 fetuses with unilateral isolated CDH evaluated between 18 and 38 weeks gestation, both in terms of mortality and morbidity (Fig. 2) [17,18]. Also it has been shown that prediction is more accurate later in gestation [19]. Transcontinental validation of the relationship of O/E LHR and mortality is an important step when considering multicenter trials. The Toronto group reviewed their records and came to a very similar relationship between O/E LHR and survival [20].

Liver herniation is another marker, which in several studies has been shown to be an independent predictor. Though identifiable by ultrasound, fetal MRI can quantify the degree of liver herniation [16]. Interestingly, the amount of herniated liver may be independent of lung volume. Recent meta-analyses confirmed its prognostic value, next to that of LHR [21]. It remains uncertain whether liver herniation should be used as a single stratifier. In clinical decision making, both the LHR and the position are taken into account when predicting outcome (Fig. 2).

3. Prenatal intervention for CDH

As it is possible to prenatally detect which fetus is very likely to succumb in the neonatal period, one can identify the theoretical candidate for fetal therapy. We recently reviewed the history of fetal surgery for CDH, which started by anatomical repair through open access [22]. Today, the procedure clinically used consists in percutaneous Fetoscopic Endoluminal Tracheal Occlusion (FETO). The procedure is believed to work because it prevents egress of lung fluid, increasing airway pressure, causing proliferation, increased alveolar airspace and maturation of pulmonary vasculature [23]. In experimental conditions, sustained TO was shown to reduce the number of type II pneumocytes hence surfactant expression, which can be improved by in utero release ("plug–unplug sequence") [24]. Our group first described TO as an experimental endoscopic technique using an endoluminal device, which opened the door to a percutaneous, hence clinically acceptable technique [25]. This, together with the miniaturization of endoscopes, obviated the need for open surgery or mini-laparotomy (reviewed in [1]). Invasiveness was also reduced by moving away from general or loco-regional to a 10 min procedure under local anesthesia with fetal pain relief and immobilization [26]. Soon after the start of the program of the so-called "Fetal Endoscopic Tracheal Occlusion — Task Force" the results of the single-center N.I.H. sponsored randomized controlled trial (RCT) were published [27]. Survival rate after FETO was over 75%, which was no different from the (unexpected high) survival rate in the expectantly managed group. At closer look, the vast majority of patients had moderate pulmonary hypoplasia. With only three patients with an LHR <1.0 (corresponding around 26–29 weeks to an O/E LHR 25–27%), the trial