Is the prolongation of pregnancy less than 32 weeks with PPROM risk or benefit?

MILENA DOKOUPILOVA¹, MICHAL KOUCKY², ANDREA GERMANOVA², ZDENEK HAJEK²

Abstract

Objective: To evaluate the perinatal and early neonatal mortality and morbidity in premature infants to 32 weeks after spontaneous preterm original rupture of membranes (PPROM) before their delivery, over a period of 4 years. Methods: Retrospective analysis of premature infants with PPROM that resulted in delivery at less than 32 weeks at our institution from January 2006 to December 2008. The expectant management was used. All liveborn infants were divided according to the latency period into 3 categories (I. 1-48 hrs, II. 48-168 hrs, III. more than 168 hrs). Results: During the study interval, 191 infants with spontaneous PPROM were born before 32 weeks. 102 (49%) newborns were included to Category I, 56 (27%) to Category II, and 49 (24%) to Category III. The gestational age at PPROM in Category III was significantly lower than in Category I and II (24.1 vs 28.1; 28.0; p < 0.0001). The infection was the general cause of delivery in all categories, the fetal asposition with hypoxia were significantly increased in Category II and III than Category I (46%; 42% vs 12%; p < 0.0001) The incidence of chorioamnionitis and funisitis was the same in all three categories. Neonatal mortality and morbidity did not significantly increase with latency period. Conclusion: The prolongation of the latency period in pregnancies to 32 weeks does not deteriorate the neonatal mortality or morbidity.

Key words: prematurity, PPROM, expectant management, neonatal outcome

Introduction

Pre-term premature rupture of the membranes (PPROM) is defined as prelabour rupture of the membranes before the 37th week of gestation and complicates about one-third of all preterm deliveries [1-4]. The incidence is double in multiple gestations. The studies did not find differences in the frequency of PPROM according to socio-economic status [5, 6]. The optimal management of pregnancies complicated by PPROM has not been known to this time. Controversy exists regarding the optimum gestational age at which expectant management is discontinued and delivery is expedited. The lung maturity assessment may be useful to plan the timing of the delivery in gestational range of 32-34 weeks [7]. The particular pathogenesis of PPROM and premature labour is an inflammation, which entails high risk for fetal and maternal morbidity [8-10]. The highest incidence of chorioamnionitis is associated with lower gestational age and with prolongation of the latency period. The intrauterine infection as well as chorioamnionitis may be associated with subsequent development of adverse neonatal outcomes such as neonatal death, severe intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD) and congenital neonatal sepsis [8, 12]. New studies reflect more benefit from the elective prolongation of pregnancy with PPROM than the risk of these complications [13, 14]. The benefits of conservative management are mainly in prolonging pregnancy, which has the potential to decrease gestational age-related morbidity associated with preterm birth. The gestational age at birth is the most important factor for neonatal outcome. Antibiotics, tocolytic therapy and corticosteroids are basic therapy after PPROM. During conservative management, women should be monitored closely for placental abruption, infection and labour [15, 22]. The management of pregnancy with PPROM remains difficult. Some prenatal standard after the PPROM is lacking.

We reviewed neonatal outcome in all infants that were born in less than 32 weeks with perinatal complication of PPROM and were managed at our department, using a standardized expectant protocol. The aim of the study was to evaluate whether the different duration of an expectant management following PPROM can deteriorate the prognosis of these infants.
Material and methods

The retrospective cohort study included all inborn alive newborns born up to 31 + 6 weeks with perinatal complication of PPROM and admitted to NICU of the Regional Perinatal Centre in Prague from January 1, 2006 to December 31, 2009. The infants without the histological examination of the placenta were excluded (total of 3 infants). The latency period in PPROM was defined as the interval from spontaneous rupture of membranes to delivery up to 31 + 6 weeks.

The newborns were divided according to the latency period, Category I – 1-48 hrs; Category II – 48-168 hrs (7 days) and Category III – more than 168 hrs (7 days).

There were no differences in the treatment of multiple and singleton pregnancies. The PPROM was diagnosed by Actim PROM test (Medix Biochemica Ab, Finland).

The expectant management was used in all newborns and the termination of pregnancy was determined by the standard protocol in Figure 1. The expectant management included the administration of antibiotics (azitromycin or combination of ampicilin and gentamicin) and tocolytic therapy (betamimetic – hexoprenalин /Gynipral/, magnesium sulfuricum or Atosiban), and the dynamic monitoring of the inflammatory markers (leukocyte count, C-reactive protein – CRP). The bacterial swabs were taken. The ultrasound examination was targeted to the respiratory and general fetal movements. The cardiotocographs were recorded once or twice a day since 24 weeks of gestation. If the clinical and laboratory markers did not suggest an active infectious/inflammatory response of the mother and/or fetus, the pregnancy continued even after withdrawal of the antibiotics. The antibiotics were usually applied for 5-6 days. The timing of the induction of pulmonary maturity by corticosteroids was managed according to the probable risk of delivery. The tocolytic therapy was continuous if the inflammatory markers were negative. The decision about the discontinuation of the expectant management and the delivery management was based on the dynamic evaluation of the clinical condition as well as on the laboratory, the ultrasound examinations and the cardiotocographs. The arguments for termination of the pregnancy were the elevation of the clinical or laboratory markers of an inflammation (leukocyte count, CRP, maternal temperature > 38.0°C, fundal tenderness), anhydramnion (risk of umbilical cord compression) and severe bleeding (placental abruption). All placentas were submitted for histopathological examination.

The fundamental demographic data, the time of PPROM before delivery, the induction of the lung maturation, the cause of delivery, the maternal laboratory markers of inflammation, the histological signs of chorioamnionitis and funisitis, the 1st min and the 5th min Apgar score and neonatal mortality and morbidity were collected during the hospital stay. “Mortality” included neonatal death during hospitalization in a neonatal unit from delivery. Only the moderate and severe forms of bronchopulmonary dysplasia (BPD) were registered [21]. The retinopathy of prematurity (ROP) ≥ Stage III was evaluated according to the International Classification of Retinopathy of prematurity from 1987 [22] and cryocoagulation was indicated by the same team of ophthalmologic experts according to the same criteria during all investigated periods. The relevance of intraventricular haemorrhage (IVH) was defined with reference to the classification by Papile and stage III and more [23] was registered. Only cystic form of periventricular leukomalacia (PVL) was observed. The congenital neonatal sepsis (or early onset sepsis) was defined as positive blood cultures within first 72 hrs of life. All data were entered into a Microsoft Excel database during the hospital stay and at discharge or at time of death. The χ² test or Fisher’s exact test for categorical variables and unpaired t test for continuous variables were used in statistical evaluation. P value < 0.05 was considered as statistically significant.

Results

Between January 2006 and December 2009 a total of 541 newborns up to 31 + 6 were born and admitted to Intensive care unit of perinatology centre in Prague. One hundred ninety one (35%) liveborn newborns with perinatal complication of PPROM were included to this study during a four-year period, 102 (49%) newborns had the duration of the latency period to 48 hrs (Category I), 56 (27%) 48-168 hrs (Category II), and 49 (24%) newborns were born more than 168 hours (7days) after PPROM (Category III). The demographic data are listed in Table 1.

There were no significant differences in maternal leukocyte count before delivery, antenatal corticosteroid use, and Caesarean delivery between all Categories. The levels of maternal CRP before delivery were 2 times higher in Category I than in other categories, but without statistical significance. The incidence of chorioamnionitis and funisitis were not statistically increased with duration of PPROM. The infection was the general
cause of delivery in all categories; the fetal appositions with hypoxia were statistically significant frequent cause of delivery with duration of the latency period more than 48 hrs (12% vs 46%; 42%; $p < 0.0001$). The gestational age at PPROM in Category III was significantly lower than in I and II (24.1 vs 28.1; 28.0; $p < 0.0001$), Table 1.

There were no significant differences in birth weight, gestational age at birth, the Apgar score at the
Table 1. Demographic dates of pregnancy and delivery

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>Gestation age at PPROM, wks; mean ± SD (range)</th>
<th>Duration of PPROM, hrs (mean ± SD)</th>
<th>Maternal leukocyte count, (×10^9/l) (mean ± SD)</th>
<th>Maternal CRP, mg/l (mean ± SD)</th>
<th>Antenatal corticosteroid use, %</th>
<th>Chorioamnionitis, %</th>
<th>Funisitis, %</th>
<th>Multiple gestation, %</th>
<th>Caesarean delivery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>92</td>
<td>28.1 ± 1.9 (21-31)</td>
<td>17.2 ± 14.1</td>
<td>14.0 ± 4.1</td>
<td>23.1 ± 32.2</td>
<td>90</td>
<td>43</td>
<td>24</td>
<td>23</td>
<td>71</td>
</tr>
<tr>
<td>II</td>
<td>52</td>
<td>28.0 ± 2.1 (22-31)</td>
<td>84.7 ± 32.2</td>
<td>13.9 ± 3.1</td>
<td>14.7 ± 17.2</td>
<td>90</td>
<td>61</td>
<td>42</td>
<td>19</td>
<td>73</td>
</tr>
<tr>
<td>III</td>
<td>47</td>
<td>24.1 ± 3.1* (18-29)</td>
<td>542.9 ± 412.3</td>
<td>13.8 ± 4.2</td>
<td>12.4 ± 14.1</td>
<td>89</td>
<td>57</td>
<td>42</td>
<td>14</td>
<td>78</td>
</tr>
</tbody>
</table>

* completed and uncompleted course; \(p\) – value means comparison between category I and II, III: * \(p < 0.001\)

Table 2. Demographic data of infants, neonatal mortality and morbidity

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>Birthweight, g (mean ± SD)</th>
<th>Gestational age at delivery, wk (mean ± SD) (range)</th>
<th>Apgar score, 1 min, median (range)</th>
<th>Apgar score, 5 min, median (range)</th>
<th>Mortality, %</th>
<th>BPD, %</th>
<th>Number of ventilated infants, n (%)</th>
<th>Mechanical ventilation, day (median)</th>
<th>IVH, %</th>
<th>ROP, %</th>
<th>PVL, %</th>
<th>Early onset sepsis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>92</td>
<td>1191.1 ± 380.1</td>
<td>28.2 ± 2.1 (23-31)</td>
<td>7 (0-10)</td>
<td>8 (3-10)</td>
<td>5</td>
<td>12.5</td>
<td>20 (23)</td>
<td>9.5</td>
<td>2</td>
<td>4.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>52</td>
<td>1270.1 ± 363.9</td>
<td>28.6 ± 2.3 (23-31)</td>
<td>7 (1-10)</td>
<td>8 (1-10)</td>
<td>6</td>
<td>4</td>
<td>7 (14)</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>47</td>
<td>1142.7 ± 349.9</td>
<td>28.1 ± 2.2 (23-31)</td>
<td>7 (1-10)</td>
<td>8 (5-10)</td>
<td>6</td>
<td>4</td>
<td>13 (29)</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

BPD moderate and severe forms; ROP ≥ Stage III; IVH ≥ Grade III, PVL cystic forms

Table 3. Neonatal mortality and morbidity all infants with PPROM by the gestation age at delivery

<table>
<thead>
<tr>
<th>GA</th>
<th>n</th>
<th>Mortality (%)</th>
<th>Chorioamnionitis (%)</th>
<th>BPD (%)</th>
<th>IVH (%)</th>
<th>PVL (%)</th>
<th>ROP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>6</td>
<td>17</td>
<td>67</td>
<td>60</td>
<td>20</td>
<td>0</td>
<td>20</td>
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<tr>
<td>24</td>
<td>8</td>
<td>38</td>
<td>87</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>25</td>
<td>14</td>
<td>14</td>
<td>78</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>26</td>
<td>19</td>
<td>21</td>
<td>68</td>
<td>13</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>27</td>
<td>19</td>
<td>0</td>
<td>73</td>
<td>21</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>28</td>
<td>23</td>
<td>0</td>
<td>43</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>29</td>
<td>33</td>
<td>3</td>
<td>39</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>31</td>
<td>0</td>
<td>41</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>31</td>
<td>38</td>
<td>0</td>
<td>39</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
1st and the 5th minute. The neonatal mortality and morbidity did not increase with the latency period. The early onset infection was defined only in one newborn in Category III, Table 2.

At last we found the incidence of the neonatal mortality and morbidity in these infants by the gestational age at delivery regardless of the latency period duration. We declared the reduction of chorioamnionitis, neonatal mortality and morbidity with increasing gestational age at delivery, Table 3.

Discussion

Preterm PROM is a major cause of the neonatal morbidity and mortality. It complicates 20-30% of all preterm births. The expectant management of pregnancy with PPROM requires a careful assessment of the potential risks of intrauterine infection depending on the gestational age-related risks for neonatal mortality and morbidity.

The spontaneous PPROM complicated 35% of pregnancies up to 31+6 weeks in our considered period. We found the answer to the question whether the prolongation expectant of the management to more than 48 hours before 32 weeks of gestation brings any profit for the premature newborns. We can say that prolongation of the latency period does not affect the growth in majority of the newborns. The most frequent cause of delivery after PPROM in less than 32 weeks of gestation was an inflammation and fetal apposition with hypoxia after 48 hour duration of the latency period. The pulmonary maturity induction by corticosteroids was high in all categories (90%) and can relate to no difference in neonatal morbidity after PPROM.

The Ramsay’s study [24] demonstrates the development of chorioamnionitis associated with an increasing incidence of neonatal morbidity after PPROM. The result of Dexter’s study shows an increasing incidence of early onset neonatal sepsis with development of chorioamnionitis [25]. In our retrospective study we did not prove a higher incidence of neonatal mortality or morbidity with an increasing incidence of chorioamnionitis with a longer latency period. On the other hand we state that the gestational age at delivery is the most important point of neonatal mortality and morbidity.

The results of the latency period longer than 7 days do not worsen the outcome for the newborns in our retrospective analysis. In some cases the prolongation of gestational age for more than 1-3 weeks can bring better outcome for premature newborns. Future research should focus on the finding of how to prolong the gestational age after PPROM for more than 1-3 weeks.

References

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