

The Association Between Early Membrane Rupture, Latency, Clinical Chorioamnionitis, Neonatal Infection, and Adverse Perinatal Outcomes in Twin Pregnancies Complicated by Preterm Prelabour Rupture of Membranes

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The objective of this study was to evaluate associations between adverse outcomes in twin pregnancies and preterm prelabour rupture of membranes (PPROM). A chart review of 246 consecutive twin pregnancies with confirmed PPRM was conducted. Regression analysis (β [natural log of the odds ratio] and odds ratio [OR]) was performed to identify independent predictors. Two hundred and forty-six twin pregnancies, 492 liveborns, and 20 neonatal deaths. Mean (SD) PPRM gestational age (GA): 31.3 (3.8) wk; delivery GA: 32.0 (3.3) wk. PPRM < 30wk was associated with increased parity (OR: 2.66), and log (admission leukocyte count) (OR: 9.99). Shortened latency was associated with PPRM GA ($\beta = -0.17$) and chorioamnionitis ($\beta = 0.95$). Neonatal sepsis was predicted by lower delivery GA (OR: 2.04). Adverse perinatal outcomes were protected against by older GA at PPRM (OR 0.53) and shortened latency (OR 0.73). It was concluded that increased leukocytosis and parity implies an infectious aetiology in earlier PPRM. Increased risk for neonatal sepsis at earlier delivery GA is consistent with gestation-dependent fetal immunocompetence. Early PPRM and long latencies were associated with increased adverse perinatal outcomes.

Background

Preterm prelabour rupture of membranes (PPROM) complicates 2–4% of singleton pregnancies (Duff, 1996), and 3–7% of twin pregnancies (Kovacs et al., 1989; Sassoon et al., 1990b). Specific concerns attach themselves to PPRM in multiple pregnancies, as these pregnancies are predisposed to premature delivery (Skupski & Chevernak, 1996), and, increasingly frequent, result from assisted reproduction technologies following a period of subfertility (Gall, 1996; von Dadelszen et al., 1999). Both multiple pregnancy and PPRM are independent predictors of neonatal intensive care admission, with multiple pregnancy alone contributing 19% of all neonatal intensive care unit days

(Ross et al., 1999). In addition, the presence of an intact sac with a normal amniotic fluid volume for fetal growth and development, but at risk for infection, provides the clinician with a series of clinical (Lewis & Mercer, 1996), sometimes ethical (De Catten et al., 1998), challenges.

For singletons at term, the International Multicentre Term PROM Study Group (Seaward et al., 1997; Seaward et al., 1998b) identified independent predictors of chorioamnionitis, postpartum fever, and neonatal infection (Table 1). PPRM in twin pregnancies has been associated with both shorter (Bianco et al., 1996) and the same (Hsieh et al., 1999) PPRM to labour latency than in singleton pregnancies, but similar perinatal outcomes (Bianco et al., 1996; Seaward et al., 1998b).

This retrospective study was performed to identify the important associations between membrane rupture before 34 weeks' gestation, the latent interval between PPRM and labour onset, clinical chorioamnionitis, neonatal sepsis, and adverse perinatal outcomes in twin pregnancies complicated by PPRM. Although PPRM is known to increase the risk of infectious morbidity, not all patients will develop these complications. The identification of important factors may permit judicious obstetric and neonatal management to reduce the impact of these sequelae.

Patients and Methods

All women delivering twins were identified by review of the health records, Mount Sinai and Women's College

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Hospitals, Toronto, and British Columbia's Women's Hospital and Health Centre over a 2-year period. Charts were reviewed, and data abstracted for cases with a confirmed diagnosis of PPRM. PPRM was defined as clinically confirmed spontaneous rupture of membranes occurring after 24 completed weeks, and before the completion of the 37th week of pregnancy (i.e., 24wk + 0 – 36wk + 6d). Clinical diagnosis required at least two of: (i) fluid pooling on speculum examination, (ii) Nitrazine positive on vaginal secretions, and (iii) ferning-positive dried secretions. Clinical chorioamnionitis was defined as one or more of the following: (i) persistent maternal fever $\geq 37.5^{\circ}\text{C}$ on two or more occasions $\geq 1\text{h}$ apart, or a single temperature $\geq 38^{\circ}\text{C}$, prior to delivery, (ii) a maternal leukocytosis $\geq 20,000/\text{ml}$, or (iii) foul smelling amniotic fluid. Postpartum fever was defined as a maternal temperature $\geq 38^{\circ}\text{C}$. Criteria for definite neonatal sepsis were clinical signs of infection and one or more of the following: (i) a positive culture from blood, cerebrospinal fluid (CSF), urine, tracheal aspirate, or lung tissue, (ii) a positive gram stain of CSF, (iii) a positive antigen detection test from blood, CSF, or urine, (iv) a chest radiograph compatible with pneumonia, and, (v) a histological diagnosis of pneumonia.

We undertook this analysis to identify the important associations between early PPRM (before 30 weeks), the latent interval, clinical chorioamnionitis, neonatal sepsis, and adverse perinatal outcomes in twin pregnancies complicated by PPRM. There were five a priori questions: in cases of PPRM complicating twin pregnancy, what are associated with (i) PPRM before 30 completed weeks of pregnancy; (ii) duration of the latent interval; (iii) development of chorioamnionitis; (iv) development of neonatal sepsis; and (v) an adverse perinatal outcome (summary measure)? The combined outcome included perinatal mortality, sepsis, bronchopulmonary dysplasia, necrotising enterocolitis, and severe intraventricular haemorrhage (\geq grade III).

Splus and SPSS software packages were used for statistical analysis. Separate analyses were performed to identify those variables associated with: (i) the occurrence of PPRM prior to 30 completed weeks of pregnancy; (ii) the duration of the latent interval; (iii) the development of chorioamnionitis; (iv) the development of neonatal sepsis; and (v) the development of the combined adverse neonatal outcome. The relationship between duration of latent interval and predictive variables was explored via linear regression. Logistic regressions were used to evaluate effects of variables on the development of chorioamnionitis, neonatal sepsis, and the combined neonatal outcome. The most parsimonious logistic model was determined in all three analyses by forward and backward stepwise regression utilizing the Wald criteria. Results of the logistic regression analyses are expressed as odds ratios (OR) with their 95% confidence intervals (CI). Where appropriate, results are also reported in terms of their level of statistical significance. All p -values were based on two-tailed tests, with $p < .05$ considered statistically significant. To maintain power, we have not corrected for multiple testing. Thus, our overall Type I error rate may be greater than 5%.

The variables considered in the regression analyses are listed in Table 2.

Results

Two hundred and forty-six cases of PPRM complicating twin pregnancy were identified. Data were retrieved on all cases. All 492 babies were liveborn, and there were 20 neonatal deaths. The mean maternal age was 30.7 years ($SD = 5.3$). 151 (61%), 29 (12%), and 37 (15%) women were nulliparous, smoked or underwent amniocentesis, respectively, in the index pregnancy. The pregnancy outcome data are summarized in Table 3.

The occurrence of PPRM prior to 30wk was associated with increased parity (OR: 2.66 [95% CI: 1.25, 5.66]), non-cephalic fetal presentation (OR: 2.80 [95% CI:

Table 1

Independent Predictors of Adverse Outcome from the International Multicentre Term PROM Study Group (Seaward et al., 1997; Seaward et al., 1998b)

| Complication | Independent Predictors |
|--------------------|--|
| Chorioamnionitis | Number of digital vaginal examinations Time from membrane rupture to active labour ≥ 24 hours Meconium-stained liquor amnii Active labour ≥ 12 hours |
| Postpartum fever | Clinical chorioamnionitis Active labour ≥ 12 hours Caesarean section Operative vaginal delivery Group B streptococcal colonisation Administration of maternal antibiotics before delivery |
| Neonatal infection | Clinical chorioamnionitis Group B streptococcal colonisation Number of digital vaginal examinations Time from membrane rupture to active labour ≥ 48 hours Administration of maternal antibiotics before delivery |

Table 2

Variables Included in Logistic Regression Analyses

| Complication(s) | Variables |
|--|--|
| 1. Early PPROM and 2. Latency | Maternal age Parity Smoking Amniocentesis APH in 3rd trimester or after admission Gestational age (GA) at PPROM GA at delivery Log of latent interval (PPROM to onset of labour) Log of PPROM to delivery interval Log of white blood cell (WBC) count at admission Cervical dilatation on admission Number of vaginal examinations (PPROM to delivery) Chorioamnionitis Duration of labour Antibiotic use Epidural use Fetal presentation (of each twin) Meconium (complicating either sac) Fetal scalp electrode (for each twin) Type of delivery (Caesarean section (for each twin)) Birthweight (for each twin) Apgar score at 5min (for each twin) Neonatal sepsis (in each twin) |
| 3. Chorioamnionitis | Maternal age Parity Log of latent interval Log of time from onset of labour to delivery Log of WBC count at admission Number of vaginal examinations (PPROM to delivery) Meconium (complicating either sac) Antenatal betamethasone Fetal scalp electrode (for each twin) |
| 4. Neonatal sepsis and 5. Combined adverse perinatal outcome* | GA at PPROM GA at delivery (for each fetus) Log of latent interval Log of time from onset of labour to delivery Log of WBC count at admission Number of vaginal examinations (PPROM to delivery) Antenatal betamethasone Fetal scalp electrode (for each twin) Caesarean section (for each twin) Birthweight (of each twin) Apgar at 5min (for each twin) |

Note: *The combined adverse perinatal outcome included perinatal mortality, sepsis, bronchopulmonary dysplasia, necrotising enterocolitis, and severe intraventricular haemorrhage (\geq grade III).

APH: antepartum haemorrhage; GA: gestational age; PPROM: preterm prelabour rupture of membranes; WBC: white blood cell.

1.28, 6.14]), and log (white blood cell count at admission) (OR: 9.99 [95% CI: 2.76, 36.2]).

Latency and Chorioamnionitis

Shortened latency and chorioamnionitis were mutually associated ($\beta = -0.17$ [95% CI: $-0.12, -0.21$], $p < .0001$, for chorioamnionitis being predictive of short latency), where β is the natural log of the odds ratio. Shorter latency was also associated with increasing gestational age at PPROM ($\beta = .95$ [95% CI: 0.47, 1.42], $p = .0001$).

Neonatal Sepsis

The best predictors of neonatal sepsis were higher Apgar scores (twin A: OR: 7.20 [95% CI: 1.21, 42.7]; twin B:

OR: 11.24 [95% CI: 1.79, 70.64]), and lower gestational age at delivery (OR: 2.04 [95% CI: 1.56, 2.70]).

Combined Severe Perinatal Complications

Both older gestational age at PPROM (OR: 0.53 [95% CI: 0.40, 0.72]) and shortened latency (OR 0.73 [95% CI: 0.54, 0.98]) were protective against the combined severe perinatal outcome of perinatal mortality, sepsis, bronchopulmonary dysplasia, necrotising enterocolitis, and severe intraventricular haemorrhage (\geq grade III).

Discussion

This is the first published series describing a multivariate analysis of associations between pregnancy outcome and

Table 3

Pregnancy Outcome Data (*N* = 246 Pregnancies; Frequencies Are Quoted for Count Data, Means [\pm SD] Are Quoted for Symmetric Data, Medians {Range} Are Quoted When the Data Were Skewed)

| Variable | Number (%), Mean [\pm SD], Median {Range} | |
|---|--|----------------|
| APH in 3rd trimester or after admission (+/–) | 5.0 (2.0%) | |
| GA at PPRM (wk) | 31.3 [3.8] | |
| GA at delivery (wk) | 32.0 [3.2] | |
| Latent interval (PPROM to onset of labor) (h) | 13.5 {0, 2976} | |
| PPROM to delivery interval (h) | 22.5 {1, 2982.5} | |
| Admission WBC count ($\times 10^9/L$) | 11 {5.02, 34.9} | |
| Cervical dilatation (admission) (cm) | 0 {0, 10} | |
| Number of vaginal examinations (PPROM to delivery) | 3.8 [2.2] | |
| Complete course of betamethasone of those under $34/_{40}$ (y/n)* | 94 (38.7%) | |
| Chorioamnionitis (y/n) | 34 (13.8) | |
| Duration of labor (h) | 6 {0, 76} | |
| Antibiotics (y/n) | 6 (12.5%) | |
| Meconium (y/n) | 11 (4.6%) | |
| Internal fetal heart rate monitoring (y/n) | 93 (38.4%) | |
| Epidural (y/n) | 35 (72.9%) | |
| Presentation of twin A† | | |
| cephalic | 177 (74.4%) | |
| breech/other | 61 (14.6%) | |
| unknown | 8 (3.3%) | |
| Caesarean section (all other deliveries vaginal) (y/n) | 93 (37.8%) | |
| | Twin A | Twin B |
| Birthweight (g) | 1739.0 [565.6] | 1778.2 [544.6] |
| Apgar at 5min | 8 [1.7] | 8 [1.5] |
| TTN/RDS (y/n) | 79 (40.0%) | 81 (41.1%) |
| IVH/porencephalic cysts/seizures (y/n) | 3 (6.3) | 6 (12.5) |
| Neonatal sepsis, meconium aspiration, pneumothorax (y/n) | 23 (9.4%) | 35 (14.3%) |
| Neonatal death (y/n) | 11 (4.5%) | 9 (3.7%) |

Note: * 38 cases < $34/_{40}$, two incomplete courses of betamethasone also given (5.3%).

† Presentation documented in 238 cases, by ultrasound in or within 48h of labor.

APH: antepartum haemorrhage; GA: gestational age; IVH: intraventricular haemorrhage; PPRM: preterm prelabour rupture of membranes; RDS: respiratory distress syndrome; TTN: transient tachypnoea of the newborn.

PPROM complicating twin pregnancy. Mercer et al. (1993) have reported on the outcomes of 99 twin pregnancies complicated by PPRM in a case-control study, and found an incidence of PPRM of 7.4% (vs. 3.7% in singletons). We were unable to determine the denominator for the incidence of PPRM in twin pregnancy for our cohort, as these three Canadian units are tertiary referral centers receiving antenatal transfers from other hospitals. Mercer et al. (1993) also found that the median latency from PPRM to delivery was 26h and that 91% of pregnancies had delivered within 7d of membrane rupture similar to our series in which the median latency to delivery was 22.5h, and 218 women (89%) had delivered within 7d.

As in Mercer et al. (1993), PPRM prior to 30wk gestation was associated with a prolonged latency period in this study. However, the < 30wk PPRM group in both the Mercer study and this study include pregnancies with PPRM at earlier gestations than viability (24wk), which will have pre-selected pregnancies destined to have prolonged latency. However, in this study, with the exclusion of the two cases of PPRM prior to 24wk, the difference in latency period was no longer significant.

It was not surprising that earlier-onset PPRM (< 30wk) was associated with an increased incidence of non-cephalic presentation of twin A, as spontaneous version increases towards term (Albrechtsen et al., 1998). However, the increased white blood cell count with earlier presentation implies that the etiology of early PPRM differs from later PPRM, especially as pregnancy leukocytosis increases with advancing gestational age in normal pregnancy (Taylor & Lind, 1979). A possible explanation for this would be a greater association with infectious etiologies at earlier gestational ages, and that mechanical distension may play a larger role later in pregnancy. Similarly, the association between increased parity and earlier membrane rupture might be explained by poorer membrane protection from infectious agents by a patulous parous cervical canal.

The association between better Apgar scores at 5 min for either twin and worse neonatal sepsis is unclear, and may represent a Type I error. An alternative explanation is that infants with poor Apgars were more likely to succumb prior to developing overt sepsis or to have intercurrent illness that disguised a clinically significant septic event. Premature infants with poor Apgars are often given prophylactic antibiotics,

and, therefore, even though blood cultures were drawn, these may have been culture negative. Increasing immunocompetence during fetal life (Vetro et al., 1991) may explain the reduction in neonatal sepsis risk associated with increased gestational age at delivery. It may be also explained by the higher rates of intervention at earlier gestational ages. It was anticipated that older gestational age at PPROM would be protective against the combined severe perinatal outcome of perinatal mortality, sepsis, bronchopulmonary dysplasia, necrotising enterocolitis, and severe intraventricular haemorrhage (\geq grade III), as these are primarily consequences of prematurity. The protective effect of shortened latency against this outcome may be explained in part by association between shortened latency and older gestational age at membrane rupture. However, gestational age was included in the regression model, and, therefore, these data raise concern that assiduous prolongation of PPROM pregnancies may not always provide maximum perinatal benefit. Certainly we support the view that any trials in this field should use a summary adverse perinatal outcome as the primary outcome measure, rather than PPROM-to-labour latency, as these data suggest that latency may not be a sufficiently robust surrogate marker of perinatal outcome.

Betamethasone, or dexamethasone, is recommended in singleton pregnancies complicated by PPROM before 34 wk gestation (Crowley, 2000; Crowley, 1992), as it reduces the incidence and severity of RDS and improve neonatal survival. However, for multiple pregnancy, the evidence for benefit is lacking (Quist-Therson et al., 1999). In this series, which predated firm recommendations in North America, 94 (30.7%) of the 242 women under 34 wk gestation received a completed course of antenatal steroids. We did not find a protective effect of steroid administration in this study, supporting the findings of Quist-Therson et al. (1999).

This study is limited by its retrospective nature and the lack of a comparison group of either singleton PPROM pregnancies or twin pregnancies not complicated by PPROM. Chorionicity was not used as a variable in this study, primarily because of the paucity of either ultrasound or placental pathology data on which to make this determination. The inclusion of somewhat interdependent variables in the regression modeling, and the inclusion of both fetuses in the analyses, confound the analyses, but we believe that our logistic approach has identified independent associations between the parameters and outcomes of interest. There were no monoamniotic twin pairs in this series.

In summary, it appears that twin PPROM is similar to singleton PPROM in that earlier gestational at rupture predicts greater latency and that infection may play an important role in its etiology (especially remote from term) and clinical course. Specific studies of antenatal steroids in multiple pregnancies are required to define the optimal dosage regime in these particularly at risk pregnancies. It is of concern that increased PPROM-to-labour latency was associated with worse perinatal outcomes despite gains in gestational age.

Acknowledgments

Supported by the MFM group, Mt Sinai Hospital, Toronto (PvD MFM fellowship salary), the BC Research Institute

for Children's and Women's Health and BC Women's Hospital and Health Centre Foundation (PvD clinician scientist salary and establishment award), and the BC Ministry of Health (M-FD fellowship salary). We wish to thank the Medical Records Departments of all three hospitals for their assistance with this study.

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