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NEONATAL OUTCOME FOLLOWING EARLY ONSET PRETERM PREMATURE RUPTURE OF THE MEMBRANES - A CASE CONTROLLED STUDY*

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SUMMARY: Acunas B, Greenough A, Dimitriou G, Gamsu H. (Children Nationwide Regional Neonatal Intensive Care Centre, King's College Hospital, London, United Kingdom). Neonatal outcome following early onset preterm premature rupture of the membranes - a case controlled study. Turk J Pediatr 1999; 41: 429-436.

A case-controlled study was performed to determine whether preterm premature rupture of the membranes (PPROM), particularly if occurring in the second trimester, increased the duration of ventilatory support or hospital admission. Infants born after membrane rupture of at least 24 hours duration and prior to 37 weeks of gestation were identified. It was possible to match for gestational age and birthweight 40 PPROM infants, 15 of whom had onset of rupture of the membranes (ROM) prior to 27 weeks of gestation, with a control (an infant whose mother had not suffered PPROM). A greater proportion of the mothers of the PPROM infants had received antenatal steroids ($p<0.01$), had an antepartum hemorrhage ($p=0.06$) or delivered vaginally ($p<0.02$). More PPROM infants had pulmonary hypoplasia ($p<0.03$) or infection ($p<0.01$). Overall, however, and if only those matched pairs where membrane rupture had occurred prior to 27 weeks of gestation were considered, there were no statistically significant differences in the duration of ventilatory support or hospital admission. Step-wise regression analysis confirmed that in the study population overall and in the matched pairs where membrane rupture had occurred at less than 27 weeks of gestation, neither the duration of ventilation nor hospital admission significantly related to PPROM. These findings have implications when counselling parents. *Key words: antenatal steroids, infection, preterm premature rupture of the membranes, pulmonary hypoplasia.*

Preterm, premature rupture of the membranes (PPROM) is a common pregnancy complication. Antenatally, parents are counselled that their infant is likely to be at increased risk of poor outcome due to the development of pulmonary hypoplasia or infection. Yet, comparison of infants whose mothers had or had not ruptured their membranes prior to 37 weeks of gestation demonstrated that infants born following PPROM did not require significantly more respiratory

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support or a longer hospital admission[1]. A possible explanation for that surprising finding was the greater use of antenatal steroids in mothers who had PPROM. Certain complications associated with PPROM, most importantly pulmonary hypoplasia, are more likely if membrane rupture occurs prior to 27 weeks of gestation[2]. Thus, it is essential that a comparison of the duration of therapy involves that high risk population. The aim of this study was, therefore, to perform a case-controlled study of infants admitted to the neonatal intensive care unit (NICU) following PPROM to determine, in particular in those whose mothers had membrane rupture prior to 27 weeks of gestation, whether their duration of ventilatory support or hospital admission differed from matched controls.

Material and Methods

Infants admitted to the NICU during a 12-month period who were born after membrane rupture of at least 24 hours duration and prior to 37 weeks of gestation were retrospectively identified. Matching for gestational age and birth weight was then attempted with an infant whose mother had not suffered PPROM (a control). The control's birth weight had to be within 95-105 percent of the corresponding PPROM infant's.

The maternal notes were then examined to obtain data regarding the timing and duration of PPROM, occurrence of antepartum hemorrhage (APH), administration of antenatal corticosteroids and mode of delivery. Membrane rupture was diagnosed from the maternal history and confirmed if fluid, seen in the posterior vaginal fornix at a sterile speculum investigation, gave a positive nitrazine test. During the study period, routine policies were followed regarding antenatal administration of corticosteroids, antibiotics or tocolytic agents. Corticosteroids were routinely administered between 26 and 32 weeks of gestation to promote lung maturation. Antibiotics were given only if there was significant maternal infection or Streptococcus agalactiae was grown from a low vaginal swab. Spontaneous labor was not inhibited at any time following membrane rupture. Delivery was prompted if there was evidence of chorioamnionitis: vaginal discharge, uterine tenderness, fever, tachycardia or labor.

The neonatal notes were reviewed. The infant's gestational age was determined from the mother's last menstrual period and an ultrasound examination prior to 21 weeks of gestation, and from the infant's physical appearance and neurological score. Throughout the study period, routine policies were followed regarding respiratory management, in particular with respect to resuscitation and criteria for intubation, mechanical ventilation and surfactant administration. The Apgar scores, maximum inspired oxygen concentration and peak inspiratory pressure for each infant were noted. The infant's respiratory diagnosis was made by the clinician in charge of the case. Respiratory distress syndrome (RDS) was

diagnosed if the infant developed tachypnea, retractions, and grunting and/or cyanosis within four hours of birth persisting for longer than 24 hours, in association with a chest radiograph appearance demonstrating symmetrically affected opaque lung fields with a ground-glass appearance[3]. Exogenous surfactant therapy was administered routinely in the latter part of the study to infants with RDS if they were ventilated and required an inspired oxygen concentration of at least 30 percent.

Pulmonary hypoplasia was diagnosed on the basis of clinical and radiological criteria[2] and in non-survivors, whenever possible, by postmortem examination. Chronic lung disease (CLD) was diagnosed if the infant had required intermittent positive pressure ventilation (IPPV) for at least three days during the first week of life and had ongoing evidence of respiratory distress (tachypnea, retraction, rales and oxygen dependence) for at least 28 days. Congenital infection was diagnosed if the infant had positive blood cultures or gastric aspirate immediately after birth. All infants of less than 33 weeks of gestational age had regular cranial ultrasound examinations in the first week of life.

Statistical analysis

Differences between the PPROM and control groups were assessed for statistical significance using either chi-square or Wilcoxon rank sum test as appropriate. To assess the significance of relationships, Spearman's correlation coefficients were calculated. Step-wise regression analysis was performed to determine the relationship of the duration of mechanical ventilation or hospital admission to PPROM, antenatal steroid usage, APH, mode of delivery, gestational age, birthweight, gender, surfactant usage, occurrence of infection and pulmonary hypoplasia.

Results

Forty of the 51 infants born following PPROM could be matched with a control infant. A greater proportion of the mothers of PPROM infants had received antenatal steroids or delivered vaginally (Table I). In addition there was a trend for more PPROM mothers to have suffered from an APH.

Significantly more PPROM infants had pulmonary hypoplasia or infection (Table II). Three PPROM infants died of pulmonary hypoplasia with membrane rupture at 23, 26 and 26 weeks of gestation respectively; a fourth died of congenital sepsis with membrane rupture at 28 weeks. One control died of congenital septicemia and another of renal failure; both were born at 23 weeks of gestation. If only infants with PPROM prior to 27 weeks of gestation and their matched controls are considered (Table III), the use of antenatal steroids and the occurrence of pulmonary hypoplasia differed significantly between the two groups. There were no significant differences, however, (Table II), nor in the

subgroup with PPROM ≤26 weeks of gestation (Table III), between the PPROM and control groups in either the duration of ventilation or hospital stay.

Table I: Maternal and Infant Demographic Data Expressed as Median (Range) or n (%)

n	PPROM 40	No PPROM 40	p
Gestational age (weeks)	29 (23-36)	29 (23-36)	ns
Birth weight (g)	1423 (490-2790)	1390 (510-2740)	ns
Male gender	31 (78%)	24 (60%)	ns
Vaginal delivery	31 (78%)	20 (50%)	<0.02
Antenatal steroids	18 (45%)	4 (10%)	<0.001
Antepartum hemorrhage	10 (25%)	3 (8%)	=0.06
PPROM duration (days)	5 (1-94)	–	–
Apgar score at 1 minute	6 (0-9)	5 (0-10)	ns
Apgar score at 5 minutes	8 (1-10)	8 (4-10)	ns

PPROM: preterm premature rupture of the membranes.

Table II: Neonatal Outcome Data Expressed as Median (Range) or n (%)

n	PPROM 40	Controls 40	p
Ventilated	27 (68%)	28 (70%)	ns
Maximum inspired oxygen concentration (FiO_2)	0.55 (0.26-1.0)	0.60 (0.25-1.0)	ns
Max PIP (cmH_2O)	28 (16-45)	19 (18-26)	ns
Duration of ventilation (days)	2 (0.5-41)	5 (0.5-38)	ns
RDS	19 (48%)	21 (53%)	ns
Surfactant administration	5 (13%)	6 (15%)	ns
Pulmonary hypoplasia	6 (15%)	0	<0.03
Infection	20 (50%)	8 (20%)	<0.01
Air leak	6 (15%)	4 (10%)	ns
CLD	6 (16%)	6 (16%)	ns
Intracranial hemorrhage	6 (15%)	7 (18%)	ns
Death	4 (10%)	2 (5%)	ns
Duration of hospital stay (days)	26 (1-125)	32 (3-127)	ns

PPROM: preterm premature rupture of the membranes.
PIP : peak inflating pressure.
RDS : respiratory distress syndrome.
CLD : chronic lung disease.

Table III: Outcome of Infants with Membrane Rupture ≤26 Weeks of Gestation

n	PPROM 15	Controls 15	p
Gestational age (weeks)	27 (23-31)	27 (23-31)	
Birth weight (g)	1082 (490-1460)	928 (510-1740)	ns
Antenatal steroids	10 (67%)	1 (9%)	<0.002
APH	7 (47%)	2 (13.3%)	<0.06
Vaginally delivered	13 (87%)	9 (40%)	ns
PPROM duration (days)	14 (2-94)	-	
Male	12 (80%)	6 (40%)	=0.06
Ventilated (n)	15 (100%)	15 (100%)	
Max FiO_2	0.88 (0.30-1.00)	0.62 (0.25-1.00)	ns
Max PIP (cmH_2O)	28 (16-45)	23 (19-26)	ns
Duration of ventilation (days)	8 (0.5-41)	7 (0.5-38)	ns
RDS	9 (60%)	12 (80%)	ns
Surfactant	5 (36%)	3 (20%)	ns
Pulmonary hypoplasia	6	0	<0.02
Infection	10 (67%)	5 (33%)	ns
Chronic lung disease	4 (27%)	6 (46%)	ns
Duration of hospital stay (days)	46 (4-125)	58 (23-127)	ns
Deaths	3 (20%)	2 (13%)	ns

PPROM: preterm premature rupture of the membranes.
APH : antepartum hemorrhage.
PIP : peak inflating pressure.
RDS : respiratory distress syndrome.

Pulmonary hypoplasia ($p<0.003$) and infection ($p<0.08$) tended to occur in the immature infants, and the duration of ventilation was inversely related to the gestational age at the onset of membrane rupture ($p<0.05$). In the study population overall, step-wise regression analysis demonstrated that prolonged ventilation related significantly only to low gestational age ($p<0.01$) and not PPROM and also that the duration of admission was significantly related to infection, low gestational age and male gender only ($p<0.01$). In the infants with early onset membrane rupture, both the duration of hospital stay and ventilatory support were significantly associated with low gestational age ($p<0.01$); the duration of hospital stay was also significantly related to lack of antenatal steroids ($p<0.01$).

Discussion

These data demonstrate that even infants born following very early onset PPROM do not require an increased duration of ventilatory support or hospital admission

compared to matched controls. Although pulmonary hypoplasia was, as expected, commoner in the PPROM infants, the number of deaths was very similar in the two groups and thus did not bias our results. The infants were matched for gestational age and as closely as possible for birth weight, but there were significant differences between them. APH was commoner in mothers who had PPROM, regardless of whether or not they delivered very immaturely. Meta-analysis has demonstrated that women with pregnancies complicated by PPROM are three times as likely to develop placental abruption[4]. The groups also differed significantly with respect to mode of delivery and antenatal steroid use, factors both known no impact on neonatal status[5-7]. We have previously demonstrated that steroid administration is more common in pregnancies complicated by PPROM than in pregnancies without that complication, but delivering at a similar early gestation[1]. Antenatal corticosteroid therapy has very few contraindications, but to be most effective should be administered for at least 24 hours prior to the delivery[6-8]. Patients with pregnancies complicated by PPROM may deliver many days after their initial presentation and thus there is sufficient time to give them antenatal steroids. This is in contrast to the control population who were selected only because of a similarly premature delivery and many of whom would have delivered with little warning. In a previous series[1] we demonstrated that, without antenatal steroid therapy, infants born following PPROM tended to require a longer duration of ventilation and hospital stay than controls. Thus, in the present population, the significantly higher steroid usage in the subjects may have improved their outcome. Indeed, regression analysis confirmed that the occurrence of PPROM was not significantly related to prolonged respiratory support or hospital admission; those adverse outcomes were explained by other factors, including lack of antenatal steroids as well as immaturity.

There were no significant differences in the incidence of RDS between our two groups, and the proportion of patients affected was similar to that quoted in previous series[9,10]. Antenatal steroid administration has not been suggested to reduce the incidence of RDS in PPROM[9], but our previous results suggest it may reduce its severity[1]. In the present series, the maximum peak inflating pressure (PIP) tended to be higher, but not significantly so, in the PPROM infants, likely due to the fact that only that group included infants with pulmonary hypoplasia. Only a small proportion of our population received surfactant. Yet, had it been routinely available throughout the study period, as a similar number of babies in each group were diagnosed as suffering from RDS and hence eligible for surfactant administration, this would not have changed the results.

The reported incidence of pulmonary hypoplasia following PPROM varies. This reflects the difficulty of diagnosing this condition accurately in survivors[11]. The importance of early gestational age at onset of membrane rupture associated

with an increased incidence of pulmonary hypoplasia has been highlighted in a number of studies[12,13]. In the present report, all six of the 40 PPROM infants in whom pulmonary hypoplasia was diagnosed had PPROM prior to 27 weeks of gestation. There remains controversy, however, whether the duration of membrane rupture is significantly associated with the development of pulmonary hypoplasia[14-16]. Not all studies reported whether the patients with PPROM had oligohydramnios, but it has been claimed[16] that only if that association occurs will pulmonary hypoplasia follow. It should be noted, however, that a later series[13] suggested that gestational age at membrane rupture and oligohydramnios were independent predictors of pulmonary hypoplasia.

Neonatal sepsis is increased following PPROM, perhaps as high as a five-fold increase in frequency compared to controls[17], but that assumption was based on a positive blood culture rate of three in 208 infants. The occurrence of infection following PPROM inversely relates to gestational age[16], as found in the present series. We also noted that the incidence of sepsis was significantly greater in the PPROM compared to the control group, but that did not significantly influence the duration of admission. It may, however, have long-term consequences. Infants born following PPROM have been reported to be at higher risk of subsequent moderate-to-severe neurological and developmental impairment[18]; 28 percent of infants in one cohort exhibited major neurological or developmental deficits when membrane rupture occurred in the mid trimester[19]. A possible mechanism is via prenatal intrauterine infection resulting in elevation of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor-α[20]. In our series, nine of the PPROM infants had positive blood cultures taken immediately after birth and thus were likely to have prenatal infection.

We conclude that, even when PPROM occurs in the mid trimester, if the mother is given antenatal steroids, it is not associated with a significantly increased duration of either respiratory support or hospital admission.

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