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Two-year neonatal outcome following PPROM prior to 25 weeks with a prolonged period of oligohydramnios

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ABSTRACT

Background: Improved neonatal survival data have been reported following early preterm prelabour rupture of membranes (PPROM) prior to 25 weeks gestation with a prolonged latency to delivery and persistent oligohydramnios. However, data regarding long-term respiratory and neurological morbidity are lacking.
Aims: To evaluate the respiratory and neurological outcome data at two years of age in a cohort of infants born following PPROM prior to 25 weeks with a prolonged latency (14 days) to delivery and compare the data to an aged matched group of infants.
Methods: Retrospective case note analysis over a 43-month period at Saint Luc University Hospital, Brussels.
Results: 15 surviving infants born following PPROM were matched to a group of 30 control infants. Although there was no significant difference in the incidence of BPD between the groups (33% vs 27%, $p = 0.24$), the length of hospitalisation, duration of respiratory support and number of hospital readmissions for respiratory indications were all significantly higher for infants born following a prolonged period of oligohydramnios. There were no major anomalies on cranial ultrasound in the PPROM group and Baileys developmental assessment at 20–24 months corrected gestational age showed no difference between the two groups (Mental development index 93.9 vs 94.4 and Psychomotor development index 95.5 vs 95.8 respectively p = ns).
Conclusion: Neurodevelopmental outcome appears encouraging in this cohort although these infants are at high risk of prolonged initial hospitalisation and significant respiratory morbidity in the first two-years of life.

1. Introduction

Mid-trimester preterm prelabour rupture of the membranes (PPROM) is a complication which occurs in approximately 0.4–0.7% of pregnancies [1]. It is associated with a poor outcome due to the high risk of very preterm delivery and the risk of exposure to perinatal infection and inflammation. Mid trimester PPROM may be followed by a prolonged latency to delivery and specific complications attributed to a sustained period of oligohydramnios include pulmonary insufficiency, musculoskeletal anomalies, and an increased risk of cord compression around the time of birth [2]. The optimal management of pregnancies complicated by mid trimester rupture of membranes remains a challenge [3]. Whilst there is evidence regarding the benefit of the use of antenatal corticosteroids, the true risk–benefit ratio of other strategies aimed either at prolonging the pregnancy or restoring amniotic fluid volume remains unclear. Equally the optimal timing of delivery when the risk of prematurity is less than the risk of potential exposure to a harmful antenatal environment is unknown. Postnatal care is also controversial with no consensus regarding ventilation strategies and management of pulmonary hypertension in infants suffering from pulmonary hypoplasia. The use of specific therapies such as inhaled nitric oxide has been reported but value and the long-term outcome of this treatment needs to be clarified [4].

A number of clinical series published over the last decade have all shown a gradual improvement in neonatal survival to hospital discharge following pregnancies complicated by mid trimester PPROM. In the context of rupture prior to 25 weeks with a prolonged latency to delivery neonatal survival rates to hospital discharge are estimated to be around 70% [5–7].

Whilst survival to discharge rates appears to be encouraging, long term follow up is essential as it is possible that infants born following early PPROM with a prolonged latency to delivery are at higher risk of long-term neurodevelopmental and pulmonary sequelae than age matched preterm controls. The effects of exposure to antenatal inflammation and a high risk of chorioamnionitis preceding delivery are potentially deleterious to long-term outcome [8]. PPROM with a latency to delivery has also been identified as a risk factor for the development of cystic periventricular leukomalacia in preterm infants [9]. In addition to this, the use of novel therapies, such as inhaled nitric oxide, in a preterm population requires a close attention to long-term outcome.

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We published a retrospective review of neonatal outcome following rupture of the membranes prior to 25 weeks with a latency of over 14 days to delivery and persistent oligohydramnios that showed an overall neonatal survival to discharge of 73% [5]. Short-term neonatal outcomes are however a poor predictor of long-term morbidity and outcome. We have therefore evaluated the infants in our original study in an effort to assess both neurodevelopmental outcome and respiratory morbidity as compared to an age matched control group.

2. Methods

We conducted a retrospective case note analysis of all pregnancies delivered at a single tertiary centre (Saint Luc University Hospital, Catholic University of Louvain, Brussels, Belgium) presenting with pre-labour, mid trimester (18–24 + 6 weeks gestation) rupture of membranes over a 43-month period (January 2006–August 2009). All pregnancies had severe persistent oligohydramnios but those delivering before 24 weeks or before a latency of 14 days were excluded leaving a cohort of babies deemed to be at highest risk (pregnancies with confirmed oligohydramnios prior to 25 weeks and latency to delivery of over 14 days). All cases were delivered at our hospital.

An aged matched contemporary control group was established by selecting two control infants for each index case from the list of neonatal admissions over this time frame. The infants selected were those born chronologically closest to the index case within a gestational window of either 4 days prior to or 4 days after the gestational age of the index case. Outborn infants, infants from multiple gestations, those suffering from congenital malformations or born following rupture of the membranes for more than 5 days were excluded from the study.

2.1. Respiratory outcome

The primary outcome measure was the presence of moderate or severe bronchopulmonary dysplasia (BPD) at 36 weeks gestational age according to the NIH diagnostic criteria [10]. Moderate BPD was defined as a persistent oxygen requirement at 36 weeks CGA of less than 30% inspired oxygen and severe BPD was defined as the need for over 30% oxygen at 36 weeks CGA with or without either continuous positive airway pressure or positive pressure ventilation.

Total duration of respiratory support (CGA at which infant starts to breathe room air with no pressure support), length of initial hospitalization (length of stay, LOS) and number of hospital readmissions in the first two-years of life for respiratory indications were also recorded as secondary outcome measures.

2.2. Neurodevelopmental outcome

Primary neurodevelopmental outcome measures were cranial ultrasound scan (CUSS) findings during neonatal hospitalisation and neurodevelopmental assessment at the age of 20–24 months.

All infants born prior to 32 weeks are offered systematic follow up in our department and are seen by one of four attending neonatologists. Since 2008, standardized neonatal follow up for infants born prior to 32 weeks gestation is fully reimbursed by the Belgian health care providers. A multidisciplinary team consisting of a neonatologist, a psychologist, a paediatric neurologist, a physiotherapist and a speech and language therapist assesses such infants. Standardised tests performed at a CGA of between 20 and 24 months were assessed for the purposes of this study. The Baileys scale of infant and toddler development ®, third edition (Bailey-III®, BSID-III) was used for all formal neuro-developmental assessments. The BSID-III comprises two subscales: the mental development index (MDI) and the psychomotor development index (PDI). The BSID-III is scaled to a mean score of 100 (range 50–150) and a standard deviation of 15. An MDI and PDI score of >85 is considered normal, a score of >70–84 is considered a mild delay and scores of <69 are regarded as a sign of moderate to severe neurodevelopmental delay.

2.2.1. Statistical evaluation

Statistical analysis was performed using NCSS 2004 software (Kaysville, UT). All population variables assumed a Gaussian distribution and were analysed using an unpaired student T test. Categorical data were analysed using a Fisher's exact test. A p value of less than 0.05 was taken as statistically significant. Values are expressed as means and ranges with the exception of oxygenation indices that have been expressed as median and ranges.

3. Results

3.1. Patients

A total of 18 infants were born during the study period following an antenatal history of rupture of the membranes prior to 24 weeks and 6 days and with a proven period of sustained severe oligohydramnios (Amniotic fluid index<5) for a latency period of over 14 days. The detailed antenatal management of these patients is described in a previous publication [5].

Mean gestational age at PPROM was 22.4 weeks (range 18–24.8) and mean gestational age at delivery was 29 weeks (range 25.7–32.4 weeks). Mean latency to delivery was 48.1 days (range 14–84 days). Characteristics of index cases are detailed in Table 1.

Twelve (66%) of these infants showed signs of pulmonary hypoplasia at birth. All of these had severe hypoxic respiratory failure (median maximum oxygenation index was 42 — range 18.8–170) despite mechanical ventilation and surfactant therapy. All had a radiological picture consistent with pulmonary hypoplasia (small bell-shaped chest) and either cardio-echographic or clinical evidence (pre and post ductal saturation difference of >15%) of persistent pulmonary hypertension of the newborn (PPHN). Ten infants received inhaled nitric oxide therapy.

Two infants died of severe hypoxic respiratory failure at less than six hours of life despite maximal therapy. A further infant, born at 25 weeks and 5 days, died on day 77 of life following necrotising enterocolitis and overwhelming sepsis. The remaining 15 infants survived to hospital discharge. These 15 infants were matched to 30 control infants. Control and index patient variables are detailed in Table 2.

In the PPROM cases, 14 of the placentas were available for histological analysis and 6 of these showed signs of chorioamnionitis and three of these were culture positive (see Table 1). There was however only one case of confirmed neonatal infection.

Indication for delivery of the control infants are as follows: 7 (23%) were born for maternal indications (5 cases of pre-eclampsia, 1 mother with a cardiac condition and 1 following a road traffic accident), 3 (10%) were born following ante-partum haemorrhage, 5 (16.5%) were born following concerns regarding foetal growth, 7 (23%) were born following preterm labour with intact membranes, 1 (3%) infant was born in the context of maternal listeriosis and 7 (23%) were born following preterm rupture of the membranes for a maximum duration of 5 days prior to delivery. Placental histology and culture were available for six of the infants born following rupture of the membranes prior to delivery. There was confirmed histological chorioamnionitis in all six cases and culture was positive in two of these (one case of enterococcus and one of *Prevotella bivia*). There were no confirmed neonatal infections in this group.

A full course of foetal maturation by betamethasone was given to the mothers of all fifteen surviving infants in the prolonged PPROM group. In the control group, 16 (53%) received a full course of betamethasone, 6 (20%) received a single dose prior to delivery and 8 (27%) received no antenatal corticosteroid treatment ($p = 0.08$).