Neonatal outcome and two-year follow-up after expectant management of second trimester rupture of membranes

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Abstract

Objective: To assess neonatal outcome and 2-year follow-up of pregnancies complicated by second trimester preterm premature rupture of membranes (PPROM). Methods: A retrospective review of obstetric and neonatal records for 87 pregnancies (56 singletons, 6 twins, 1 triplet) with PPROM between 14 + 0 and 24 + 6 weeks of gestation. Patients received antibiotics and steroids for fetal lung maturity once they reached 24 weeks of gestation. Placentas were examined histopathologically. Surviving infants were followed-up at 2 years of age. Results: Median latency from PPROM to delivery was 4 days. Survival rate of 56 singletons was 45% (25/56); and 13 died in hospital. Survival rate of infants discharged from hospital was 23% (12/56). Chorioamnionitis was seen histologically in 42% (5/12) of surviving infants compared with 92% (12/13) of those that died in hospital. Of the 12 surviving infants, 50% had a normal neurological and developmental outcome at 2 years of age.

Conclusion: Gestational age, birth weight, and histologic chorioamnionitis have prognostic importance in pregnancies complicated by PPROM. Surviving infants have a 50% chance of achieving an adequate health status at 2 years of age.

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KEYWORDS
Chorioamnionitis; Fetal risk; Neonatal outcome; Preterm premature rupture of membranes; Two-year follow-up

1. Introduction

Preterm premature rupture of membranes (PPROM) complicates about one-third of all preterm deliveries [1,2], and entails a high risk for fetal and maternal morbidity. Major problems for surviving neonates include bronchopulmonary dysplasia, cerebral damage, retinopathy, and motor/cognitive impairment [3–5]. The challenge in affected pregnancies is to maximize the period of latency to birth without fetal or maternal risk. The management of patients with PPROM remains difficult. Robust criteria for prolonging or terminating a pregnancy complicated by PPROM are lacking. We reviewed the neonatal outcome of pregnancies complicated by PPROM between 14 + 0
and 24+6 weeks of gestation managed expectantly with close surveillance. A 2-year follow-up of surviving infants was provided by a neonatologist specialized in developmental assessment.

2. Materials and methods

We retrospectively reviewed the clinical records of 87 patients with PPROM between 14+0 and 24+6 weeks of gestation from a total of 20,633 deliveries (representing a frequency of 0.4%) at our institution between January 1998 and July 2005. Obstetric, neonatal, and pediatric records were reviewed regarding gestational age at membrane rupture, gestational age at birth, latency period between these events, signs of clinical chorioamnionitis defined according to the criteria of Gibbs et al. [6], mode of delivery, fetal gender, and neonatal outcome.

We excluded 15 women from the study: 4 women with membrane rupture after amniocentesis because of the significantly better perinatal outcome compared with pregnancies complicated by spontaneous PPROM at a similar gestational age [7], 7 women in labor (regular uterine contractions), 2 women with clinical signs of chorioamnionitis at admission, and 2 women with either cervical incompetence or cerclage. Nine patients (10.3%) decided not to continue with pregnancy after being offered pregnancy termination. A total of 63 pregnancies were included in the study.

No difference existed in treatment regimens for multiple and singleton pregnancies. Gestational age was based on early ultrasound or menstrual history. PPROM was diagnosed by visible loss of amniotic fluid exiting the cervical os (sterile specula) and confirmed by Actim PROM (Medix Biochemica Ab, Finland), a test for insulin-like growth factor binding protein 1 (IGFBP1). Ultrasound was performed to confirm gestational age, evaluate amniotic fluid status, and to screen for fetal anomalies. Cervicovaginal cultures were taken. Fifty-nine of the 63 women were treated promptly with intravenous antibiotics (penicillin, amoxicillin-clavulanate, cephalosporin) for 7 days. Tocolytics were applied for 48 hours while corticosteroids were given to promote lung maturation after 24 weeks of gestation [8]. Ultrasound was performed weekly for fetal size and amniotic fluid volume; leukocyte and C-reactive protein (CRP) values were measured every second day. Cardiograms were recorded twice a day after 24 weeks of gestation. Treatment was expectant unless there was clinical or laboratory evidence of intra-amniotic infection, changes in the biophysical profile, or regular uterine contractions.

Surviving neonates were transferred to the neonatal intensive care unit (NICU). All placenta were submitted for histopathology. Histologic chorioamnionitis was identified as infiltrate of neutrophils (>10 neutrophils per high-power field) at 2 or more sites in the chorionic plate and decidual floor. After discharge from hospital the infants were followed-up regularly by pediatricians.

Surviving infants were assessed neurologically and developmentally at 2 years of age (corrected for prematurity) by a single neonatologist specialized in developmental assessment. Mental and psychomotor development was assessed by the German version of the Griffith Mental Developmental Scales [9]. Examinations were focused on major and minor neurological dysfunctions according to Touwen [10]. Infants with cerebral palsy were classified as levels 1–5 using the Gross Motor Function Classification (GMFC) by Palisano et al. [11]. Infants were classified into 4 groups (severe/moderate/mild disability or normal outcome) using the definition according to Marlow et al. [12].

Data were analyzed using analysis of variance, the Kruskal–Wallis test after checking for normality of data, and $\chi^2$ tests for categorical data using SPSS version 12.0 (SPSS, Chicago, IL, USA). $P\leq0.05$ was considered statistically significant.

3. Results

A total of 63 women were managed expectantly for spontaneous PPROM between 14+0 and 24+6 weeks of gestation (Fig. 1). The pregnancies were 56 (89%) singleton, 6 (9%) twin, and 1 (2%) triplet – a total of 71 fetuses. Mean

![Figure 1](image-url) Study protocol. Abbreviations: PPROM (preterm premature rupture of membranes); IUFD (intrauterine fetal death).
maternal age was 30 years. Thirty-six women were primipara and 27 were multipara. Mean gestational age at time of diagnosis was 21 + 3 weeks and mean gestational age at delivery was 23 + 2 weeks. The median interval from PPROM to delivery was 4 days (mean 13 days, range 0 – 118 days). No infants from multiple pregnancies survived. A total of 25 of the 71 (35%) fetuses were alive at birth. Table 1 shows the survival rates of all fetuses by gestational age at membrane rupture. Mean latency was 7 days (range, 0 – 118 days) for 27 fetuses with PPROM at less than 20 + 6 weeks, 4 days (range, 0 – 48 days) for 25 fetuses with PPROM between 21 + 0 and 22 + 6 weeks, and 3 days (range, 0 – 50 days) for 19 fetuses with PPROM between 23 + 0 and 24 + 6 weeks.

Live birth rate for the 56 singleton pregnancies was 45% (25/56); 13 infants died in the NICU and 12 were eventually discharged from hospital. Neonatal outcome data classified by gestational age at PPROM and birth are shown in Fig. 2.

Regarding prenatal antibiotic treatment, 31 (49%) patients received broad-spectrum penicillin, 20 (32%) received amoxicillin-clavulanate, and 8 (13%) received cephalosporin; 4 (6%) patients received no antibiotics. Mean latency period in the group of patients treated with penicillin was 14 days, 16 days with amoxicillin-clavulanate, and 7 days with cephalosporin. Without antibiotics the mean latency was 1 day. No severe maternal complications occurred.

A total of 23 patients (37%) received corticosteroids (lung maturation) after 24 weeks of gestation. Birth was induced because of clinical signs of chorioamnionitis in 15 (24%) and cardiotocograph abnormalities in 2 (3%) pregnancies. Spontaneous onset of labor occurred in 46 (73%) pregnancies.

Of the 63 placentas analyzed, 38 showed histologic signs of chorioamnionitis; and of those 38, 26 had a pathologic cervical culture compared with 14 without histologic chorioamnionitis. Only 15 of the 38 women showed clinical signs of chorioamnionitis. One patient showed clinical signs of chorioamnionitis without histologic evidence. The placentas of the 12 infants discharged from hospital showed histologic chorioamnionitis in 5 (42%) cases compared with 12 of the 13 (92%) that died in hospital (P = 0.01). Two of the 5 women who delivered neonates with early onset sepsis showed histologic chorioamnionitis.

No significant difference existed in maternal leukocyte count or CRP at the time of PPROM among patients with stillbirth, a fetus that died, or an infant discharged from hospital (leukocytes: P = 0.95; CRP: P = 0.35). In addition, no difference was found in maternal leukocyte count and CRP among these 3 groups at the time of delivery (leukocytes: P = 0.56; CRP: P = 0.55).

Nine of the 12 (75%) infants discharged from hospital were delivered by cesarean compared with 5 of the 13 (38.5%) that died in hospital (P = 0.11).

Of the 25 neonates born alive, 16 (64%) were female and 9 (36%) male. There were 9 (75%) females and 3 (25%) males among the infants discharged from hospital compared with 6 (46%) females and 7 (54%) males that died in hospital.

### Table 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Gestational age at PPROM, weeks (No. of fetuses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20 + 6</td>
</tr>
<tr>
<td>IUFD and stillbirth</td>
<td>(n=27)</td>
</tr>
<tr>
<td>Live born</td>
<td>23 (85)</td>
</tr>
<tr>
<td>Died in hospital</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Discharged from hospital</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: PPROM, preterm premature rupture of membranes; IUFD, intrauterine fetal death.
Values are given as numbers (percentage).

Figure 2 Neonatal outcome data classified by gestational age at PPROM and birth. Key: + = intrauterine death and stillbirth; ○ = died in hospital; ● = discharged from hospital.
Overall assessment showed 1 child with severe disability, 1 child with moderate disability, 1 child with mild disability, and 6 children with normal outcome.

### 4. Discussion

The rate of premature deliveries has continued to increase in recent years. Survival rates of neonates delivered prematurely have improved with progress in obstetric and neonatal care even as the gestational age—considered to limit viability—has decreased. However, morbidity associated with PPROM is common and includes chronic lung disease, retinopathy, and neurologic and developmental disabilities [12]. The overall survival rate of the 71 fetuses in the present study was 17% (12/71), lower than the 26% reported by Falk et al. [13] and 47% reported by Dinsmoor et al. [14]. This discrepancy probably results from our inclusion of intrauterine fetal death within 24 hours after PPROM occurred.

Nine of the surviving infants were female and 3 were male. This gender distribution is consistent with reported data [15,16]. Nine of the 12 surviving infants were delivered by cesarean, as were 5 of the 13 that died within 31 days of delivery. Malloy et al. [17] reported no clear morbidity benefit of performing cesarean delivery in very-low-birth-weight infants, but their retrospective study was limited to neonates born alive. They found a significantly lower mortality of neonates weighing 501–750 g delivered by cesarean compared with neonates born vaginally (P = 0.046). Bottoms et al. [18] found that willingness to perform cesarean delivery for fetal indications between 23 and 25 weeks of gestation reduces fetal death rate, increases serious fetal morbidity, and virtually eliminates intrapartum fetal death. There is considerable potential for selection bias regarding mode of delivery of very-low-birth-weight neonates.

The majority of women (59/63) received antibiotics for at least 7 days. Antibiotics seem to be beneficial [19,20], but duration of treatment and type of antibiotics remain unclear. Segel et al. [21] found no benefit in giving antibiotics for 7 days compared with 3 days for prolonging latency to birth. In the present study, the patients who received amoxicillin-clavulanate had the longest latency period (16 days) and no neonatal complications attributed to this treatment were seen [22].

A total of 16 of the 63 patients had clinical signs of chorioamnionitis, confirmed by postnatal histology in 15 of

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### Table 2

Neonatal complications of the 12 infants discharged from hospital by gestational age at PPROM

<table>
<thead>
<tr>
<th>Neonatal complications</th>
<th>Gestational age at PPROM, weeks (No. of infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20 + 6 (n=2)</td>
</tr>
<tr>
<td>RDS</td>
<td>*</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>*</td>
</tr>
<tr>
<td>Sepsis a</td>
<td>*</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>*</td>
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<tr>
<td>Intraventricular hemorrhage III–IV</td>
<td>*</td>
</tr>
<tr>
<td>Periventricular leucomalacia</td>
<td>*</td>
</tr>
</tbody>
</table>

Abbreviations: PPROM, preterm premature rupture of membranes; RDS, respiratory distress syndrome.

Each asterisk represents a neonatal complication. Multiple complications are recorded separately.

### Table 3

Neonatal complications of the 12 infants discharged from hospital by gestational age at birth

<table>
<thead>
<tr>
<th>Neonatal complications</th>
<th>Gestational age at birth, weeks (No. of infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 + 0 - 6 (n=3)</td>
</tr>
<tr>
<td>RDS</td>
<td>*</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>*</td>
</tr>
<tr>
<td>Sepsis a</td>
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<tr>
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</tbody>
</table>

Abbreviations: RDS, respiratory distress syndrome. Each asterisk represents a neonatal complication. Multiple complications are recorded separately.

a Sepsis defined as: I/T ratio of neutrophils > 0.2; CRP > 8 mg/L, and hypotension.
these 16 cases. According to Sebire et al. [23], who reported a significantly higher prevalence of histologic inflammation in pregnancies with PPROM, the outcome in pregnancies without histologic chorioamnionitis was significantly better than in those with histologic chorioamnionitis.

The limitations of the present study include the small study population, caused by low frequency of PPROM. In addition, the inconsistent management in some cases (e.g., 4 patients received no antibiotics) shows the clear disadvantage of a retrospective study.

In conclusion, gestational age, birth weight, and histological chorioamnionitis have prognostic importance in pregnancies complicated by PPROM. Surviving infants who reach their second birthday have a 50% chance of a normal developmental and neurological outcome. Following spontaneous PPROM in early gestation – especially before viability – the decision of whether to induce labor or wait remains difficult. After consulting with neonatologists and obstetricians, the parents’ choice is of great importance. Owing to the possible medical complications for both mother and fetus, decisions regarding expectant management have to be re-evaluated periodically. With our current knowledge, decisions regarding PPROM pregnancies before 24 weeks of gestation must be made on an individual basis.

References