Pulmonary Effects of Prolonged Oligohydramnios following Mid-Trimester Rupture of the Membranes – Antenatal and Postnatal Management

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Key Words

Pulmonary hypoplasia · Persistent pulmonary hypertension of the newborn · Preterm prelabour rupture of the membranes · Oligohydramnios

Abstract

Mid-trimester, preterm prelabour rupture of the membranes (PPROM) with prolonged oligohydramnios remains a challenge for both obstetricians and neonatologists. Although survival rates have improved, morbidity remains common particularly due to pulmonary insufficiency and pulmonary hypertension. The aetiology of abnormal lung development is unknown but may depend critically on pulmonary vascular development. Antenatal evaluation of at-risk fetuses by three-dimensional ultrasound and MRI is possible but the techniques need to be further assessed. Antenatal corticosteroids given in cases of PPRM reduce the incidence of neonatal death, respiratory distress syndrome, intraventricular haemorrhage and necrotising enterocolitis without increasing maternal or neonatal infection. The true risk-benefit ratio of antibiotics, tocolysis and strategies to normalise amniotic fluid volume remains less clear. There is no consen-

sus regarding the optimal ventilation strategy to support infants with pulmonary insufficiency following PPRM, and further work is required to determine whether and which pulmonary vasodilators improve long-term outcome in these infants.

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Introduction

Mid-trimester preterm prelabour rupture of the membrane (PPROM) occurs in approximately 0.4–0.7% of pregnancies [1]. It is associated with poor foetal outcome due mainly to the high risk of very premature delivery. The mean gestational age at delivery following mid-trimester PPRM ranges from 23 to 27 weeks, and there may be a long latency of greater than 14 days membrane rupture prior to the delivery of the infant. Following a prolonged period of oligohydramnios, there is an increased risk of cord compression, joint contractures, skeletal anomalies and pulmonary hypoplasia. The neonatal outcome following prolonged preterm rupture of the membranes has improved over the last decades. Early

studies reported neonatal survival following rupture prior to 25 weeks to be 24% [2], whereas recent studies report increased survival rates of around 70% [3–5]. Despite the reduction in mortality rates, the morbidity remains high, with 40% of survivors developing bronchopulmonary dysplasia (BPD). Infants born following rupture of the membranes prior to 24 weeks and a mean latency to delivery of 45 days had a fourfold increased risk of a composite adverse outcome (death, severe retinopathy of prematurity, BPD and severe neurological injury) when compared to age-adjusted controls [6]. The aim of this review is to evaluate critically the evidence regarding mechanisms of abnormal lung growth in PPRM and the efficacy of antenatal and postnatal diagnostic and therapeutic interventions.

Lung Development following Oligohydramnios

Following a period of prolonged oligohydramnios during mid-gestation, a proportion of infants develop pulmonary hypoplasia. Their lung to body weight ratio and total lung DNA are reduced and the radial alveolar count is decreased [7]. The pulmonary vascular bed is reduced in size with a decreased vessel count and increased pulmonary vascular muscular development [8, 9].

Possible Mechanisms of Abnormal Lung Growth

Mechanical Effects – Lung Fluid Production

Adequate lung fluid is essential for normal lung development. Initial theories regarding pulmonary hypoplasia development in PPRM were that reduced amniotic fluid volume would be associated with increased chest compression, reducing foetal breathing movements and causing an outflow ('squeeze') of lung fluid from the foetus. Subsequent studies, however, failed to confirm this, finding either reduced amniotic fluid pressure [10] or no change in either the amniotic or tracheal pressure [11].

In the rat, tracheal ligation resulted in a distension of the foetal lungs and an increased expression of growth factors, including insulin-like growth factor 1, fibroblast growth factor 18 (FGF18) and connective tissue growth factor (CTGF), all vital for normal pulmonary growth. CTGF plays an important role in promoting alveolarisation and microvascular development in the later stages of foetal lung development [12]. It is theoretically possible therefore that a decrease in lung fluid may be associated with reduced production of these growth factors.

Foetal Breathing Movements

Foetal breathing movements are essential for normal lung growth. Decreased foetal breathing movements in the presence of prolonged oligohydramnios have been documented. This is likely to be multifactorial in origin and not purely as a result of thoracic compression from a lack of amniotic fluid. For example, cervical cord transection in the presence of oligohydramnios produced more severe pulmonary hypoplasia than cervical cord transection alone [13], suggesting that oligohydramnios independently affects lung development. In addition, PPRM is commonly associated with infection and inflammation, and these are known to reduce foetal breathing movements [14]. As well as gross breathing movements, fine peristaltic smooth muscle airway contractions have also been documented in the developing lung of various species [15], and these rhythmic contractions may create a flux of fluid in the lungs towards the distal lung buds. Therefore, both extrinsic and intrinsic muscle contractions in the lung create stretch and shear forces on foetal lung cells which have the capacity to regulate gene expression and alter both cell proliferation and differentiation (see below) [16].

Clinical studies of foetal breathing movements in pregnancies with prolonged oligohydramnios, however, have produced contradictory results. Some have identified the prolonged absence of foetal breathing movements as predictive for the development of pulmonary hypoplasia [17], whilst others have reported that foetuses affected by oligohydramnios spend significantly more time breathing than controls [11]. Foetuses have variable breathing efforts and may have periods of prolonged apnoea. Therefore, they should be observed over at least 2 h and on a number of occasions in order to determine reliably whether foetal breathing movements are present or not.

Transcription and Growth Factors

Foetal lung development is closely controlled by the sequential production of a large number of transcriptional regulators, and disruption of these has the potential to alter lung development. FGF and Sonic hedgehog play a role in determining the pattern of airway branching in mammalian lung development [18, 19]. The lungs fail to develop in knockout mice lacking FGF10 [20]. Structural lung development is closely coupled to, and dependent on, normal vascular development. Vascular endothelial growth factor (VEGF) is a potent regulator of lung vascular growth and development, and also plays a role in the differentiation of type II pneumocytes and surfactant

production [21]. Other factors implied in pulmonary vascular development include angiopoietins, endothelins and platelet-derived growth factor (PDGF); the latter is important in pulmonary vascular remodelling. Oligohydramnios induced in a rat model at the pseudoglandular stage of lung development resulted in reduced gene and protein expression of PDGF A and B, which was associated with smaller overall lung volumes and reduced alveolarisation [22].

In a study examining the expression of various proteins involved in angiogenesis in hypoplastic human lungs of various aetiologies, von Hippel-Lindau protein was expressed more frequently in the arterial smooth muscle cells of congenital diaphragmatic hernia (CDH) lungs but not in hypoplastic lungs following PPRM or renal agenesis [23]. Similarly, hypoxia-inducible factor-1 α expression was reduced within the vasculature of CDH lungs but not in the hypoplastic lungs of other aetiologies. This suggests that the mechanisms of disrupted lung development may differ according to the underlying aetiology.

Inflammation and Infection

There is a high incidence of both acute and subacute infection following prolonged rupture of the membranes, but it is unclear as to whether this is in part responsible for the relatively high incidence of BPD (40%) seen in these infants. In sheep models, endotoxin-simulated chorioamnionitis has been associated with a beneficial effect on lung maturation, increased epithelial surface area and airspace volume, improved compliance and increased surfactant production [24]. However, there is a detrimental effect on pulmonary vascular development such as smooth muscle hypertrophy of the distal pulmonary arterioles and decreased production of endothelial nitric oxide synthase, VEGF and platelet endothelial cell adhesion molecule-1 [25, 26]. These effects are likely to be mediated by cytokines such as interleukin-6 and tumour necrosis factor- α [27], and the vascular changes observed are similar to those in BPD and in severe pulmonary hypoplasia.

The clinical link between chorioamnionitis and BPD is uncertain. Wattenberg et al. [28] reported a higher incidence of BPD following chorioamnionitis, but there have been at least 18 subsequent studies investigating the relationship between BPD and chorioamnionitis and in those in which multivariate adjustment has been undertaken, no significant difference in BPD risk related to chorioamnionitis was demonstrated. In a recent case-control study, chorioamnionitis was associated with an increased risk of BPD but only if the infants subsequent-

ly developed postnatal infection or required mechanical ventilation for more than 7 days. This led the authors to postulate a 'double hit' theory for BPD development [29]. Therefore, the relatively high incidence of BPD in the context of prolonged oligohydramnios may be related to a combination of altered antenatal lung development, infection, inflammation and the effects of postnatal respiratory management.

Antenatal Prediction of Pulmonary Hypoplasia

A variety of reference ranges for normal lung biometry have been established using two-dimensional ultrasound, but none reliably predict pulmonary hypoplasia. More recently, three-dimensional ultrasound has been used to identify pulmonary hypoplasia in at-risk foetuses. In a recent series [30], a sensitivity of between 85 and 92% for predicting pulmonary hypoplasia was achieved when the results were adjusted for gestational age, estimated foetal weight and two-dimensional biometric measurements. In foetuses with varying risks of pulmonary hypoplasia such as those with CDH or anterior abdominal wall defects, the results of 3-D ultrasound significantly correlated with the durations of ventilation and supplementary oxygen dependency [31]. An MRI study demonstrated that foetuses exposed to PPRM had decreased lung volume measurements and decreased signal intensity in T₂-weighted images [32]. As well as reduced lung volume, these babies may also exhibit persistent pulmonary hypertension of the newborn (PPHN). Prediction of PPHN is difficult to assess before birth. Despite this, reduced diastolic and systolic velocities in the pulmonary arteries have been demonstrated by Doppler examination of foetuses affected by pulmonary hypoplasia [33], but measurements can be technically difficult in the absence of amniotic fluid. A combination of clinical, biometric and Doppler parameters may be most predictive in identifying lethal pulmonary hypoplasia. Although antenatal prediction may be useful in guiding management and counselling parents, it should be noted that a lethal outcome is also dependent on the postnatal management including intention to treat and level of neonatal care offered.

Antenatal Management

The management of mid-trimester PPRM centres on efforts to prolong safely the pregnancy in an effort to improve neonatal outcome [1], although this should be bal-

anced against a possible increase in risk of maternal morbidity. Potential complications include infection, thromboembolic events, and an increased incidence of both caesarean section and placenta accreta [34].

Surveillance of Infection

Clinical signs of chorioamnionitis and serum markers such as an elevated white cell count and an increased high-sensitivity serum C-reactive protein are used to identify infection. There is, however, a concern that intrauterine infection may predate the appearance of clinical and biological signs. For these reasons, it has been suggested that amniocentesis should be undertaken to identify infection at an early stage, either routinely at first presentation following PPROM or at the development of subtle clinical signs such as uterine sensitivity. Microbiological examination of the amniotic fluid, bacterial culture and a raised lactate dehydrogenase and decreased glucose in the amniotic fluid are used to identify if infection is present [35]. Amniocentesis, however, may provoke preterm birth, and sterile amniotic fluid does not exclude the possibility of choridecidual infection [36].

Antibiotic Therapy

Approximately 30–75% of cases of PPROM are associated with low-grade chorioamnionitis. Women with PPROM also have a higher incidence of abnormal colonisation of the lower genital tract than matched controls [37]. Studies therefore have been undertaken to determine whether antibiotics following PPROM might reduce the risk of foetal and maternal infection, prolong the pregnancy and improve neonatal outcome. In the ORACLE I study, the efficacy of erythromycin and/or amoxicillin clavulanate was compared to placebo in women with PPROM without overt signs of infection. Oral erythromycin following PPROM was associated with prolongation of pregnancy, less use of surfactant, lower proportions of infants being oxygen dependent at 28 days and 36 weeks post-menstrual age, fewer cerebral abnormalities and fewer positive blood cultures [38]. Follow-up data, however, did not show any significant differences in outcomes between the two groups [39]. Current American College of Obstetricians and Gynecologists' guidelines do recommend routine use of antibiotics following PPROM, but the short-term benefits need to be balanced against the lack of evidence for either long-term benefit or improved perinatal mortality.

Corticosteroids

Antenatal corticosteroids should be given to women presenting with PPROM prior to 32 weeks as they reduce the incidence of neonatal death, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis and the duration of respiratory support, without increasing maternal or neonatal infection [40], although the evidence for a beneficial effect below 26 weeks' gestational age is less clear [41].

Tocolysis

Therapeutic tocolysis may result in a slight delay before delivery allowing for the administration of corticosteroids, but a beneficial effect has not been demonstrated [42].

Normalising Amniotic Fluid Volume

Amnioinfusion

In small retrospective studies, serial amnioinfusions were not reported to have adverse effects. In those pregnancies in which the amniotic fluid index remained elevated for more than 48 h after amnioinfusion (approximately 25% of cases) [43], the outcome in terms of neonatal survival, incidence of pulmonary hypoplasia and neurological anomalies were better than if the oligohydramnios persisted [44]. Serial invasive procedures, however, increase the risk of infection or provoking bleeding; in the absence of positive results from randomised trials, this procedure cannot be recommended.

Amniopugging

Various agents have been used experimentally to re-seal the leak of fluid following spontaneous membrane rupture. Hydrogel sealant was applied successfully to the cervical canal in a case of prelabour rupture of membranes at 20 weeks of gestation [45]. Transvaginally applied intracervical fibrin sealant prior to 24 weeks of gestation resulted in increased amniotic fluid volume in 10 patients and apparent resealing in 2 patients from a total of 12 cases treated [46]. The use of gelatin sponge (Gelfoam) administered into the amniotic cavity in order to plug the cervical canal has been successfully used in cases of PPROM. The overall neonatal survival rate, however, was 40% [47]. Amniopugging has been used successfully following invasive foetal techniques. An amniopatch consisting of platelets and cryoprecipitate may be injected into the amniotic fluid [48], and the addition of platelets and plasma improved port site occlusion and repair following foetoscopy [49].

Promotion of Foetal Lung Growth and Development

In animal models, tracheal occlusion led to the build-up of lung fluid with gradual expansion of the lungs and increased lung growth [50]. Tracheal occlusion in fetuses with CDH increased lung growth and enhanced lung development [51]. In pregnancies with oligohydramnios due to PPRM, however, this procedure would be technically more difficult due to the reduced access and manoeuvrability at foetoscopy.

Retinoids, derived from vitamin A, are essential for normal lung development. They promote alveogenesis and induce alveolar regeneration. Administration of maternal retinoic acid in a nitrofen-induced CDH model promoted lung growth and alveogenesis [52]. The administration of retinoic acid in an 'oligohydramnios-induced' pulmonary hypoplasia rat model, however, did not have a positive effect on pulmonary growth or differentiation [53].

Tetrandrine is a bisbenzylisoquinolone alkaloid with a variety of antihypertensive, antioxidant and anti-inflammatory effects. In a CDH model, tetrandrine reversed foetal lung immaturity and normalised thickened pulmonary vascular walls. It also decreased the levels of transforming growth factor- β_1 which are raised in CDH models and have been implicated in the development of pulmonary hypoplasia [54]. No data are available related to its use in the context of prolonged oligohydramnios.

Neonatal Management

Diagnosis

In infants with pulmonary hypoplasia, lung function is abnormal at birth with reduced tidal volume, increased respiratory rate and reduced static lung compliance and functional residual capacity. The gold standard to confirm pulmonary hypoplasia is a lung to body weight ratio of less than 0.015 at postmortem [55] with reduced radial alveolar count or total DNA count [7]. Characteristic findings on the chest radiograph are of a small bell-shaped chest with raised hemi-diaphragms and clear lung fields, although 'clear lung fields' may be masked by radiographic signs of respiratory distress in prematurely born infants. A radiographic diagnosis may be supported by clinical findings of an infant unresponsive to ventilatory support and exogenous surfactant therapy. Echocardiography is an essential investigation both to confirm the diagnosis of PPHN and to guide subsequent management.

Management

A high level of neonatal intensive care is likely to be necessary, and delivery should take place, where possible, in a tertiary neonatal centre. Initial aggressive management should be attempted even if the infant shows signs of severe respiratory failure compatible with pulmonary hypoplasia. It is recognised that a subset of infants suffer from isolated PPHN, which responds well to immediate ventilatory and pulmonary vasodilator therapy with relatively few long-term complications [3, 56].

The optimal ventilatory management of infants born following prolonged oligohydramnios and exhibiting signs of pulmonary hypoplasia remains to be defined. There is a theoretical advantage of high-frequency ventilation (HFOV) amongst infants suffering from pulmonary hypoplasia, as it provides the possibility of optimal alveolar recruitment whilst reducing the risk of excessive barotrauma. Retrospective case series appear to show a beneficial effect of HFOV in the management of CDH [57]. The use of HFOV in the context of pulmonary hypoplasia following PPRM has not been formally evaluated, although a positive effect has been proposed in a number of retrospective reviews [3, 56]. In addition, there is evidence that HFOV augments the response to inhaled nitric oxide (iNO) in cases of PPHN [58].

Pulmonary hypertension is common in infants with pulmonary hypoplasia following PPRM. In some small case series, a short-term positive effect following administration of iNO therapy was highlighted [3, 59, 60]. A recent subset-analysis of the infants enrolled in the PiNO trial found that infants born with suspected pulmonary hypoplasia following PPRM who received iNO had a trend towards increased survival and a reduced incidence of BPD and IVH, but the numbers were too small to be subjected to meaningful statistical analysis [61]. Randomised studies are needed to assess the value of iNO and other pulmonary vasodilators in this group of preterm infants. iNO promotes distal lung growth in experimental models following hyperoxia exposure or specific VEGF inhibition [62, 63]. Prolonged low-dose iNO for the prevention of BPD has been explored in a general preterm population, but was found to be unsuccessful [64, 65]. There are case reviews describing the successful use of bosentan, milrinone and iloprost as alternative vasodilators in a preterm population [66–68], but further randomised controlled studies are necessary in order to define the value and safety of these more novel therapies in such a population.

Preterm infants born following mid-trimester PPRM may also suffer from respiratory distress syn-

drome, and 'conventional' surfactant therapy is indicated. Infants with severe pulmonary hypoplasia, however, may fail to show a positive response to surfactant therapy alone.

Due to the high incidence of neonatal infection following prolonged oligohydramnios, appropriate investigations should be undertaken, and treatment with broad-spectrum antibiotics is mandatory if an infection with an unknown pathogen is suspected.

Supplementation with vitamin A has a modest positive effect on both mortality and on the incidence of BPD (OR 0.93) [69]. The effect, however, has not been explored in infants with pulmonary hypoplasia following PPRM. Recent animal work suggests that the positive effects of vitamin A on lung growth septation and capillary growth are mediated by a reduction in elastin deposition and an upregulation of various vascular growth factors [70]. Further studies are needed to ex-

plore the efficacy of treatment in specific groups of prematurely born infants.

In conclusion, mid-trimester PPRM with a prolonged latency to delivery remains a challenge for both obstetricians and neonatologists. Despite improvements in neonatal outcome, mortality and morbidity remain high, and there are few long-term data for infants born in this context. Further research is needed in order to understand the pathophysiological mechanisms causing pulmonary disease and to identify optimal antenatal and postnatal management strategies.

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