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EDITORIAL

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Pulmonary hypoplasia – size is not everything

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Pulmonary hypoplasia is a common problem in newborn infants. Wigglesworth and Desai reported an incidence of 14% in a series of perinatal autopsies [24]. Husain and Hessel found that 26% of foetuses, babies and infants (18 weeks gestation to 2 years of age) had pulmonary hypoplasia at autopsy when they used a combination of lung weight, post inflation radial alveolar count and histological assessment of lung maturity for diagnosis [14]. In this second series, pulmonary hypoplasia was considered to be the immediate cause of death in 22%.

Rarely, pulmonary hypoplasia may be primary, but in the vast majority of cases it is secondary to an underlying abnormality. The mechanisms responsible for lung growth are not completely understood, but it has been shown that a normal-sized and structured thoracic cavity, foetal breating movements, foetal lung liquid at positive pressure and normal amniotic fluid volume are prerequisites. Underlying abnormalities resulting in pulmonary hypoplasia can, thus, be divided into:

a. Space-occupying lesions in the chest, such as misplaced abdominal organs in congenital diaphragmatic hernia (CDH), congenital cystic adenomatoid malformation (CCAM) and pleural effusions
b. Malformations of the chest wall resulting in a small thoracic cavity, as may occur in some skeletal dysplasias
c. Oligohydramnios which may result from lack of functioning renal tissue (bilateral renal agenesis or cystic dysplasia), urinary outflow obstruction or prolonged premature rupture of the membranes
d. Neuromuscular disorders which prevent normal foetal breathing movements

In many of the conditions associated with pulmonary hypoplasia, the underlying abnormality is so severe that survival would not be possible even if the pulmonary hypoplasia could be corrected. However, there are some situations where pulmonary hypoplasia is the only abnormality, for example, when it is secondary to oligohydramnios due to prolonged premature rupture of the membranes or where the underlying malformation is amenable to surgical correction, such as diaphragmatic hernia. Current management relies on removal of a space-occupying lesion, if one is present, and supportive care is aimed at maintaining adequate oxygenation while pulmonary growth occurs. Despite the use of new technology, such as extra corporeal membrane oxygenation (ECMO) and new drugs, e.g. nitric oxide, there has been little improvement in the outcome for these infants. CDH is the most common malformation associated with pulmonary hypoplasia and paediatric surgeons have long been frustrated by the poor results following surgery, which are frequently due to the pulmonary hypoplasia rather than the hernia itself. It is tempting to think that, in these circumstances, an ability to correct pulmonary hypoplasia in utero would have a considerable impact on the overall prognosis.

Hypoplastic lungs have a decreased number of airway generations, with fewer and smaller peripheral airspaces than normal. Wigglesworth et al. [23] have reported that lungs which are hypoplastic as a result of oligohydramnios are, in addition, structurally and biochemically immature for gestational age. There is failure of growth and maturation of the peripheral parts of the acinus, delay in the development of the blood–air barrier, delay in epithelial maturation, lack of elastic tissue development and low concentrations of lung phospholipids. In contrast, lungs that are hypoplastic from all causes other than oligohydramnios usually have a structure that is appropriate for gestational age. The authors sugget that the maturation arrest which occurs with pulmonary hypoplasia due to oligohydramnios may be specifically related to failure to retain foetal lung liquid. However, other studies have shown no difference in the structure and maturity of hypoplastic lungs secondary to renal agenesis or dysplasia compared with those associated with other types of malformations [13, 18]. In animal models of CDH, the lungs are immature, hypocellular and surfactant deficient [7, 20]. However, the amniotic fluid lecithin/sphingomyelin ratio and phosphotidylglycerol levels showed no differ-

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ences among 18 human foetuses at 33–38 weeks of gestation with diaphragmatic hernia and published control values from uncomplicated pregnancies. The authors concluded that human babies with CDH are not surfactant deficient [21]. Wigglesworth et al. showed that the left lung in babies with a left-sided diaphragmatic hernia was surfactant deficient and less histologically mature than the right lung [23].

It has been observed that obstruction of the upper respiratory tract, such as occurs in laryngeal atresia, results in larger than normal lungs. This was confirmed by Carmel et al. who ligated the trachea of foetal rabbits in an experiment to demonstrate that the lungs produce liquid that is independent of the amniotic fluid. As an incidental finding, the authors also noted a marked increase in the size of the lungs following tracheal ligation [2]. Similar experiments have been carried out since, predominantly on foetal sheep. The issues that need to be addressed before a similar approach is used in a clinical setting are, first, whether the lungs will function normally (a large non-functioning lung is of no more use than a small non-functioning lung) and, second, the practical problems of in utero surgery. The latter includes prevention of pre-term labour and the development of an occlusve device that is reversible and non-traumatic to the trachea.

Animal experiments have shown that tracheal ligation results in dramatic growth of hypoplastic lungs and that, when the hypoplasia is secondary to surgically produced diaphragmatic hernia, the lung growth is sufficient to return the abdominal organs (stomach, intestines and spleen) to the abdominal cavity [4, 12]. Descriptions of the histology and morphometry of the lungs following tracheal ligation vary in the different reports. In all cases, the lungs are larger than controls with increased DNA but normal DNA/total protein ratio, indicating that the increased size is due, at least in part, to cellular proliferation. Some papers describe the lung histology as normal [4], others report slight increases in alveolar size and number [25, 11], but all describe the lungs as being mature, with thin alveolar septa, when compared with controls.

Assessment of lung function is less reassuring. One study showed normal total lung capacity but decreased functional residual capacity and decreased lung compliance [16]. Some foetal sheep have been ventilated for 1–2 h after delivery and achieved oxygenation comparable with the controls, but there are no reports of ventilation for a longer time [4, 12]. In another study, neither of two foetal sheep could maintain adequate oxygenation with unsupported respiration, following tracheal occlusion in utero and removal of the plug after delivery [19].

Biochemical analyses have shown that tracheal ligation does not increase biochemical maturity [12]. There is a decreased amount of total phospolipid including phosphotidylcholine, which is the most active component of surfactant, and levels were lower than in control animals with CDH but without tracheal ligation, i.e. tracheal ligation has an adverse effect on surfactant levels [16].

An article in this volume elegantly demonstrates that tracheal occlusion for more than 2 weeks in foetal sheep produces a significant reduction in the surfactant system [3]. Type 2 pneumocytes were decreased in number and showed degenerative changes which were thought to be irreversible after six weeks of tracheal ligation. The mechanism by which tracheal ligation causes lung growth has not yet been fully elucidated. It is postulated that it may be a combination of the raised pressure of the lung liquid since it is known that chronic drainage of foetal lung liquid results in pulmonary hypoplasia [1] and the presence of growth factors which are likely to be increased in concentration when the trachea is obstructed [4]. Gastrin-releasing peptide (GRP), which is thought to be a pulmonary growth factor, was found to be decreased by a factor of five in six cases of pulmonary hypoplasia associated with renal anomalies, three cases associated with hydrops and one case of CDH. However, GRP was similar to controls in a case of hypoplasia associated with Werdnig-Hoffman disease and markedly increased in a case of hypoplasia associated with exomphalos [5]. The same authors found that the growth fraction, as indicated by immunohistochemistry for Ki-67 in hypoplastic lungs of foetuses of greater than 24 weeks of gestation, was about 25% of that in normal controls but was normal before 24 weeks. They, therefore, suggest that successful intervention might be possible before 24 weeks [22].

Despite the problems encountered with tracheal ligation in experimental animals, it has been used in humans to treat CDH with pulmonary hypoplasia, and this has involved the development of reversible method of obstructing the trachea. Initially, a foam plug was inserted into the trachea using an endoscopic technique which also had the advantage that a hysterotomy was not required, theoretically reducing the risk of pre-term labour. However, this produced significant tracheal damage. Subsequently, a clip was used which did not appear to damage the trachea, but there are no long-term survivors to verify this. Eight human foetuses were operated on in the late second trimester [10]. In two, the lungs did not grow – presumably because the trachea was not completely occluded. There was one death in utero, 4 weeks after the trachea was clipped, and one foetus aborted 8 h after surgery. One baby developed a severe intraventricular haemorrhage, which led to hydrocephalus, and died when support was withdrawn. Three babies were delivered alive, long enough after tracheal obstruction for their lungs to have grown and their CDH to be repaired. Of these, one initially did well but died from postoperative complications following a Nissan fundoplication for recurrent aspiration pneumonia at 4 months of age. Another had his CDH repaired at 5 weeks of age, required 3 months of ventilatory support including ECMO, underwent a fundoplication for gastro-oesophageal reflux and was eventually weaned to nasal oxygen. However, a magnetic resonance imaging (MRI) scan showed cerebral atrophy and poor myelination which was presumed to be secondary to prolonged intensive care and he died when support was withdrawn. Both of these babies are

reported to have had normal lungs at autopsy, but no detailed description is provided. The one long-term survivor required tracheal stenting for 2 months for tracheomalacia caused by the tracheal plug and, despite some periventricular leucomalacia, was described as doing well at the age of 18 months. There is also a report of the use of tracheal occlusion with a clip to correct pulmonary hypoplasia associated with a right-sided diaphragmatic hernia. The clip was applied using open hysterotomy at 27 weeks of gestation and the baby was delivered at 32 weeks by elective Caesarian section. The hernia was repaired and he was extubated at 2 weeks of age. He was doing well at 4 months of age when reported [6].

The survival rate for CDH treated with surgical correction in the neonatal period is 65% (range 44–78%) in the latest series which all come from centres with ECMO [8]; therefore, only two survivors of nine attempts at in utero foetal tracheal occlusion in the published literature do not compare well. Open foetal repair of CDH has resulted in a 29% success rate in 14 patients [9].

There might be concerns about whether tracheal occlusion was likely to work since the voluminous lungs that develop in association with laryngeal atresia are morphologically abnormal with a structure that is very reminiscent of a CCAM. The similarity is such that it has been suggested that CCAM is secondary to localised bronchial obstruction [15], although not all would agree with this. A lung with the morphological appearance of a CCAM would not be expected to function well since the airspaces are larger than normal alveoli, separated from each other by relatively wide septa and there is not the close relationship between capillaries and air spaces that is present in the normal lung. However, naturally occurring laryngeal atresia is likely to have been present from the embryonic period, whereas tracheal occlusion for treatment of pulmonary hypoplasia secondary to CDH is carried out later in gestation. In addition to the gestational age at which the trachea is occluded, the length of time that the trachea is occluded is also important. Sufficient time is needed to allow pulmonary growth to occur (in the human foetuses, it was about 1 week between the tracheal occlusion and the identification of lung growth as determined by ultrasound scan), but not so long that damage occurs. In De Paepe's paper, irreversible degeneration of the type 2 pneumocytes had occurred by 6 weeks post ligation [3]. The two babies who died after tracheal occlusion for CDH and whose lungs were described as histologically normal had had the tracheal clips in place for 3.5 and 5 weeks. Unfortunately, there was no detailed description of the histology and no indication that morphometry or ultrastructural analysis of the type 2 pneumocytes was undertaken. The baby with the clip in the place for 3.5 weeks had a period of unsupported respiration, but the baby with the clip on for 5 weeks required ventilatory support of some type throughout his life.

Long-term chronic pulmonary morbidity related to pulmonary hypoplasia is beginning to appear since ECMO has allowed treatment of infants who would previously have died. Some now survive, dependent on mechanical ventilation, and it has been suggested that foetal therapy with tracheal occlusion might prevent this [8]. This may be the case, but I can only agree with the authors of the paper in this volume who conclude that a greater understanding of the pathophysiology of tracheal occlusion is required before there is widespread clinical application of its use. A previous paper by the same group showed that lung growth following tracheal occlusion depended more on the composition of the lung liquid than its pressure [17]. They, therefore, suggested that, if the mechanism by which tracheal occlusion affected pulmonary growth was better understood, it might be possible to avoid tracheal occlusion and, instead, act directly on the regulatory mechanisms to reverse or prevent pulmonary hypoplasia.

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