Risk Factors for Neonatal Bronchopulmonary Dysplasia in Extremely Preterm Premature Rupture of Membranes: A Retrospective Study

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Abstract

Background:

Determination of the optimal timing for termination of pregnancy in cases of preterm premature rupture of membranes (pPROM) during the extremely preterm period is still difficult. Bronchopulmonary dysplasia (BPD) is a major disease widely taken into account when determining the prognosis of respiratory disorders in a neonate. Many aspects of this disease remain unclear. With the aim of further improving the prognosis of neonates born to mothers with pPROM, this study examined cases who were diagnosed with pPROM before 28 weeks of gestation. The study analysed risk factors for neonatal BPD and the optimal timing for termination of pregnancy in pPROM cases.

Methods:

Subjects were 73 cases of single pregnancy who were diagnosed with pPROM during the period from 22 weeks and 0 days to 27 weeks and 6 days of gestation. The following factors were retrospectively examined: the gestational week at which a diagnosis of pPROM was made; the gestational week at which delivery occurred; the period for which the volume of amniotic fluid was maintained; and neonatal BPD as a complication. A receiver operating characteristic (ROC) curve was drawn in order to analyse the relationship between the duration of oligohydramnios and the onset of BPD.

Results

The mean gestational week at which a diagnosis of amniorrhexis was made was 24.5 ± 1.9 weeks (mean ± SD), and that at which delivery occurred was 27.0 ± 3.0 weeks. Fifty-seven cases (78.1%) were diagnosed with oligohydramnios, the mean duration of which was 17.4 ± 20.5 days. The mean birth weight of neonates was 1000 ± 455 g, of which 49 (67.1%) were diagnosed with BPD following birth. No neonates died in this study. Multivariate analysis of various risk factors for the onset of BPD indicated that oligohydramnios is an independent risk factor for BPD. The ROC curve indicated that the cut-off value was 4 days. In this case, the levels of sensitivity and specificity for predicting the onset of neonatal BPD were 0.941 and 0.917 respectively.

Conclusion

Our findings suggest that oligohydramnios is an independent risk factor for BPD in cases who are diagnosed with pPROM before 28 weeks of gestation.

Background

Premature rupture of membranes is associated with a high risk of chorioamnionitis (CAM) and is likely to cause oligohydramnios as a complication. This may lead to non-reassuring foetal status (NRFS) requiring early termination of pregnancy. However, in cases of preterm premature rupture of membranes (pPROM) during the extremely preterm period, it is difficult to determine the optimal timing for termination

of pregnancy due to the following two opposing factors: foetal development that can be achieved by prolonging pregnancy; and damage to the foetus due to infection. To date, no consensus has been reached on this issue (1).

Meanwhile, a large number of cases in which neonates born to mothers with pPROM were complicated by bronchopulmonary dysplasia (BPD) have been reported (2). Possible causes of neonatal BPD in pPROM cases include the underdevelopment of the lungs due to premature birth (3); the impact of CAM (4), and a decrease in pulmonary extensibility accompanying oligohydramnios (5). While it is considered that these causes are intricately interrelated, there is a dearth of research on predictors of BPD in cases diagnosed with pPROM during the extremely preterm period (less than 28 weeks of gestation).

This study retrospectively analysed the treatment results of cases who were diagnosed with pPROM before 28 weeks of gestation, and the prognosis of neonates following delivery, particularly the onset of BPD. The study aimed to elucidate predictors of BPD and accumulate primitive data that may contribute to clinical decision-making for cases who are diagnosed with pPROM before 28 weeks of gestation.

Methods

This study retrospectively analysed 73 single pregnancy cases diagnosed with pPROM during the gestational period from 22 weeks and 0 days to 27 weeks and 6 days. These cases were selected from 4833 cases who underwent delivery at our hospital from April 2013 to March 2018. From there, we limited the cases in which the maternal and neonatal course could be confirmed retrospectively.

The following patient background factors were analysed: mother’s age, previous delivery, delivery method (vaginal delivery or caesarean section), the administration of betamethasone to the mother, the gestational week at which a diagnosis of pPROM was made, time of delivery, oligohydramnios, and the presence of clinical CAM as a complication. Also, the following factors were analysed for perinatal prognosis: neonatal weight, APGAR score, umbilical arterial blood pH, small for gestational age (SGA) as a complication, neonatal death, use of mechanical ventilation management, neonatal sepsis as a complication, CAM stage in pathologic examination of the placenta, and BPD as a complication.

Diagnosis definition

The diagnosis of pPROM was made through a combination of the following methods: checking leaked amniotic fluid in speculum examination; basic pH testing; and quantitative testing for amniotic proteins. Oligohydramnios was defined as an amniotic fluid index (AFI) of less than 5 cm on transabdominal ultrasonography.

Blanc's classification (6) was adopted in staging CAM in the pathological examination of the placenta. The most severe stage in this classification is Stage III, which is defined as a case in which the presence of inflammatory cells in the amniotic membranes is observed in pathological examination.

Diagnostic criteria by the National Institute of Child Health and Human Development (NICHD) (7) were adopted in making a diagnosis of BPD. In other words, a diagnosis of BPD was made when the administration of oxygen at a fraction of inspiratory oxygen (FiO_2) > 21 was required for a duration of 28 days or longer.

pPROM treatment procedure

This section explains a treatment plan at our hospital for cases diagnosed with pPROM before 28 weeks of gestation. A blood test is performed when a case is diagnosed with pPROM. If it is confirmed that the mother is not complicated by clinical CAM, details of which are given below, a total of two doses of 12 mg of betamethasone will be administered to the mother every 24 hours. Ritodrine hydrochloride, magnesium sulphate or a combination of these will be consecutively administered as a tocolytic agent. For antibiotic therapy, 6 g/day of ampicillin/sulbactam (ABPC/SBT) will be administered for one week following the diagnosis of pPROM. The well-being of the foetus will be evaluated on NST two to four times a day. The patterns of foetal heart rate will be evaluated each time. The mother will be required to rest in bed, and an indwelling urinary catheter will be inserted. The mother will be closely monitored for deep venous thrombosis if she is required to rest in bed for an extended period of time. Provided that pregnancy can be prolonged by approximately two weeks, the level of rest may be increased. Foetal ultrasonography will be performed weekly to evaluate the growth of the foetus; transabdominal ultrasonography will be performed twice weekly to evaluate the amount of amniotic fluid.

The early delivery of the foetus will be determined in the following cases: 1. diagnostic criteria for clinical chorioamnionitis are met; or 2. a diagnosis of NRFS is made based on foetal heart rate monitoring. Criteria by Lencki and colleagues (8) will be used when making a diagnosis of clinical chorioamnionitis. According to the criteria, a case will be diagnosed with the condition if the mother has a temperature of 38 °C or higher and exhibits any of the following conditions: 1. a tachycardia at a rate ≥ 100 bpm; 2. a tender uterus; 3. odour from vaginal discharge/amniotic fluid; or 4. a white blood cell count ≥ 15000/μL. Alternatively, a case will be diagnosed with the condition if the mother exhibits all of the above four conditions while her body temperature is lower than 38 °C.

Statistical analysis

IBM SPSS Statistics for Windows, version 25® (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis. The $\chi 2$ test, t-test and Fisher's exact test were used in two-group comparison; multiple logistic regression analysis was used for multivariate analysis. The following variables were considered confounding factors: gestational age at delivery, oligohydramnios, CAM stage III in pathologic examination of the placenta, small for gestational age, the male sex of the neonate, and the use of positive pressure ventilation after birth. The level of statistical significance was set at $p < 0.05$. The cut-off value for the receiver operating characteristic (ROC) curve was set by using Youden's index (8). In this method, the cut-off point is defined as the point where the sum of the levels of sensitivity and specificity reaches its maximum on the ROC curve. At our hospital, termination of pregnancy is determined when a

case is diagnosed with clinical CAM. Hence, 16 cases who were diagnose with clinical CAM during pregnancy were excluded from analysis in which the ROC curve was used. The remaining 57 cases were analysed.

Results

Table 1 shows patient background factors. The mean gestational week at which the case was diagnosed with premature rupture of membranes was 24.5 ± 1.9 weeks (mean ± standard deviation). Seventy-two cases (98.6%) gave premature birth at mean gestational week 27.0 ± 3.0. Oligohydramnios was observed in 57 cases (78.1%) with a mean duration of 17.4 ± 20.5 days. Sixteen cases (21.9%) were diagnosed with clinical CAM during pregnancy.

Table 1
Patient background factors

	n = 74
Maternal age(years)	32.6 ± 5.2
Primiparity	31 (42.5%)
Delivery by caesarean section	56 (76.7%)
Administration of corticosteroid	59 (80.8%)
Gestational age at PROM (weeks)	24.5 ± 1.9
Gestational age at delivery (weeks)	27.0 ± 3.0
Delivery at less than 37 weeks of gestation	72 (98.6%)
≧34 weeks	3
30–33 weeks	8
26–29 weeks	31
22–25 weeks	31
Days form PROM to delivery (days)	17.4 ± 20.5
Clinical CAM	16 (21.9%)
Oligohydramnios	57 (78.1%)
Duration of oligohydramnios before delivery (days)	17.4 ± 20.5
Oligohydramnios: Oligohydramnios was defined as an amniotic fluid index (AFI) of ≤ 5 cm on transabdominal ultrasonography.	

Table 2 shows perinatal prognosis. The mean birth weight was 1000 ± 455 g, and small for gestational age (SGA) was observed in four cases (5.5%). No neonates died in this study. Forty-four cases (60.3%) were diagnosed with CAM stage III in postpartum pathologic examination of the placenta. Sixty-seven

cases (91.8%) required positive pressure ventilation (PPV) following birth, of which six (8.2%) were diagnosed with neonatal sepsis. Forty-nine cases (67.1%) were diagnosed with neonatal BPD.

Table 2
Perinatal prognosis

	n = 73
Birth weight (g)	1000 ± 455
Male sex of the neonate	39 (53.4%)
Small for gestational age (< 10% tile)	4 (5.5%)
APGAR score (1 min)	4.4 ± 2.1
APGAR score (5 min)	6.6 ± 1.7
Umbilical artery pH	7.34 ± 0.08
Neonatal death	0
Use of positive pressure ventilation after birth	67 (91.8%)
Neonatal sepsis	6 (8.2%)
CAM stage III in pathologic examination of the placenta	44 (60.3%)
Bronchopulmonary dysplasia	49 (67.1%)
Neonatal death: defined as the death of the neonate within 28 days after birth.	

Table 3 shows the results of univariate analysis comparing the BPD and non-BPD groups. In univariate analysis, the number of gestational weeks at which rupture of membranes occurred was significantly smaller in the BPD group, but no significant difference was observed between the groups in terms of the number of gestational weeks at which delivery occurred. When cases were stratified by the number of gestational weeks at which delivery occurred, it was found that a significantly larger number of cases gave birth at gestational week 22–25, which is the stratum for the earliest delivery, in the BPD group than in the non-BPD group. Also, a significantly larger number of cases were complicated by oligohydramnios in the BPD group. The duration of the condition was significantly longer in this group as well. Apart from these, no significant differences were observed between the groups in aspects which have already been reported as risk factors for BPD, such as complication with SGA (10), the male sex of the neonate (11), and complication with chorioamnionitis (12).

“Please insert Table 3 here.

The results of multivariate analysis for the onset of neonatal BPD are shown in Table 4. A significant correlation was observed only in oligohydramnios, which was found to be an independent predictor for the onset of BPD (odds ratio 12.4; 95% CI 2.940–52.30).

Table 4
Results of multivariate analysis for the risks of BPD

	Odds ratio	Lower limit of 95% CI	Upper limit of 95% CI	P value
Gestational age at delivery(weeks)	0.900	0.695	1.170	n.s.
oligohydramnios	12.40	2.940	52.30	< 0.05
CAM stage III in pathologic examination of the placenta	0.730	0.207	2.570	n.s.
Small for gestational age(< 10% tile)	0.747	0.059	9.350	n.s.
Male sex of the neonate	0.719	0.215	2.400	n.s.
Use of positive pressure ventilation after birth	0.543	0.037	7.970	n.s.
Multiple logistic analysis was used for multivariate analysis.				

n.s.: not significant

Figure 1 shows an ROC curve for the duration of oligohydramnios (in days) in relation to the onset of neonatal BPD. The degree of correlation was analysed by using the curve. The area under the curve (AUC) of the duration of oligohydramnios (in days) relative to the onset of neonatal BPD was 0.956 (95% CI: 0.902-1.000). Using Youden's index, the cut-off value for the duration of oligohydramnios (in days) as a risk factor for BPD was four days. In this case, the levels of sensitivity and specificity in predicting the onset of neonatal BPD were 0.941 and 0.917, respectively.

Discussion

The multivariate analysis performed in this study excluded the impact of confounding factors. The study then suggested that oligohydramnios may be a risk factor for BPD. Additionally, analysis in which an ROC curve was used indicated that oligohydramnios that lasts for four days or longer may be a risk factor for BPD.

No consensus has been reached on how to deal with pPROM cases. At present, each case is individually treated, taking into consideration factors such as: estimated body weight, number of gestational weeks, the capacity of the facility for neonatal resuscitation and management (13). Past studies have found that prolonged oligohydramnios is associated with contracture and abnormalities of the musculoskeletal system (14) as well as pulmonary hypoplasia (15).

It is still extremely difficult to determine whether the termination of pregnancy is appropriate or not for pPROM cases. The following conditions may be clear criteria for the termination of pregnancy in pPROM cases: NRFS, clinical CAM, and clearly recognisable premature separation of the normally implanted

placenta (16). On the other hand, if these conditions are not observed, the termination of pregnancy must be carefully determined on an individual basis by taking into account the number of gestational weeks (16).

BPD was first coined by Northway et al. in 1967 (17). Since then, subsequent studies gradually shed light on its pathophysiology. The pathology of BPD in a preterm neonate is as follows: pulmonary development in the neonate is inhibited after birth as the neonate with the disease starts pulmonary respiration while their lungs are underdeveloped. Since the structure of their lungs is not fully developed, the neonate suffers from hypoxemia, which may require mechanical ventilation management and the administration of oxygen. These interventions damage pulmonary tissue. Moreover, while cytokine-induced, intrauterine inflammatory changes frequently cause premature birth, a study has pointed out that inflammatory changes are also associated with pulmonary tissue injuries (18).

This study took into account the above-mentioned pathophysiological findings in analysing factors associated with the onset of BPD. Existing studies have reported that oligohydramnios is a risk factor for BPD (19). However, as mentioned above, it is considered that various factors are intricately interrelated when a neonate develops BPD, such as: premature birth, intrauterine infection and infection after birth, the sex of the neonate and SGA. After excluding the impact of confounding factors such as the number of gestational weeks and intrauterine infection, multivariate analysis in this study found that oligohydramnios is a risk factor for BPD. Prolonged oligohydramnios may be associated with neonatal pulmonary hypoplasia (15, 20). It has been pointed out that various factors, including premature lungs, oxygen toxicity and inflammatory mediators, are also involved (21). Diagnostic criteria for and the definition of BPD vary, and consensus is yet to be reached (22, 23). Meanwhile, risk factors for neonatal BPD during pregnancy include intrauterine growth restriction and chorioamnionitis (21). One study reported that the incidence rate of BPD was higher in cases who experienced pPROM before 31 weeks of gestation than those who did not experience the condition (24), Another study reported that from among 36 neonates who were born to mothers diagnosed with pPROM before 24 weeks of gestation and who were discharged following delivery, 17 (47%) developed BPD (25). Oligohydramnios was found to be a risk factor for BPD. It can be considered that neonates with BPD required the administration of oxygen after birth because the extensibility of their pulmonary tissue was reduced, from prolonged oligohydramnios that prevented the foetal development of the lungs.

It has been found that a neonate with BPD has increased mid- to long-term risks of pulmonary hypertension syndrome and chronic obstructive pulmonary disease (26). Since this study did not examine the mid- to long-term prognosis of neonates, the studied neonates should be closely monitored for the onset of prolonged pulmonary hypertension going forward.

The ROC curve indicated that oligohydramnios that lasts four days or longer increases the risk of BPD. If a mother has persistent oligohydramnios for a period of four days or longer, an onset of BPD should be taken into account in managing the case. There has been some research that has reported that a neonate develops respiratory complications if prolonged oligohydramnios was observed in their mother (27).

However, to the best of our knowledge, no research has been identified that explores the relationship between the duration of preterm oligohydramnios and the onset of neonatal BPD. The authors agree that the appropriateness of early pregnancy termination for a pPROM case should be determined on an individual basis by taking into account the number of gestational weeks and other individual background factors (13). However, it is still necessary for health professionals to consider the risks of neonatal BPD when attempting to prolong pregnancy in a mother with persistent oligohydramnios in whom NRFS or clinical chorioamnionitis is not observed.

This study has several limitations. In this study, the endpoint for analysis was the onset of neonatal BPD. Future studies may need to examine the long-term prognosis of neonates as well. Also, although the onset of BPD was examined by using an ROC curve, pregnancy termination was determined on an individual basis by taking into account the number of gestational weeks and patient background factors. Hence, it should be noted that interventions were performed at the discretion of the attending health professionals.

The following aspects should also be noted: firstly, this study is a retrospective epidemiological study which was performed at a single centre and which did not involve large-scale data; and secondly, there was a bias in selecting patients because the study site was a general perinatal care hospital which primarily accepts severe cases in its area.

Conclusions:

Findings from this study suggested that oligohydramnios is an independent risk factor for BPD in cases diagnosed with pPROM before 28 weeks of gestation. Also, the results of this study indicated that oligohydramnios that lasts four days or longer increases the risk of BPD. If pregnancy is extended and prolonged oligohydramnios is observed, the neonate should be closely monitored after birth for the onset of BPD.

Abbreviations

APGAR
Appearance, Pulse, Grimace, Activity, Respiration
AUC
area under the curve
BPD
bronchopulmonary dysplasia
CAM
chorioamnionitis
CI
confidence interval
NRFS

non-reassuring foetal status
ROC
receiver operating characteristic
pPROM
preterm premature rupture of membrane
SD
standard deviation
SGA
small for gestational age

Declarations

Ethics approval and consent to participate

This study was conducted after obtaining approval from the human research ethics committee of the Saitama Medical Center, Saitama Medical University. This study is a retrospective study using existing samples and does not require informed consent. The opt-out was posted on the homepage and the inquiries from patients were responded appropriately.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

SM analysed and interpreted the patient data. EN performed the histological examination of this study, and was a major contributor in writing the manuscript. YN structured design of the work, and HS have drafted the work or substantively revised it. All authors read and approved the final manuscript.

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Figures

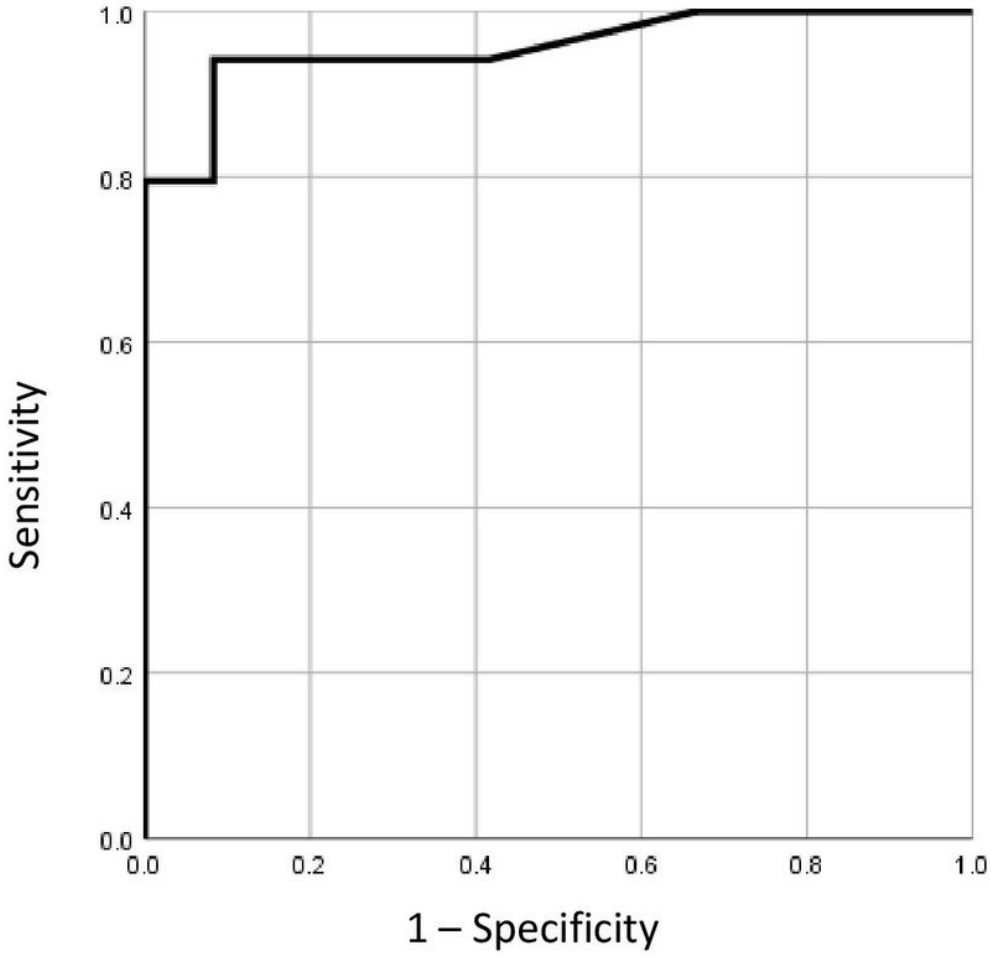

Figure 1

A receiver operating characteristic curve for the number of days for which oligohydramnios persisted in relation to the onset of neonatal BPD. The cut-off value was calculated by using Youden's index. Sixteen cases who were diagnosed with clinical CAM during pregnancy were excluded from a total of 73 cases. Analysis was performed for the remaining 57 cases. AUC was 0.956 (95% CI: 0.902-1.000). The cut-off value for the duration of oligohydramnios as a risk factor for BPD was four days. In this case, the levels of sensitivity and specificity in predicting the onset of neonatal BPD were 0.941 and 0.917 respectively.