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Current and future antenatal management of isolated congenital diaphragmatic hernia

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A B S T R A C T

Congenital diaphragmatic hernia is surgically correctable, yet the poor lung development determines mortality and morbidity. In isolated cases the outcome may be predicted prenatally by medical imaging. Cases with a poor prognosis could be treated before birth. However, prenatal modulation of lung development remains experimental. Fetoscopic endoluminal tracheal occlusion triggers lung growth and is currently being evaluated in a global clinical trial. Prenatal transplacental sildenafil administration may in due course be a therapeutic approach, reducing the occurrence of persistent pulmonary hypertension, either alone or in combination with fetal surgery.

1. Introduction

Congenital diaphragmatic hernia (CDH) occurs in about one in 2500 births; therefore, in the EU-27, about 2100 babies with CDH are born annually. The defect is left-sided in 85% (LCDH), 13% are right-sided (RCDH), whereas the remainder are bilateral or have complete agenesis [1,2]. From the embryonic phase, abdominal organs herniate through the defect, interfering with lung growth, resulting in developmental arrest of both airways and vasculature. Hypoplastic lungs have fewer and less mature airway branches and impaired vascular development, including a smaller cross-sectional area of pulmonary vessels, structural vascular remodeling and altered vasoreactivity [3]. At birth, this results in respiratory insufficiency and persistent pulmonary hypertension (PHT), which cannot be solved simply by the surgical repair of the diaphragm. Despite improved and more standardized neonatal management, overall survival of neonates with CDH remains at around 70% [4]. PHT is a major cause of neonatal death and morbidity.

2. Antenatal assessment

Prenatal ultrasound identifies two out of three cases of CDH [5], providing the opportunity for in-utero referral to a tertiary care center for expert assessment and perinatal management. Additional genetic and morphologic assessment using ultrasound or magnetic resonance imaging may be used to rule out associated malformations [6]. For isolated cases clinicians can individualize prognosis to counsel parents about prenatal options. A detailed description of potential prognostic indices goes beyond the purpose of this review. Briefly, most of the prediction methods are based on lung size, liver herniation and pulmonary circulation, and more recently stomach position [7–12]. Ultrasound measurement of the lung-to-head ratio (LHR) is most widely used. It involves a standardized two-dimensional ultrasound measurement of the lung contralateral to the defect at the level of the four-chamber view of the heart. The observed LHR is expressed as a proportion of what is expected in a normal fetus of the same gestational age (o/eLHR), allowing prediction of prognosis independently of gestational age [7,13]. The combination of liver herniation and o/eLHR is currently used by prenatal management centers to stratify fetuses with LCDH and RCDH into groups with different increasing pulmonary hypoplasia and corresponding mortality rates (Fig. 1).

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Those with the worst prognosis may be offered intrauterine treatment.

Severity assessment by magnetic resonance imaging (MRI) theoretically has several advantages over ultrasound. Visualization is not limited by maternal habitus, amniotic fluid volume, or fetal position. Furthermore, MRI volumetric measurement of both lungs may better predict postnatal lung function. Volumetry may also accurately quantify liver and stomach herniation [15,16]. Though one may claim that MRI better predicts outcome than ultrasound [17], in clinical practice it may be difficult to prove [18].

Lung size and liver herniation also predict neonatal morbidity, such as the duration of assisted ventilation, the need for supplemental oxygen, the need for patch repair and the time it takes to full enteral feeding [19,20]. The literature on prediction of PHT is more limited (systematically reviewed in Ref. [21]). Several candidate parameters have been suggested in single case series, including lung size, presence of visceral herniation, and also direct assessment of the pulmonary vasculature, which may provide additional information.

3. Fetal therapy for CDH today

The ability to identify a future non-survivor prenatally prompts the quest for a prenatal intervention that can improve outcome. In fetuses with poor prognosis, fetal lung growth can be stimulated by fetoscopic endoluminal tracheal occlusion (FETO) with a balloon [9,22–24]. The concept “plug the lung until it grows” is inspired by clinical observations in fetuses with laryngeal atresia who have a markedly increased lung volume and alveolar number. Airway obstruction prevents egress of pulmonary fluid which experimentally has been shown to prompt lung growth by a mechanism of stretch of lung parenchymal cells [25]. Those experimental findings have been clinically translated into a percutaneous procedure without serious maternal morbidity (Fig. 2).

3.1. Technique for balloon insertion

We perform FETO under local anesthesia and sono-endoscopic guidance. First the fetal and placental position are determined for optimal trocar insertion. When necessary, the fetus is externally manipulated to enable a safe and effective access to the mouth. A neuromuscular blocking agent, fentanyl, and atropine are administered to the fetus for immobilization, anesthesia, and prevention of fetal bradycardia, respectively. A disposable, thin-walled flexible cannula, loaded with a pyramidal trocar or using the Seldinger technique, is inserted through the skin and myometrium, avoiding the placenta. Under ultrasound guidance the cannula is targeted to or above the fetal nose tip. Fetoscopic instruments specifically designed for FETO include a slightly bent 3.3 mm sheath loaded with a fiberoptic endoscope (1.3 mm; Karl Storz, Tuttlingen, Germany) and the balloon occlusion system (catheter loaded with a detachable inflatable latex balloon with an integrated one-way valve; Goldbal 2, Balt Extrusion, Montmorency, France). This balloon can accommodate an increasing diameter as the fetal trachea grows during pregnancy. It appears on ultrasound examination as a fluid-filled structure. Through the sheath we also pass a stylet and/or forceps to remove the balloon if wrongly positioned. Irrigation for clearing the operative field and improving visualization can be connected to the side port. Fetoscopic landmarks are the philtrum and upper lip, the tongue and raphe of the palate, uvula, epiglottis, and eventually the vocal cords. The endoscope is advanced into the trachea until identification of the carina, above which the balloon is positioned by inflation and detachment from the catheter. The median duration of FETO is 10 min (range: 3–93), dependent on both the experience of the operator and the position of the fetus [26]. A longer operation time is the main risk factor for membrane rupture.

3.2. Technique for balloon removal

Experimental data suggest benefit of temporary tracheal occlusion (“plug–unplug” sequence) by stimulating lung maturation [27,28], which prompted clinicians to attempt timely in-utero reversal as much as possible. Also clinical data suggest that prenatal balloon removal increases neonatal survival [22] and reduces neonatal morbidity [8]. Leaving the tracheal occlusion until delivery may provide additional lung growth and theoretically avoid the risk for preterm delivery from the second fetoscopic intervention of balloon removal [24,29]. Conversely, it may lead to more emergency removals at the time of birth, which are challenging and risky [30].

We therefore schedule elective intrauterine occlusion reversal at 34 weeks in patients with an uneventful postoperative course. We have used ultrasound-guided puncture, fetoscopic removal, tracheoscopic removal on placental circulation, and postnatal puncture. Ultrasound-guided in-utero balloon puncture is done after fetal immobilization and fetal analgesia. The lung fluid, which is at high pressure under the occlusion, pushes the punctured balloon into the pharynx, from where it is either swallowed or falls into the amniotic cavity. Tracheal patency may be confirmed by a change in tracheal diameter and flushing under ultrasound power Doppler examination. Fetoscopic removal is done with similar

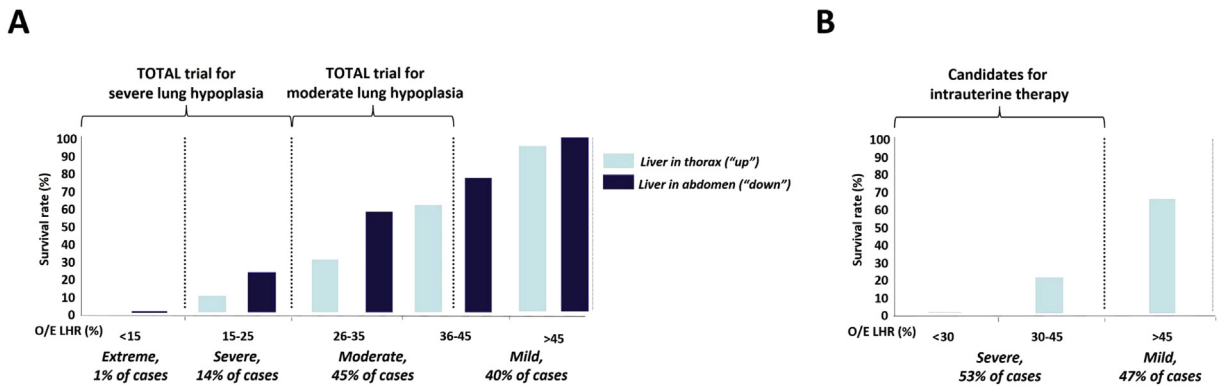

Fig. 1. Patient stratification and selection of candidates for intrauterine therapy according to the observed/expected lung-to-head ratio (O/E LHR) for left-sided (A) and right-sided (B) congenital diaphragmatic hernia. Adapted from Jani et al. [13] and DeKoninck et al. [14].

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