Inhaled nitric oxide therapy for hypoxaemic respiratory failure following preterm prelabour rupture of membranes

Infants delivered following a prolonged period of membrane rupture can often be critically unwell. In addition to concerns of prematurity and infection, they often display signs of respiratory failure. Classically it was understood that the respiratory failure was due to pulmonary hypoplasia and often these infants were given a grave prognosis. In this case series the authors demonstrate a marked improvement in respiratory function with the use of inhaled nitric oxide therapy. The findings are encouraging and suggest that the causative pathology is persistent pulmonary hypertension, which is potentially treatable and survivable.

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Key points

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1. Hypoxic respiratory failure is often seen in neonates following preterm, prelabour rupture of membranes.
2. In this group of infants the oxygenation index improves following administration of inhaled nitric oxide (iNO) therapy.
3. This suggests persistent pulmonary hypertension is the primary cause for respiratory failure in this group of infants, which is potentially treatable if iNO therapy is available.
4. Clinicians should consider arranging delivery in a unit where iNO therapy is immediately available.

Background

Preterm prelabour rupture of membranes (PPROM) complicates approximately 2% of pregnancies.[1] Optimal management of these pregnancies has always been a challenge but recent advances have improved neonatal survival. Approximately 70% of infants now survive following PPROM once the fetus reaches a viable gestation.[2,3]

Historically it has been understood that babies born after a prolonged period of oligohydramnios, secondary to premature rupture of membranes (PROM) at an early gestation, have pulmonary hypoplasia leading to severe respiratory failure. The Royal College of Obstetrics and Gynaecology guideline on PPROM lists the three main causes of subsequent neonatal death as prematurity, sepsis and pulmonary hypoplasia.[1]

In pulmonary hypoplasia the lungs are abnormally small and structural development is incomplete. The condition is not acutely treatable and is associated with a high mortality.

This study describes a case series of infants with history of PPROM who presented in the first few hours of life with severe hypoxic respiratory failure and evidence of persistent pulmonary hypertension (PPHN). Echocardiogram – often performed early to exclude congenital heart disease – is a useful tool for identifying PPHN via measurement of the regurgitation velocity across the tricuspid valve. Inhaled nitric oxide (iNO) is an established therapy for term infants with PPHN but literature concerning its use in the preterm population is limited.

Aim

The authors aim to show that the positive clinical response to iNO therapy suggests that the underlying cause of the respiratory failure in preterm infants following PPROM is predominantly PPHN rather than pulmonary hypoplasia.

Methods

A retrospective search of hospital records was conducted to identify preterm infants admitted to the Princess Royal Maternity unit over a three-year period who were born to mothers with PPROM (>24 hours) and received iNO therapy during their admission. Infants with a diagnosis of meconium aspiration syndrome were excluded.

One gestation and sex matched control without PROM was identified for each case to allow comparison of the clinical course. Each control was selected by identifying the next infant delivered in the maternity unit of the same gender and gestation period.

With the aim of predicting those infants that might develop respiratory problems, the maternal notes for each of the cases were reviewed. Maternal details for a group of infants born following PPROM who did not develop respiratory failure were also reviewed and formed a separate control group for this sub-analysis of the case

series. Again the women were selected by identifying the next infant born in the unit with PPROM for >24 hours who did not receive iNO therapy.

Results

Thirteen infants born to mothers with PPROM for >24 hours who received iNO therapy were identified in the three-year period: nine males and four females. Ten infants were delivered in the Princess Royal Maternity Hospital and three infants were unplanned transfers from other hospitals soon after birth.

TABLE 1 shows the gestational age at the time of membrane rupture, the gestational age at delivery and the latency period between membrane rupture and the onset of labour for each of the 13 infants.

The median duration of rupture of membranes was 40 days (range 2-102).

Therapy with iNO commenced within 0.5-21.0 hours of birth. Not surprisingly, those infants transferred from other neonatal units commenced therapy later than those born at Princess Royal Maternity Hospital (mean 12 hours *vs* 3 hours).

iNO was delivered via the INOmax delivery system. Local practice is to commence at 20 parts per million and maintain this dose for approximately 24 hours. Assuming that there has been a significant fall in the oxygenation index and a reduction or abolition of any difference in pre/post-ductal oxygen saturation (SpO_2), the treatment is then weaned over the next 1-2 days. Reduction is by multiple small decrements ensuring that there is <10% reduction in SpO_2 and/or <10% increase in the fraction of inspired oxygen (FiO_2) following each decrement.

The clinical response of each infant to iNO therapy is shown in **FIGURE 1**. As this was not a prospective study there were no set intervals for gases to be taken following initiation of therapy; the intervals between assessments of oxygenation index are variable. Sequential values are given to demonstrate that the response is sustained. In practice, for the majority of infants in this group the response to iNO was seen within a few minutes of initiation of treatment although there were some who had a slower response.

The number of days on any ventilation in the case series ranged from 1-53 days (median 7 days). For the control group, the days on ventilation ranged from 1-84 days (median 6 days). There is no significant difference in days on ventilation when compared to gestation-matched controls without PPROM using a Mann-Whitney U test.

An examination of the maternal notes revealed that ultrasound-diagnosed oligohydramnios was a more common antenatal finding in those infants who required iNO therapy following PROM than in those with PROM who did not have severe respiratory failure (89% *vs* 31%). A diagnosis of chorioamnionitis by pathology was also a more common finding in the case group (67%) versus the control (46%).

Designated case number	Gender	Gestational age at time of membrane rupture (weeks^{+days})	Gestational age at birth (weeks^{+days})	Latency period (hours)
1	Male	19	27^{+2}	1392
2	Male	24^{+1}	27^{+1}	504
3	Female	27	27^{+1}	47
4	Male	20	27^{+3}	1248
5	Male	25^{+3}	28^{+3}	504
6	Male	24	28^{+6}	824
7	Male	25^{+5}	26^{+1}	63
8	Male	27^{+1}	29^{+5}	435
9	Male	15	29^{+4}	2448
10	Female	20	26^{+5}	1137
11	Male	15	28^{+3}	2247
12	Female	18	29^{+1}	1872
13	Female	26	29^{+4}	598

TABLE 1 Key features of each of the 13 infants included in the case series. Latency is calculated to the nearest hour from the time of membrane rupture to the time of birth.

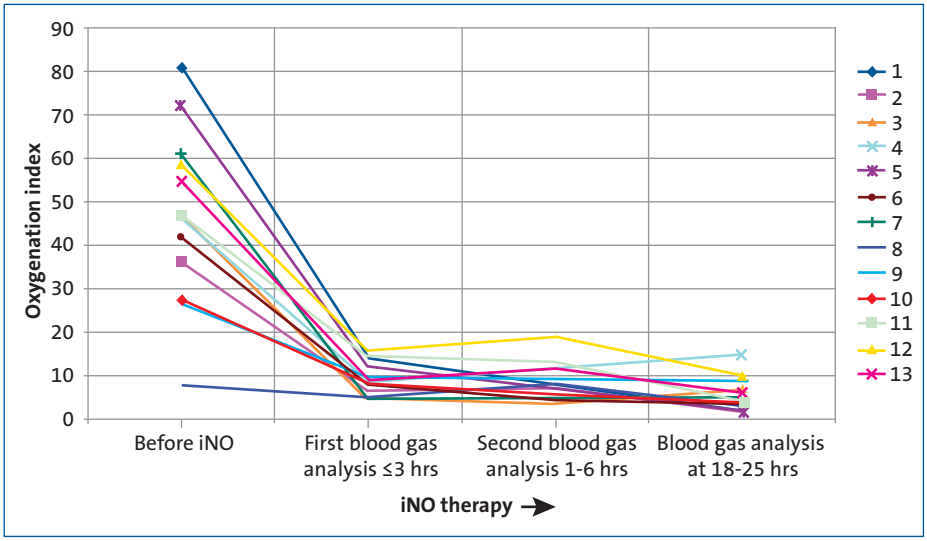

FIGURE 1 The clinical response to iNO therapy.

Discussion

This case series demonstrates a marked reduction in hypoxic respiratory failure (as indicated by the oxygenation index) in infants with severe respiratory failure following PPROM and oligohydramnios upon administration of iNO therapy. At a cellular level, an interesting study by Aikio et al demonstrated a reduction in the oxidative by-products of NO in infant airway specimens following PROM.[4] The reduction of native NO is likely to be a significant precipitating factor in the

development of hypoxic respiratory failure and would fit with the clinical improvement seen on administration of iNO.

The authors aimed to challenge the common understanding that hypoxaemic respiratory failure following PPROM is primarily due to pulmonary hypoplasia. If pulmonary hypoplasia was the primary pathology, a response to the introduction of iNO would not be expected.

The rapid reversal of the hypoxaemic respiratory failure on initiation of iNO therapy is supportive of a reversible process of PPHN rather than a more permanent structural abnormality. In addition, infants with pulmonary hypoplasia often require a significantly prolonged period of respiratory support and this was not a problem for the majority of the cohort.

A cohort study in the Netherlands reported that PPHN occurred significantly more in infants with PPROM from <20 weeks' gestation compared to those with PPROM >20 weeks' gestation.[5] This was not the case in the small cohort presented in this article where the majority had a history of PROM after 20 weeks' gestation. This may be because a number of pregnancies complicated by PPROM end in miscarriage or termination, which may account for the higher proportion of 'late' PPROM seen in this study.

A sub-analysis suggested that antenatal findings of oligohydramnios and chorioamnionitis may be more commonly associated with respiratory complications in the newborn infant. The authors compared only a small number of cases with one control for each; larger numbers may yield more convincing data and aid in the development of a predictive score for likely respiratory complications in the neonate.

Many women who experience PPROM and oligohydramnios at early gestations are still counselled that neonatal survival is unlikely due to pulmonary hypoplasia and their babies continue to be cared for in centres that do not offer iNO therapy. Some may still be offered termination of pregnancy based on the presumed grave outcome.

The authors wish to change this understanding and promote the use of iNO therapy following PPROM and oligohydramnios. They suggest that, where possible, mothers with PPROM and oligohydramnios should be delivered in a tertiary referral centre where iNO therapy is immediately available as the babies experience hypoxaemia very shortly after delivery. The alternatives to managing these infants without iNO therapy involve high pressure ventilation frequently associated with pulmonary barotrauma and pulmonary air leak. Infants requiring transfer to a tertiary unit *ex utero* may experience a prolonged period of hypoxia while transfer is arranged.

A case example is detailed in **FIGURE 2** that illustrates the potential morbidity associated with management of PPHN when iNO is not immediately available.

Baby X was delivered at 29 weeks' gestation due to concerns of maternal chorioamnionitis following a history of PPROM from 15 weeks' gestation. He was delivered in poor condition with Apgar scores of 2 and 7 at one and five minutes. He required significant resuscitation for poor oxygenation and was managed with high ventilation pressures. He developed bilateral pneumothoraces requiring chest drains. An echocardiographic assessment was consistent with pulmonary hypertension and transfer to a tertiary neonatal unit was arranged. His oxygenation index improved with the introduction of iNO upon arrival. He continued to have problems with recurrent pneumothoraces over the next few days requiring further chest drains. His iNO was weaned by day six and he was extubated to non-invasive respiratory support on day 12. His recovery was complicated by intraventricular haemorrhage and he subsequently developed post-haemorrhagic hydrocephalus requiring a ventricular tap. He was discharged home at 44^{+6} weeks' corrected gestational age and continues to have neurodevelopmental and neurosurgical follow-up.

FIGURE 2 Baby X: a case example.

Conclusion

In light of the above data, the guideline on the management of women with PPROM in the West of Scotland has changed. It is now recommended that women with early PPROM are re-booked in a tertiary unit. At present this only applies to women with PPROM at <24 weeks of pregnancy but there is an ongoing audit of cases of PPROM and PPHN with the aim of revising the criteria for referral to include PPROM at later gestations.

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