Early Human Development 85 (2009) 273–277

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Contemporary neonatal outcome following rupture of membranes prior to 25 weeks with prolonged oligohydramnios

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ARTICLE INFO

Article history:
Received 10 July 2008
Received in revised form 13 November 2008
Accepted 13 November 2008

Keywords:
Inhaled nitric oxide
Pulmonary hypoplasia
Preterm rupture of membranes
Oligohydramnios

ABSTRACT

Background: Prolonged oligohydramnios following early preterm prelabour rupture of membranes (PPROM) is traditionally associated with high neonatal mortality and significant risk of pulmonary hypoplasia. However, recent evidence points to an apparent improvement in outcome.
Aims: To document current neonatal outcomes following rupture of membranes prior to 25 weeks with severe persistent oligohydramnios and a latency to delivery of at least 14 days.
Methods: A retrospective case note analysis over a 28-month period at Saint Luc University Hospital, Brussels.
Results: From 23 pregnancies that were complicated by PPROM prior to 25 weeks, 15 infants were born after 24 weeks with a latency of more than 14 days and persistent oligohydramnios. Nine infants (60%) had severe respiratory failure and clinical signs compatible with pulmonary hypoplasia. Seven of these infants (78%) responded to high frequency ventilation and inhaled nitric oxide therapy with good clinical outcome but two died from severe respiratory failure. Five infants showed no clinical signs of pulmonary hypoplasia and responded to conventional neonatal management. One of these infants died at 77 days of age of necrotising enterocolitis. One infant was not resuscitated and died within minutes of birth, following prior discussion with the perinatal team and the parents. Survivors in this high-risk group (73%) had low morbidity at the time of discharge.
Summary: The favourable neonatal survival and morbidity figures are in keeping with recent published evidence. This study confirms improved outcome even amongst the highest risk infants with documented persistent oligohydramnios.

1. Introduction

Preterm prelabour rupture of the membranes (PPROM), particularly at very early gestations, presents a management problem for obstetricians and neonatologists alike with inherent risks to both mother and fetus. Obstetric management is in general one of "watchful waiting", involving monitoring for signs of developing infection, the administration of antibiotics and antenatal corticosteroids, the use of tocolytics and the delivery of the infant once an acceptable maturity is reached or if signs of infection develop [1–3].

Neonatal outcome following second trimester rupture has traditionally been poor with a number of published series quoting survival figures of between 20 and 55% [4,5] overall. The poorest outcomes (mortality>90%) have been recorded in infants following rupture of membranes prior to 25 weeks with a latency period to delivery of over 14 days and persistent confirmed severe oligohydramnios [6]. As a result of these figures some women may be offered termination of pregnancy in severe cases of preterm rupture of membranes. There are however more recent publications suggesting that neonatal outcome has improved [7,8]. This may be due in part to the increased use of antenatal corticosteroids, improvements in antenatal care and monitoring, as well as postnatal surfactant therapy and general improvements in neonatal intensive care. The risks to the infant following extremely preterm rupture of membranes are the risks associated with the gestation at which they are born with the added risks of infection, limb contractures, cord compression during labour and pulmonary hypoplasia. The presence of pulmonary hypoplasia is associated with a poor neonatal outcome. It is however increasingly recognised that a number of infants said to have pulmonary hypoplasia also have an element of reversible pulmonary hypertension that is sensitive to inhaled nitric oxide therapy [9,10].

We sought to document the neonatal outcome in this high-risk group of infants following PPROM between 18 + 0 and 24 + 6 weeks gestation, persistent severe oligohydramnios and a latency to delivery

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doi:10.1016/j.earlhumdev.2008.11.003

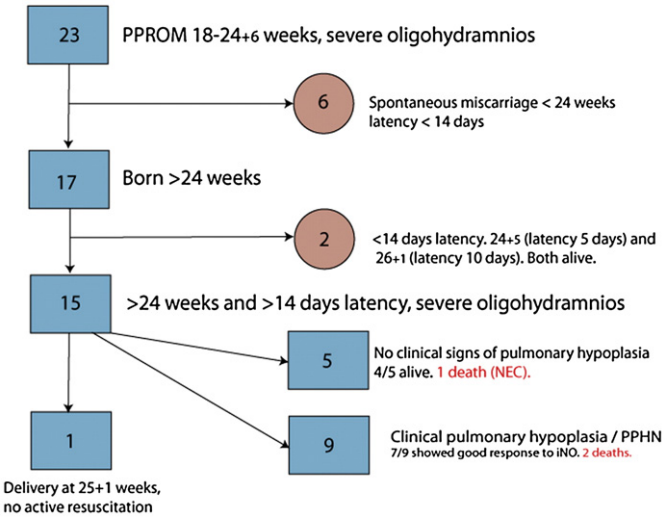

Fig. 1. Flow diagram representing all patients presenting with PPROM and severe oligohydramnios between 18–24 + 6 weeks.

of more than 14 days. Particular interest was paid to those infants who presented with severe hypoxic respiratory failure at birth including an assessment of the clinical response to inhaled nitric oxide and the short-term outcomes amongst this population.

2. Methods

A retrospective case note analysis of all pregnancies delivered at a single tertiary centre (Saint Luc University Hospital, Catholic university, Brussels, Belgium) presenting with pre-labour, mid trimester rupture (18–24 + 6 weeks gestation) of membranes over a 28-month period (January 2006–May 2008). 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 prolonged oligohydramnios prior to 25 weeks and latency to delivery of over 14 days). All cases delivered at our hospital. Primary outcome measures were neonatal survival to discharge and secondary outcome measures were presence of hypoxic respiratory failure due to pulmonary hypoplasia, presence of pulmonary hypertension and morbidity at time of discharge.

Statistical analysis was performed using Microsoft® excel® 2004 for Mac. All population variables assumed a Gaussian distribution and were analysed using an unpaired student's *T*-test. The values are expressed in means and ranges with the exception of the ventilation variables which are expressed as medians and ranges. A paired student's *T*-test was used to analyse the response to nitric oxide therapy with the values expressed as means, ranges and 95% confidence intervals.

3. Results

3.1. Patients

There were 23 pregnancies complicated by confirmed preterm prelabour rupture of the membranes (PPROM) between 18 weeks and 24 + 6 weeks during the study period. Six pregnancies miscarried rapidly (<14 days following rupture) before 24 weeks gestation and two infants were born after 24 weeks but before the latency period of 14 days. Both of these infants had a favourable neonatal outcome. Fifteen pregnancies therefore met the selection criteria of PPROM prior to 24 + 6 weeks gestation with confirmed persistent severe oligohydramnios and latency to delivery of over 14 days (Fig. 1).

3.2. Antenatal care

Gestation at membrane rupture was calculated using the date of the last menstrual period, confirmed and adjusted if necessary by first trimester ultrasound scan. All pregnancies up until rupture of the membranes were uncomplicated and ultrasound scans, when performed, had previously showed normal liquor volume. All patients were seen and scanned within 24 h of membrane rupture. Seven of the fifteen patients gave a history of possible leakage of fluid of up to one week prior to frank membrane rupture. Rupture of membranes was confirmed by visualisation of a pool of amniotic fluid in the vagina via vaginal speculum examination with confirmation of a ferning pattern on microscopy and a positive PROM test (Actim™ PROM test, Oy Medix Biochemica Ab, Kaunianen, Finland). Transabdominal ultrasound quantified the degree of oligohydramnios by measuring the amniotic fluid index (summation of the maximum vertical cord-free pool depths in centimetres in the four quadrants of the uterus). An amniotic fluid index of less than 5 was interpreted as severe oligohydramnios.

Patients were hospitalised with bed rest and treated with initial antibiotic therapy. In the presence of an accessible pool of amniotic fluid, a diagnostic amnioscentesis was attempted on admission in order to exclude infection. This was possible in 5 patients and in all five infection was ruled out. In two of these cases signs of infection were subsequently seen at the time of delivery 21 and 44 days later (patient 1 and patient 7, Table 1). Weekly ultrasound scans were performed to document amniotic fluid indices, fetal wellbeing and

Table 1
Antenatal characteristics of the patients who delivered after 24 weeks with persistent oligohydramnios and a latency period of over 14 days to delivery (CTG = cardiotocogram, NVD = normal vaginal delivery, LSCS = lower segment caesarean section).

Patients	Gestation at PPROM (weeks)	Tocolysis	Antenatal corticosteroids	Latency to delivery (days)	Mode of delivery	Indication for delivery	Confirmed neonatal infection	Placental histology	Placental culture
1	21	Atosiban/Ritodrine	no	29	NVD	Spontaneous labour	No	Chorioamnionitis	Negative
2	21 + 2	Ritodrine/Atosiban	yes	58	NVD	Spontaneous labour	No	Chorioamnionitis	Negative
3	21	Ritodrine	yes	64	LSCS	Spontaneous labour	No	Negative	Negative
4	23 + 4	none	yes	57	NVD	Spontaneous labour	No	Negative	Negative
5	22 + 5	none	yes	52	LSCS	Suspicious CTG	No	Negative	Negative
6	18 + 3	Atosiban	yes	79	NVD	Spontaneous labour	No	Chorioamnionitis	Enterobacter
7	22	Ritodrine	yes	44	LSCS	Suspected infection	Yes (*E. coli*)	Chorioamnionitis	*E. coli*
8	20 + 3	none	yes	84	LSCS	Spontaneous labour	No	Not available	Not available
9	24 + 1	Ritodrine	yes	46	LSCS	Spontaneous labour	No	Negative	Negative
10	19 + 6	none	no	44	NVD	Spontaneous labour	No	Chorioamnionitis	Enterococcus
11	23 + 5	none	yes	14	LSCS	Suspicious CTG	No	Negative	Negative
12	23 + 6	Ritodrine/Atosiban	yes	36	LSCS	Spontaneous labour	No	Not available	Not available
13	24 + 6	None	yes	21	LSCS	Suspected infection	No	Negative	Negative
14	23 + 6	Ritodrine	yes	19	NVD	Spontaneous labour	No	Negative	Negative
15	22 + 4	none	yes	48	NVD	Spontaneous labour	No	Not available	Not available

Table 2
Neonatal outcome.

Patient	Gestation at delivery (weeks)	Birthweight (gms)	Clinical evidence of pulmonary hypoplasia	Physical evidence of oligohydramnios	Outcome
1	25 + 1	960	Unknown, infant not resuscitated	None	Died day 1
2	29 + 4	1305	Yes	Joint contractures	Alive
3	30 + 1	1620	Yes	None	Alive
4	31 + 5	1890	Yes	Lower limb joint contractures	Alive
5	30 + 1	1220	Yes	None	Alive
6	29 + 5	1600	Yes	Joint contractures	Alive
7	28 + 2	1150	Yes	Joint contractures	Alive
8	32 + 3	2000	Yes	None	Alive
9	30 + 5	1825	Yes	None	Died day 1
10	26 + 1	650	Yes	Potter's facies and joint contractures	Died day 1
11	25 + 5	510	No	None	Died day 77
12	29	1250	No	Positional talipes	Alive
13	27 + 3	920	No	Positional talipes	Alive
14	26 + 4	980	No	None	Alive
15	29 + 5	1620	No	Positional talipes	Alive

fetal growth. Blood tests were undertaken on alternate days to monitor inflammatory markers (White cell count and C. Reactive protein), and were also taken if clinical signs suggestive of infection developed (uterine sensitivity, contractions, pyrexia). Fetal lung maturation by Betamethasone (Celestone ™, Schering Plough) was undertaken once the pregnancy was deemed to be viable (>24 weeks gestation). Weekly vaginal swabs were taken and antibiotic therapy was adapted according to the results.

In pregnancies where active infection was felt unlikely, on the basis of clinical and biological markers, tocolysis by ritodrine (Pre-Par™, Eumedica) or atosiban (Tractocile™, Ferring) was given. Amnioinfusion was attempted in 2 patients to confirm the clinical diagnosis of PPROM and was associated with immediate loss of the infused fluid. The antenatal details of the patients are described in Table 1.

3.3. Delivery

Delivery was at a mean gestational age of 28.8 weeks (range 25 + 1–32 + 3 weeks). Delivery was prompted in most cases by the onset of labour or a high clinical suspicion of infection. Babies that died were born significantly earlier than those that survived (mean 26.9 weeks, range 25 + 1–30 + 5 weeks vs 29.5 weeks, range 26 + 4–32 + 3, $p = 0.03$). However the difference in the duration of latency to delivery between non-survivors and survivors did not reach significance (mean 33.2 days, range 14–46 days vs 51.1 days, range 19–84 days respectively, $p = 0.07$) amongst the infants who died. Eight (53%) of the infants were delivered by caesarean section due to fetal malpresentation, signs of fetal distress or a high clinical suspicion of chorioamnionitis. Twelve of the placentas were sent for histological analysis and culture of which three (25%) were culture positive (see Table 2). There was one case of neonatal *E. coli* sepsis. In all cases of confirmed chorioamnionitis on the basis of histological studies and culture there were clinical signs of sepsis (maternal pyrexia, abdominal pains and raised inflammatory markers). The incidence of sepsis was not significantly increased in the group of infants who died.

3.4. Neonatal outcome

One infant, born at 25 + 1 weeks was not resuscitated at birth following discussion with the parents, this infant died within minutes of birth. The decision was based on the extreme prematurity, the period of prolonged oligohydramnios and a high clinical suspicion of infection. Placental histology confirmed florid chorioamnionitis with funiculitis.

Of the remaining 14 infants, 9 showed clinical signs compatible with pulmonary hypoplasia at birth. These signs were severe hypoxic respiratory failure that failed to respond to conventional treatment (ventilation and surfactant) with, in addition, a chest radiograph showing small lung volumes and a characteristic small bell shaped chest. Two infants died, one at 2 h of life and one at 6 h of life. Both of these infants showed severe intractable respiratory failure and persistent irreversible pulmonary hypertension despite maximal therapy (cardiac inotropes, high frequency oscillatory ventilation (HFOV) and inhaled nitric oxide). Oxygenation indices for these two infants were 170 and 112. An autopsy was performed on one of the infants confirming the presence of severe pulmonary hypoplasia (lung/bodyweight ratio <0.012).

Of the seven surviving infants with pulmonary hypoplasia, six were ventilated using HFOV (Sensormedics 3100 A, VIASYS healthcare, Yorba Linda, Ca, USA) and one using volume targeted pressure controlled ventilation (Babylog 8000+, Draeger Medical, Luebeck, Germany). None of these infants showed a positive response to surfactant therapy (Curosurf®Chiesi farmaceutici S.pA, Parma Italy. Mean dose 175 mg/kg, range 125–200 mg/kg), with mean airway pressures and inspired fraction of oxygen remaining the same before and after treatment. All of these infants showed clinical signs of persistent pulmonary hypertension (pre and post-ductal saturation differential of >15%) and signs of severe cardiac insufficiency. Four of the infants had cardiac echography prior to the start of nitric oxide therapy confirming supra-systemic right ventricular pressures, tricuspid regurgitation and right to left shunting. All infants required volume expanders within the first 6 h of life (mean 35 mls/kg, range 25–55 mls/kg), and all received inotropic support with dobutamine and dopamine. The seven infants were treated with inhaled nitric oxide started at a median start time of 2.5 h of life (range 0.5–12 h). The mean dosage used was 10.8 ppm (range 8–13 ppm) and duration of therapy was for a median time of 87 h (range 10–237 h). The mean oxygenation index prior to starting nitric oxide therapy was 49.1 (range 25–80), mean airway pressure was 16.8 cm H2O (range 15–19.4 cm H2O), and FiO2 was 1.0 in all cases. The immediate response to nitric oxide therapy is displayed in Fig. 2. This improvement was maintained allowing for progressive weaning of mechanical ventilation. Mechanical ventilation was continued for a median duration of 119 h (range 38–177 h). Supplemental oxygen therapy was required for a median duration of 33 days (range 7–88 days). Three infants had an oxygen requirement at 36 weeks gestational age but no infant was discharged on home oxygen therapy. Cranial ultrasound scans in these seven infants were consistently normal. The mean duration of hospitalisation was 68 days (range 44–106 days) with 2 infants discharged after their due date but prior to six weeks corrected age.

Five infants did not show clinical signs of pulmonary hypoplasia at birth. All had chest radiographs compatible with hyaline membrane disease. Three of these infants were ventilated using high frequency ventilation and responded well to surfactant administration

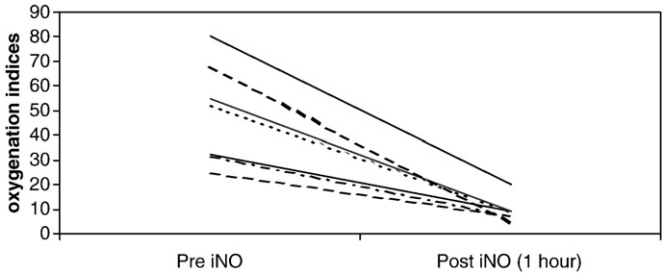

Fig. 2. Oxygenation indices prior to and 1 h after treatment with inhaled nitric oxide showing the significant improvement in oxygenation (mean oxygenation index prior to treatment 49.1 (95% confidence interval 33.9–64.3), post treatment mean 9.4 (95% confidence interval 5.7–13.1), $p = 0.001$).

Table 3
Amniotic fluid indices at various time points in relation to neonatal outcome.

	AFI at admission Mean (range)	Mean weekly AFI Mean (range)	Final AFI Mean (range)	Significance
No evidence of pulmonary hypoplasia ($n=5$)	1 (0–3)	2 (0–4)	0.6 (0–2)	ns
Surviving infants with pulmonary hypoplasia ($n=7$)	1.1 (0–4)	1.3 (0–5)	1.1 (0–5)	ns
Neonatal deaths due to respiratory failure ($n=2$)	0	0.9 (0–2.5)	0.9 (0–2.5)	ns

(Curosurf, mean dose 180 mg/kg, range 125–200 mg/kg). Two infants were treated with nasal CPAP (Infant flow™, Viasys Healthcare Yorba Linda, Ca, USA) from birth and did not require intubation. One infant, born at 25+5 weeks, died on day 77 of life following severe enterocolitis and overwhelming sepsis. This infant also had a subependymal haemorrhage on cranial ultrasound scan. The remaining four infants all had normal cranial ultrasound scans. One of the infants had an oxygen requirement at 36 weeks gestational age (supplemental O2 until 38 weeks gestational age) and all four were discharged from hospital prior to their due dates.

Further comparison of these groups appeared to show that the infants who had clinical signs of pulmonary hypoplasia were born following earlier rupture of membranes when compared to those who showed no clinical signs of hypoplasia but this trend did not reach clinical significance (mean 21.2 weeks, range 18.4–23.5 weeks vs. 24 weeks, range 23.7–24.8 weeks respectively, $p=0.07$). The latency to delivery was significantly longer in those infants with pulmonary hypoplasia (mean 62.5 days, range 44–84 days vs. 31 days, 14–48 days, $p=0.003$). Consequently the infants who showed no signs of pulmonary hypoplasia at birth were born at an earlier gestation (mean gestation of 27.1 weeks, range 25.7–29 weeks vs. 29.5 weeks, range 26.1–32.4 weeks, $p=0.05$) and with a non significant trend towards a lower birth weight (birth weight of 1056 g, range 510–1620 g vs. 1473 g, range 650–2000 g, $p=0.11$).

Eight of the 15 infants had physical evidence of prolonged oligohydramnios (joint contractures, positional limb deformities, Table 2). No infant required surgical correction of these deformities but all these cases required intensive physiotherapy and in some cases strapping of the feet. Given the small numbers no link could be made of the presence of physical deformities and neonatal outcome.

Amniotic fluid indices (AFI) were recorded on admission and then weekly thereafter until delivery. All of the pregnancies had confirmed severe oligohydramnios (AFI<5) throughout the period prior to delivery and there were no significant differences in AFI values between the different groups based on neonatal outcome (Table 3).

4. Discussion

Mid trimester rupture of membranes is traditionally associated with poor neonatal outcome with mortality rates following rupture of membranes before 28 weeks that have been documented to be in the region of 50% overall [5,6]. Neonatal mortality is increased with earlier rupture of membranes that results in a prolonged latency period with persistent oligohydramnios. The mortality for infants with rupture of membranes prior to 25 weeks and a latency period of over 14 days with severe oligohydramnios was found to be in excess of 90% in the study by Kilbride et al. in the mid 1990s [6]. It should be emphasised however that none of the infants in this study received prenatal corticosteroids, postnatal surfactant, HFOV or inhaled nitric oxide.

Our mortality and morbidity data are similar to those of two recent studies showing improved neonatal outcome. In all three studies, modern neonatal treatments including the use of HFOV and iNO were used when deemed clinically necessary. In the first study with similar inclusion criteria [7], survival to hospital discharge was 28/40 (70%) with no grade 3–4 intraventricular haemorrhage (IVH) and a 43% incidence of chronic lung disease (CLD) at 36 weeks gestational age. Amniotic fluid indices were not available in all cases and severe oligohydramnios was not a consistent feature. We observed a survival of 73% with no grade 3–4 IVH or periventricular leukomalacia (PVL) and an incidence of CLD at 36 weeks of 36%. Although the numbers included in our study were fewer, all our infants had weekly scans confirming persistent severe oligohydramnios. In the second study reporting outcome following rupture of membranes prior to 20 weeks gestation with severe oligohydramnios [8], neonatal survival was reported as 13/19 (68%) with 4/13 (31%) suffering grade 3–4 IVH or PVL and an incidence of CLD of 6/13 (46%). The authors reported a combined morbidity and mortality outcome of 15/19 (79%) that included death, IVH and CLD. Using similar criteria our combined morbidity and mortality outcome is 8/15 (53%). This difference may be explained by the fact that rupture occurred prior to 20 weeks and the mean gestational age at delivery was lower in this study. The improved neonatal outcome observed in these three series may be attributed to improved obstetric care, the widespread use of antenatal corticosteroids, the use of HFOV and inhaled nitric oxide [9]. The limitations of all three studies discussed are that they are retrospective, they include relatively small numbers of infants and they have been carried out over a large study period. Optimal management of this high-risk group of patients remains to be defined and therefore merits further evaluation in the setting of a randomised controlled trial.

The risk of pulmonary hypoplasia following mid-trimester rupture of membranes is estimated to be between 9–18%, with an increased risk following earlier rupture [5]. It is recognised after prolonged periods of oligohydramnios due to preterm rupture of membranes or fetal renal anomalies. The gold standard for diagnosing pulmonary hypoplasia remains the post-mortem findings of a ratio of the pulmonary weight to body weight of less than 0.015 (1.5%) [11]. In clinical practice the diagnosis may be made in an at risk infant suffering from hypoxic respiratory failure after birth with characteristic chest radiograph findings. Failure to respond to conventional management (mechanical ventilation and surfactant therapy) is common and airleaks may occur [12].

Pulmonary insufficiency occurring following prolonged oligohydramnios is not merely a consequence of the reduction in pulmonary volume but is also due to a degree of lung dysplasia [13]. There is a reduction in the number of alveoli and alterations in the production and differentiation of type 1 and type 2 pneumocytes. There are also associated changes in the pulmonary vasculature. These are characterised by an increase in smooth muscle proliferation, a thickening of the blood vessel walls as well as a reduction in the cross sectional pulmonary vasculature and an increased pulmonary vascular resistance [14,15]. These infants are therefore at high risk of pulmonary hypertension at birth that may be amenable to treatment with pulmonary vasodilators such as inhaled nitric oxide.

The use of nitric oxide in preterm infants with hypoxic respiratory failure remains a controversial area. There are theoretical concerns regarding potential effects on platelet aggregation and haemorrhage as well as concerns regarding the effects of superoxides and peroxynitrites on long-term lung development and lung repair mechanisms. In addition to this there is a lack of evidence regarding the long-term benefit of this therapy [16]. Despite this there is an increased amount of interest in the use of this therapy in this very specific high risk group of preterm infants with successful descriptions of its use described in a number of publications [9,10]. In our study we have shown that reversible severe pulmonary hypertension occurs in a number of infants described as having severe pulmonary hypoplasia on clinical criteria. The early use of nitric oxide is associated with immediate improvement in clinical parameters and would therefore seem justified in this group of infants who otherwise have a very high risk of mortality.

Given the fact that in pulmonary hypoplasia the lung volumes are smaller for a given body weight, it is a hypothetical concern that the volume of surfactant calculated by reference to an infant's weight may be too large for its small lungs resulting in flooding of the available air spaces. In our hospital we do not have a protocol to reduce the dose of surfactant in cases of suspected pulmonary hypoplasia and leave this to the clinical judgement of the attending neonatologist. Our infants received doses that ranged from 125–200 mg/kg but we did not observe a dose–response relationship.

Antenatal detection of the most severe cases of pulmonary hypoplasia remains difficult and we continue to rely on clinical criteria. Our results confirm those of previous studies that showed that early rupture and prolonged oligohydramnios are important risk factors for the development of pulmonary hypoplasia [5]. The infants who did not develop clinical signs of pulmonary hypoplasia in this series had later onset rupture of membranes and a shorter duration of latency to delivery. However, they were born at a consequently lower gestational age and were at increased risk of the complications of prematurity. Given that antenatal detection remains difficult, delivery should be planned and managed at an appropriate tertiary neonatal centre.

Suspicion of infection prompted delivery in a number of cases but was only confirmed by placental culture in three pregnancies and resulted in only one case of neonatal sepsis. This may be in part due to the usage of antenatal antibiotics but also suggests that, in pregnancies with a prolonged latency period, clinically evident infection is generally not the cause of rupture of membranes and that perhaps the risks of sepsis are not as high as we may imagine in this population. Interestingly, clinical evidence of infection was not observed in those infants without signs of pulmonary hypoplasia. Perinatal infection is an established independent risk factor for the development of persistent pulmonary hypertension [17] and may be an additional risk factor in these high-risk infants.

Although short-term outcome of the surviving infants in this study appears to be good and is encouraging, assessment of long-term neuro-developmental and pulmonary development in the years to come remains a better measurement of outcome and is currently being evaluated in our group of infants.

5. Conclusion

Neonatal mortality following rupture of membranes prior to 25 weeks gestation and a prolonged period of oligohydramnios has improved consistently over recent years. Survival with low short-term morbidity at the time of discharge in this high-risk group of patients was 73%. Antenatal detection of cases most at risk of pulmonary hypoplasia remains poor leaving clinicians to rely on the clinical criteria such as early gestational age of rupture and prolonged latency. In view of the high level of care necessary for these infants immediately following birth, delivery should be planned at an appropriate centre for all pregnancies complicated by mid-trimester rupture of membranes. A significant number of these infants show clinical signs of pulmonary hypoplasia but with an element of reversible pulmonary hypertension. The use of inhaled nitric oxide appears to be an essential tool in the management of this specific group of high-risk preterm infants and warrants further evaluation. This series adds to the evidence for improved outcome following early rupture of membranes and provides valuable information for antenatal counselling of patients.

Conflict of interest statement

The authors confirm that they have no conflict of interest to declare.

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