The role of latency period on the preterm premature rupture of membranes: implication for treatment

Type
Research paper

Keywords
treatment, latency period, premature rupture of membranes, care, preterm

Abstract
Introduction
Conservative treatments with latency period have been used for the treatment of preterm premature rupture of membranes (PPROM) in clinical practice, we aimed to evaluate the role and potential influencing factors of latency period, to provide insights to the clinical treatment of PPROM.

Material and methods
PPROM pregnant women treated in our hospital from January 1, 2015 to September 30, 2020 were included. PPROM patients were divided into 48~168h group and the >168h latency group, the characteristics and prognosis of this two groups were compared and analyzed. Logistic regression analyses were conducted to analyze the relevant influencing factors of latency period.

Results
A total of 131 PPROM patients were included. There were significant differences on the age, BMI, gestational age on admission, amniotic fluid volume before childbirth, and positive rate of cervical secretion culture between two groups (all p<0.05). Logistic regression analyses indicated that the latency period was shorter in the PPROM patients with age≥30y(OR0.048, 95%CI0.121~0.863) and gestational age≥32w on admission(OR0.463, 95%CI0.069~0.811), and the latency period was prolonged in the PPROM patients with BMI≥23kg/㎡(OR1.591, 95%CI1.134~1.944) and amniotic fluid volume≥6cm(OR2.129, 95%CI1.093~3.042) (all p<0.05). There were significant differences in the incidence of low birth weight and NRDS between 48~168h group and >168h group (all p<0.05).

Conclusions
Latency period plays an important role in the PPROM, which is associated with the pregnant women's age, BMI, gestational week of rupture and amniotic fluid index.
Title page

Title: The role of latency period on the preterm premature rupture of membranes: implication for treatment

Running title: latency period & PPROM

Authors: Lin Lu1*, Jianhua Li1†, Bei Gan1, Shan Zheng1, Lihong Chen#1

1, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Fujian Medical University, Fuzhou 350005, China

*, Equal contributor

#, Corresponding author

Corresponding to: Lihong Chen  ucookyq0640226@163.com

Address: No. 20, Chazhong Road, Taijiang District, Fuzhou City, Fujian Province, China

Telephone: 13645072616

Fax: 0024 07898 1023
The role of latency period on the preterm premature rupture of membranes: implication for treatment

Abstract

Introduction: Conservative treatments with latency period have been used for the treatment of preterm premature rupture of membranes (PPROM) in clinical practice, we aimed to evaluate the role and potential influencing factors of latency period, to provide insights to the clinical treatment of PPROM.

Methods: PPROM pregnant women treated in our hospital from January 1, 2015 to September 30, 2020 were included. PPROM patients were divided into 48~168h group and the >168h latency group, the characteristics and prognosis of this two groups were compared and analyzed. Logistic regression analyses were conducted to analyze the relevant influencing factors of latency period.

Results: A total of 131 PPROM patients were included. There were significant differences on the age, BMI, gestational age on admission, amniotic fluid volume before childbirth, and positive rate of cervical secretion culture between two groups (all p<0.05). Logistic regression analyses indicated that the latency period was shorter in the PPROM patients with age≥30y(OR0.048, 95%CI0.121~0.863) and gestational age≥32w on admission(OR0.463, 95%CI0.069~0.811), and the latency period was prolonged in the PPROM patients with BMI≥23kg/㎡ (OR1.591, 95%CI1.134~1.944) and amniotic fluid volume≥6cm(OR2.129, 95%CI1.093~3.042) (all p<0.05).

There were significant differences in the incidence of low birth weight and NRDS between 48~168h group and >168h group (all p<0.05).

Conclusions: Latency period plays an important role in the PPROM, which is associated with the
pregnant women's age, BMI, gestational week of rupture and amniotic fluid index.

**Keywords:** premature rupture of membranes; preterm; latency period; care; treatment

**Background**

Premature rupture of membrane (PROM) refers to the spontaneous rupture of fetal membranes before labor[1]. According to the gestational age at the time of occurrence, PROM is divided into preterm premature rupture of membranes (PPROM) and full-term premature rupture of membranes. PPROM occurs when the pregnancy is more than 20 weeks and less than 37 weeks. According to statistics[2, 3], the incidence of PPROM is 2.0%~3.5%, and 30%~40% of preterm births are related with PPROM. PPROM can cause premature birth, placental abruption, oligohydramnios, umbilical cord prolapse, fetal distress and neonatal respiratory distress syndrome (NRDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis(NEC), leading to higher perinatal morbidity and mortality[4-6]. Therefore, taking correct treatment measures for PPROM patients is crucial to reduce the perinatal complications and improve the prognosis of newborns.

It’s been reported that for PPROM patients, the less the gestational age, the higher infection rate of pregnant women, fetuses, and perinatal mortality[7]. Previous studies[8, 9] have shown that prolonging the latency period for pregnant women with PPROM can reduce the infection rate of newborns, but it is difficult to grasp the balance between prolonging the latency period and the timing of termination of pregnancy. Therefore, we aimed to retrospectively evaluate the influencing factors of latency period in pregnant women with PPROM, to provide insights to the clinical treatment and management of PPROM.

**Methods**
Ethical concerns

In this study, all methods were performed in accordance with the relevant guidelines and regulations. This study had been checked and approved by the ethical committee of our hospital (1901824-EB), all the included patients had been well informed and written informed consents had been obtained from patients.

Patients

We selected PPROM pregnant women admitted to our hospital from January 1, 2015 to September 30, 2020 as the research populations. The selection criteria of the patients in this study were as following: ① patients were admission to our hospital within 12 hours after the occurrence of PPROM; ② the gestational age of patients was 28 to 33 weeks +6 on admission; ③ pathological examination of the placenta, fetal membranes, and umbilical cord after delivery were detected in our hospital. Exclusion criteria were as following: ① The latency period after admission was less than 48 hours; ② Pregnant women with congenital abnormalities of fetus; ③ Patients who were unwilling to participate in this study. Patients with PPROM were divided into two groups according to the latency period after the occurrence of PPROM: the 48～168h group and the >168h group.

Treatment of PPROM

We routinely used dexamethasone 5 mg intramuscular injection, 1 time/12h, 2d to promote fetal lung maturity. At the same time, second-generation cephalosporins or azithromycin was used to prevent infection. For patients with ≥ 8 uterine contractions within 60 minutes, uterine pressure ≥ 60 mm Hg, and uterine orifice dilation <3 cm, magnesium sulfate, ritodrine hydrochloride, or nifedipine would be used with the patient’s consent. All patients were monitored for leukocytes,
C-reactive protein (CRP), and fetal heart rate every 3 days, and B-ultrasound monitoring and cervical secretion culture were performed once a week.

Diagnostic criteria

① Oligo and oligohydramnios: B-mode ultrasound measurement of amniotic fluid index (AFI) ≤8 cm was taken as oligohydramnios; ② Intrauterine infection: maternal fever ≥37.8 °C, accompanied by the following two or more conditions: maternal pulse >100 beats/min, white blood cell count >15×10⁹/L, fetal heart rate >160 beats/min, uterine tension and tenderness, smelly amniotic fluid, or positive amniotic cavity culture; ③ Histology Chorioamnionitis (HCA): Inflammatory cell infiltration occurred in any tissue of chorionic membrane, amniotic membrane, and umbilical cord; ④ Cervical secretion culture was positive: After PPROM occurred, we took a sterile swab to take the secretions from the cervix, and culture the bacteria, mycochlamydia, fungi, anaerobic bacteria, and gonococcus in our laboratory. Any culture with positive result was considered that cervical secretion culture was positive. All the included patients received Ceftriaxone sodium 2 g i.v.gtt before delivery.

Data collection

Two investigators collected following patient’s information: age, body mass index (BMI), first pregnancy or not, the gestational age, white blood cells, amniotic fluid volume and CRP at the timepoint of admission and before childbirth. Besides, we collected the uterine contraction inhibitor use after 48 hours, results of cervical secretion culture, the incidence of intrauterine infection and HCA.

Statistical analysis

We used the SPSS25.0 software package for statistical analysis. The measurement data were
described using mean ± standard deviation. The comparison between groups was performed by two independent sample t-test or rank-sum test. The count data was represented by rate, and the comparison between groups was performed by chi-square test. With 0.05 as the level of selected variables and 0.10 as the level of excluded variables, forward step-by-step logistic regression analysis was used to analyze relevant influencing factors. p<0.05 indicated that the difference between groups was statistically significant.

Results

The characteristics of included patients

A total of 131 PPROM patients were included in this present study. As presented in Table 1, compared the >168h group, there were significant differences on the age, BMI, gestational age on admission, amniotic fluid volume before childbirth, and positive rate of cervical secretion culture in the 48-168h group(all p<0.05). There were no statistical differences in the first pregnancy, gestational age before childbirth, white blood cell, amniotic fluid volume on admission, CRP, Uterine contraction inhibitor use after 48 hours, incidence of intrauterine infection and HCA between48~168h group and >168h group (all p>0.05).

Table 1 The characteristics of included patients

Logistic regression analysis on the influencing factors of latency period

We used global optimization logistic regression, took the latency period time as the dependent variable, and all other observed indicators as independent variables, and we used the Hosmer-Lemeshow test to detect the goodness of fit of the model. It is found that the age of pregnant women, the gestational age on admission and the latency period were negatively correlated. And BMI, the
amniotic fluid volume were positively correlated with the latency period. As presented in Table 2, we used forward stepwise logistic regression to analyze the influencing factors, it is found that the latency period was shorter in the PPROM patients with age ≥30y (OR0.048, 95% CI 0.121–0.863) and gestational age ≥32w on admission (OR0.463, 95% CI 0.069–0.811), and the latency period was prolonged in the PPROM patients with BMI ≥23kg/m² (OR1.591, 95% CI 1.134–1.944) and amniotic fluid volume ≥6cm (OR2.129, 95% CI 1.093–3.042) (all p < 0.05).

Table 2 Logistic regression analysis on the influencing factors of latency period in the PPROM patients

The prognosis of newborns

As indicated in Table 3, there were significant differences in the incidence of low birth weight and NRDS between 48~168h group and >168h group (all p < 0.05), and no significant differences in the incidence of pneumonia, sepsis, IVH, HIE, NEC were found (all p > 0.05).

Table 3 The prognosis of newborns between 48~168h and >168h groups

Discussions

At present, the specific mechanisms of PROM have not been fully understood. Studies [10-12] have shown that bacterial vaginitis, urinary tract infection, smoking during pregnancy, history of premature rupture of membranes, sexually transmitted diseases, abnormal cervical function, polyhydramnios, and invasive procedures are risk factors for premature rupture of membranes, among which genital tract infection has been considered to be the main cause of premature rupture of membranes. The hormone levels and immunity of pregnant women have changed, and their
susceptibility to a variety of pathogens has increased, and they are susceptible to infection with these pathogens[13-15]. As an active immune site, the placenta can cause inflammation and immune response under the action of pathogenic bacteria, and promote the production and release of a variety of inflammatory cytokines[16, 17]. The maternal immune system is activated in this environment, resulting in damage to the placenta, causing adverse pregnancy outcomes such as premature birth[18]. Studies[19, 20] have found that the detection rate of bacteria in the amniotic fluid for PROM reaches 30%, and another 70% of patients may also be infected by the living maternal tissues of amniotic fluid. Therefore, the early diagnosis and timely treatment is vital to the prognosis of PROM patients.

We have found that the earlier the gestational week of the PPROM is, the longer the latency period is, which is consistent with the results of previous reports[21, 22], and the pregnant women whose membrane rupture occurs before 32 weeks have a greater probability of latency period > 168h. It’s been reported[23] that expecting a time longer than 1 week does not increase the risk of HCA, so pregnant women who have ruptured membranes before 32 weeks should keep the latency period more than one week. There are still many controversies about the relationship between the number of pregnancy, age and latency period of pregnant women. The results of this study show that the patient's parity is not a risk factor that affects the latency period, which is consistent with the results of previous studies[24, 25]. It’s been reported that gestational age is closely associated with preterm premature rupture of membranes[26, 27]. Pregnant women over the age of 30 have an increased probability of shortening the latency period. It is estimated that different medical institutions have biases in the selection of latency period. Yet the specific latency period requires large-scale, multi-centered researches in the future.
In our study, the amniotic fluid index of the two groups of patients is not statistically significant at admission, but during the latency period, when the amniotic fluid index is above 6 cm, the possibility of latency period > 168 h increases accordingly. The possible reasons may be as following: rupture of the membrane lead to the fetal head closes to the lower part of the uterus, which has a mechanical expansion effect on it, causing the start of labor[28]. Besides, the fetus closes to the uterine wall, the umbilical cord is compressed, the incidence of fetal distress increases, and the termination of pregnancy is early[29-31]. The amniotic fluid volume of pregnant women is closely related to infection. Infection makes the fetus in a state of stress, reduces blood flow in the kidneys and urine output, and reduces amniotic fluid volume[9]. Amniotic fluid contains a variety of anti-infective cytokines, and the loss of amniotic fluid makes the ability resistant to infection is weakened, thereby aggravating intrauterine infections, which can easily induce contractions[32, 33]. Therefore, for pregnant women with PPROM with progressive reduction in amniotic fluid, even if there is no clinical evidence of infection, they must be highly vigilant for the occurrence of chorioamnionitis[34].

Previous studies have reported[35-37] that for PPROM patients who have fetal lung maturity and infection, simply extending the gestational week will not reduce the serious complications of preterm infants, but PPROM pregnant women have reduced amniotic fluid, higher incidence of chorioamnionitis and various inflammations in the amniotic fluid. The increase in substances can affect the growth and development of the fetus, causing the fetal body mass to not increase correspondingly with the growth of the gestational age. The more the gestational age increases, the more the fetal body mass lags behind[38]. We have found that extending the gestational age does not reduce the incidence of serious complications of preterm infants and maternal infectious diseases,
and the use of uterine contraction inhibitors does not help to extend the gestational age. Therefore, for PPROM patients, the focus should be on predicting and treating infections. For patients with increased WBC, progressive increase in CRP, and progressive decrease in amniotic fluid, even if intrauterine infection cannot be diagnosed clinically, a comprehensive assessment should be combined with the specific conditions of the patient. It’s been reported that Intrauterine infection is thought to be one cause of PPROM, antibiotic regimens use is beneficial to the control of intrauterine infection and reduce infant morbidity[39, 40]. Still, the timing and dose of antibiotic regimens in the PPROM remain further investigations.

Conclusions

In summary, we have found that for PPROM patients, pregnant women's age, BMI, gestational week of rupture and amniotic fluid index are associated with the latency period. With longer latency period, the incidence of NRDS is lower, but the incidence of low birth weight is higher. Limited by sample size and study design, future studies with larger sample size and prospective design are needed to further elucidate the potentially influencing factors of latency period, to provide evidence to the management of PPROM.

List of abbreviations

PROM: premature rupture of membrane
PPROM: preterm premature rupture of membranes
NRDS: neonatal respiratory distress syndrome
IVH: intraventricular hemorrhage
NEC: necrotizing enterocolitis
CRP: C-reactive protein
AFI: amniotic fluid index

HCA: histology chorioamnionitis

BMI: body mass index

**Declarations**

**Ethics approval and consent to participate**

In this study, all methods were performed in accordance with the relevant guidelines and regulations. This study had been checked and approved by the ethical committee of our hospital (1901824-EB), all the included patients had been well informed and written informed consents had been obtained from patients.

**Consent for publication**

Not applicable.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This study has been funded by Industry-University-Research Project of Fujian Provincial Department of Education (JAT160189). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Author contributions**

L C designed research; L L, J L, B G, S Z conducted research; L L, J L, B G analyzed data; L L wrote the first draft of manuscript; L C had primary responsibility for final content. All authors read
and approved the final manuscript.

Acknowledgments

None.


347  V, Zemlickova H, Homychova H et al: Antibiotic administration reduces the rate of
348  intraamniotic inflammation in preterm prelabor rupture of the membranes. Am J
349  Obstet Gynecol 2020, 223(1):114 e111-114 e120.
351  YA, Meis PJ, Moawad AH, Iams JD et al: Antibiotic therapy for reduction of infant
352  morbidity after preterm premature rupture of the membranes. A randomized
353  controlled trial. National Institute of Child Health and Human Development
355  40. Martingano D, Singh S, Mitrofanova A: Azithromycin in the Treatment of Preterm
356  Prelabor Rupture of Membranes Demonstrates a Lower Risk of Chorioamnionitis
357  and Postpartum Endometritis with an Equivalent Latency Period Compared with
Table 1 The characteristics of included patients

<table>
<thead>
<tr>
<th>Items</th>
<th>48~168h group (n=68)</th>
<th>&gt;168h group (n=63)</th>
<th>t/χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>30.81±8.09</td>
<td>25.53±7.16</td>
<td>1.024</td>
<td>0.027</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.72±2.55</td>
<td>22.47±1.94</td>
<td>1.217</td>
<td>0.014</td>
</tr>
<tr>
<td>First pregnancy</td>
<td>38(55.88%)</td>
<td>35(55.56%)</td>
<td>1.108</td>
<td>0.092</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>31.13±1.32</td>
<td>31.56±1.60</td>
<td>1.133</td>
<td>0.031</td>
</tr>
<tr>
<td>Before childbirth</td>
<td>31.74±1.24</td>
<td>31.89±1.39</td>
<td>1.106</td>
<td>0.072</td>
</tr>
<tr>
<td>White blood cells (×10⁹/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>12.38±4.91</td>
<td>11.95±4.14</td>
<td>1.118</td>
<td>0.097</td>
</tr>
<tr>
<td>Before childbirth</td>
<td>14.72±5.13</td>
<td>14.68±6.01</td>
<td>1.201</td>
<td>0.104</td>
</tr>
<tr>
<td>Amniotic fluid volume (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>7.63±4.35</td>
<td>8.03±5.23</td>
<td>1.186</td>
<td>0.092</td>
</tr>
<tr>
<td>Before childbirth</td>
<td>4.290±2.31</td>
<td>5.66±2.75</td>
<td>1.159</td>
<td>0.034</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission</td>
<td>5.69±4.11</td>
<td>6.04±2.96</td>
<td>3.137</td>
<td>0.121</td>
</tr>
<tr>
<td>Before childbirth</td>
<td>24.08±10.27</td>
<td>22.36±8.05</td>
<td>6.223</td>
<td>0.076</td>
</tr>
<tr>
<td>Uterine contraction inhibitor use after 48 hours</td>
<td>61(89.71%)</td>
<td>50(79.37%)</td>
<td>1.303</td>
<td>0.116</td>
</tr>
<tr>
<td>Positive cervical secretion culture</td>
<td>21(30.88%)</td>
<td>24(38.09%)</td>
<td>1.125</td>
<td>0.044</td>
</tr>
<tr>
<td>Intrauterine infection</td>
<td>7(10.29%)</td>
<td>7(11.11%)</td>
<td>1.203</td>
<td>0.089</td>
</tr>
<tr>
<td>HIE</td>
<td>56(82.35%)</td>
<td>51(80.95%)</td>
<td>1.167</td>
<td>0.105</td>
</tr>
</tbody>
</table>

Table 2 Logistic regression analysis on the influencing factors of latency period in the PPROM patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>Wald</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age≥30y</td>
<td>-0.153</td>
<td>2.127</td>
<td>0.048</td>
<td>0.121~0.863</td>
<td>0.042</td>
</tr>
<tr>
<td>Gestational age≥32w on admission</td>
<td>-0.122</td>
<td>1.199</td>
<td>0.463</td>
<td>0.069~0.811</td>
<td>0.025</td>
</tr>
<tr>
<td>BMI≥23kg/m²</td>
<td>0.113</td>
<td>2.037</td>
<td>1.591</td>
<td>1.134~1.944</td>
<td>0.038</td>
</tr>
<tr>
<td>Amniotic fluid volume ≥6cm</td>
<td>0.101</td>
<td>3.115</td>
<td>2.129</td>
<td>1.093~3.042</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Table 3 The prognosis of newborns between 48~168h and >168h groups

<table>
<thead>
<tr>
<th>Items</th>
<th>48~168h group (n=68)</th>
<th>&gt;168h group (n=63)</th>
<th>t/χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birth weight</td>
<td>32(47.06%)</td>
<td>36(57.12%)</td>
<td>1.327</td>
<td>0.011</td>
</tr>
<tr>
<td>NRDS</td>
<td>12(17.65%)</td>
<td>3(4.76%)</td>
<td>1.105</td>
<td>0.043</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>35(51.47%)</td>
<td>33(52.38%)</td>
<td>1.041</td>
<td>0.098</td>
</tr>
<tr>
<td>Sepsis</td>
<td>14(20.59%)</td>
<td>11(17.46%)</td>
<td>1.294</td>
<td>0.077</td>
</tr>
<tr>
<td>IVH</td>
<td>20(29.41%)</td>
<td>20(31.75%)</td>
<td>1.217</td>
<td>0.102</td>
</tr>
<tr>
<td>HIE</td>
<td>31(45.59%)</td>
<td>29(46.03%)</td>
<td>1.454</td>
<td>0.096</td>
</tr>
<tr>
<td>NEC</td>
<td>12(17.65%)</td>
<td>11(17.46%)</td>
<td>1.049</td>
<td>0.079</td>
</tr>
</tbody>
</table>