Management of Premature Rupture of Membranes in the Late Pre-term Period (weeks 34 to 37): Review of New Guidelines

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ABSTRACT Late, preterm premature rupture of the membranes (PPROM) presents a major obstetrical challenge balancing between iatrogenic prematurity and risk of prolonged rupture of membranes. In recent years, the pendulum has been shifting toward expectant management until gestation week 37 + 0. We examined the latest guidelines and major trials and summarized optimal management. We addressed the major dilemmas of women with PPROM during gestation weeks 34 + 0 to 36 + 6.

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Preterm premature rupture of the membranes (PPROM) refers to rupture of the membranes before onset of labor and prior to week 37 + 0 of gestation. Studies have shown that PPROM occurs in approximately one-third of all preterm births and is associated with increased risk of neonatal morbidity and mortality [1-5]. At term, immediate delivery results in lower incidence of maternal infection and compared with expectant management (EM) with no significant changes in risk of perinatal morbidity or mortality [6,7]. At early preterm, prior to week 34 + 0 of gestation, the risks of neonatal complications due to iatrogenic prematurity outweigh the risk of ascending infection, placental abruption, intrapartum fetal distress, and cord prolapse [5,8-10], and thus international guidelines recommend expectant management in these cases [11-14].

The management of women with late PPROM, which is between weeks 34 + 0 and 36 + 6, has seen major changes in recent years. Due to new studies showing the relative safety of expectant management even in these weeks [5,15-17], the pendulum has shifted toward expectant management until week 37 + 0 [11-14]. However, this change in recent guidelines has raised new questions and dilemmas regarding the optimal treatment for these cases. For this article, we reviewed the data and guidelines regarding the expectant management of PPROM between weeks 34 + 0 to 36 + 6 of gestation and accentuated and resolved problematic issues in the new guidelines.

THE OPTIMAL MANAGEMENT OF LATE PPROM HAS YET TO BE DETERMINED

TIMING OF DELIVERY

The previous American College of Obstetricians and Gynecologists guidelines (ACOG) and Royal College of Obstetrics and Gynecology (RCOG) guidelines recommended delivery for all women with PPROM beyond week 34 0/7 [18]. However, these recommendations were based on limited scientific data.

New data from the last few years have led to a change in these recommendations. Recent prospective trials and a Cochrane database analysis found that induction of labor (IOL) for near term PPROM did not reduce the rate of neonatal sepsis when compared to an expectant management (EM) regime until week 37 + 0 of gestation (risk ratio [RR] 0.93, 95% confidence interval [95%CI] 0.66–1.30). However, early IOL did result in higher rates of neonatal respiratory distress syndrome (RDS) (RR 1.26, 95%CI 1.05–1.53) and increased rates of cesarean section (RR 1.26, 95%CI 1.11–1.44) with a reduction of chorioamnionitis (RR 0.50, 95%CI 0.26–0.95]. Furthermore, there were no differences in overall perinatal mortality or intrauterine deaths (RR 1.76, 95%CI 0.89–3.50 and RR 0.45, 95%CI 0.13–1.57, respectively) when comparing early IOL to EM [5,15-17,20].

These findings led to a change in most new guidelines that now state that, in the absence of contraindications to continuing the pregnancy, a woman should be offered expectant management until 37 + 0 weeks of gestation [11-14].

An interesting question that has yet to be fully addressed by these new studies and guidelines is whether a woman presenting with PPROM prior to week 34 + 0 should be managed with the same expectant management on reaching week 34 + 0 of gestation, compared to a woman who presented with PPROM between weeks 34 + 0 and 36 + 6. The recent ACOG guidelines did not address this specific issue [11]. The new RCOG guidelines state that all women whose pregnancies are complicated by PPROM after week 24 + 0 of gestation and who have no contraindications to continuing

the pregnancy, should be offered expectant management until 37 + 0 weeks [12]. The PPROMT trial published in 2016 is perhaps the largest, adequately powered, randomized controlled study comparing IOL to EM for women with PPROM between 34 + 0 and 36 + 6 weeks of gestation. In this study, the 1839 women included were randomly assigned to each group according to a power analysis calculation. However, only 20% of those women presented with PPROM prior to week 34 + 0. A subgroup analysis of these women with duration of more than 48 hours from PPROM to randomization showed a non-statistically significant increase in neonatal sepsis (1% vs. 4% $P = 0.07$) [15]. These findings suggest that in this group of women with prolonged PPROM, a difference in rates of neonatal sepsis might exist and may be more significant in larger numbers.

RECENT STUDIES SUGGEST THAT MOST WOMEN SHOULD BE OFFERED EXPECTANT MANAGEMENT UNTIL WEEK 37 + 0

ANTIBIOTICS

Administration of broad-spectrum antibiotics prolongs pregnancy and reduces maternal and neonatal infections as well as gestational age-dependent morbidity [20-22], although there has been considerable inconsistency in primary outcomes selection in different studies [24]. A Cochrane review investigating the role of antibiotics for women with confirmed PPROM found that the use of antibiotics is associated with a statistically significant reduction in chorioamnionitis (RR 0.66, 95%CI 0.46–0.96). There was a significant reduction in the numbers of babies born within 48 hours (RR 0.71, 95%CI 0.58–0.87) and 7 days (RR 0.79, 95%CI 0.71–0.89). Neonatal infection, use of surfactant, oxygen therapy, and abnormal cerebral ultrasound prior to discharge from hospital were also reduced [20,21].

EXPECTANT MANAGEMENT SHOULD INCLUDE LATENCY ANTIBIOTICS AND A COURSE OF ANTENATAL CORTICOSTEROIDS; TOCOLYTICS SHOULD BE AVOIDED

A 7-day course of therapy of latency antibiotics with a combination of intravenous ampicillin and erythromycin, followed by oral amoxicillin and erythromycin, is recommended during expectant management of women with PPROM [11,12].

The new ACOG guidelines, allowing expectant management for women with PPROM between 34 + 0 and 36 + 6 weeks of gestation clearly state that latency antibiotics are not appropriate in this setting. However, they do not mention any reference to scientifically validate this statement.

In the PPROMT trial, perhaps the largest study regarding the management of near term PPROM and cited by the ACOG guidelines, 90% of women were treated with antibiotics as part of expectant management protocol [5]. Prior studies also included the use of antibiotics as part of treating near term PPROM [16,17]. Furthermore, European guidelines oppose this approach and recommend the use of prophylactic antibiotics even in near-term PPROM [13,14]. Therefore, it is reasonable to allow the use of prophylactic antibiotics as part of the care for woman with PPROM after week 34 + 0.

CORTICOSTEROIDS

Administration of antenatal corticosteroids (ANCS) has been considered one of the most significant management practices affecting perinatal outcomes in pregnancies complicated by preterm labor [24-26]. In 1995, the U.S. National Institutes of Health (NIH) and American College of Obstetrics and Gynecologists (ACOG) recommended treating women at risk for preterm labor with ANCS [27]. In a Cochrane review, administration of ANCS was shown to reduce rates of common complications affecting premature neonates such as intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS), and neonatal sepsis, as well early neonatal mortality [28].

Delivery during these weeks may disrupt important processes of fetal development and led to early neonatal complications, including RDS [29], and increased rates of neurodevelopmental disorders such as cerebral palsy [30]. The pioneering study by Gyamfi-Bannerman et al. [31] examined the effect of ANCS administration on late preterm birth. This double-blind randomized placebo-controlled trial evaluated women at 34 to 37 weeks of gestation who were at risk for preterm labor, including those arriving with spontaneous PPROM. A significant advantage in the primary outcome, which included a composite of respiratory disorders, was detected in women who received ANCS [RR 0.65, 95%CI 0.53–0.84, $P < 0.001$]. In addition, a systematic review and meta-analysis of randomized controlled trials also showed a reduction in rates of neonatal morbidities such as RDS and transient tachypnea of the newborn (TTN), as well as an increase in APGAR score for women treated with ANCS prior to delivery during the late preterm period [32]. Subsequently, the ACOG [11,33] and Society of Maternal-Fetal-Medicine (SMFM) [34] extended their recommendation for ANCS administration to include women at risk for preterm labor to up to 37/0 weeks of gestation, including women with PPROM.

TOCOLYTICS

There is insufficient data to support or refute the use of tocolytic therapy in the setting of preterm PROM. There have not been many trials comparing the use of tocolysis to that of placebo in the setting of PPROM, and the studies that have been published involved only small numbers of participants and inconstant use of latency antibiotics and corticosteroids.

A Cochrane review published in 2014 showed that the use of tocolysis compared with placebo in PPROM did not influence perinatal mortality [RR 1.67, 95%CI 0.85–3.29]. The use of tocolysis resulted in a prolonged latency period by a mean difference of 73 hours [95%CI 20–126] and decreased the birth rate within 48 hours [RR 0.55, 95%CI 0.32–0.95]. However,

it was also associated with increased risk of a 5-minute Apgar score of less than 7 [RR 6.05, 95%CI 1.65–22.23], increased need for ventilation support [RR 2.46, 95%CI 1.14–5.34], and increased risk of chorioamnionitis [35,36]. The review concluded that there was an increase in maternal chorioamnionitis without significant benefits to the neonate.

These finding led the ACOG and RCOG to conclude that although the use of tocolysis is reasonable in the setting of early PPROM, prior to week 34 + 0, it is not recommended for late PPROM between 34 + 0 and 36 + 6 weeks of gestation [11,12].

DISCUSSION

The management of late PPROM has changed greatly in recent years. In this article we reviewed changes in expectant management for these cases and related new challenges and considerations. We summarized the recommendations of the different international obstetrics committees.

Based on our review, we conclude that obstetric care for women with late PPROM should be offered expectant management until week 37 + 0, including latency antibiotics and a course of antenatal corticosteroids. Tocolytics should be avoided.

The main question that remains to be fully answered is whether the management of prolonged early PPROM on reaching week 34 + 0 of gestation should be any different than what was initially presented for PPROM between weeks 34 + 0 to 36 + 6. We believe that future studies should focus on examining the differences between these two groups.

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References

1. Arias F, Tomich P. Etiology and outcome of low birth weight and preterm infants. *Obstet Gynecol* 1982; 60 (3): 277-81.
2. Lee T, Silver H. Etiology and epidemiology of preterm premature rupture of the membranes. *Clin Perinatol* 2001; 28 (4): 721-34.
3. Mercer BM, Goldenberg RL, Meis PJ, et al. The Preterm Prediction Study: prediction of preterm premature rupture of membranes through clinical findings and ancillary testing. The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am J Obstet Gynecol* 2000; 183 (3): 738-45.
4. Mercer BM. Preterm premature rupture of the membranes: current approaches to evaluation and management. *Obstet Gynecol Clin North Am* 2005; 32 (3): 411-28.
5. Bond DM, Middleton P, Levett KM, et al. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. *Cochrane Database Syst Rev* 2017; 3 (3): CD004735.
6. Hannah ME, Ohlsson A, Farine D, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. TERMPROM Study Group. *N Engl J Med* 1996; 334 (16): 1005-10.
7. Middleton P, Shepherd E, Flenady V, McBain RD, Crowther CA. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). *Cochrane Database Syst Rev* 2017; 1 (1): CD005302.
8. Mercer BM, Crocker LG, Boe NM, Sibai BM. Induction versus expectant management in premature rupture of the membranes with mature amniotic fluid at 32 to 36 weeks: a randomized trial. *Am J Obstet Gynecol* 1993; 169 (4): 775-82.
9. Alexander JM, Cox SM. Clinical course of premature rupture of the membranes. *Semin Perinatol* 1996; 20 (5): 369-74.
10. Gonen R, Hannah ME, Milligan JE. Does prolonged preterm premature rupture of the membranes predispose to abruptio placentae? *Obstet Gynecol* 1989; 74 (3 Pt 1): 347-50.
11. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. *Obstet Gynecol* 2020; 135 (3): e80-e97.
12. Thomson AJ; Royal College of Obstetricians and Gynaecologists. Care of Women Presenting with Suspected Preterm Prelabour Rupture of Membranes from 24+0 Weeks of Gestation: Green-top Guideline No. 73. *BJOG* 2019; 126 (9): e152-e166.
13. Schmitz T, Sentilhes L, Lorthe E, et al. Preterm premature rupture of the membranes: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Reprod Biol* 2019; 236: 1-6.
14. Berger R, Abele H, Bahlmann F, et al. Prevention and therapy of preterm birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, February 2019) - Part 1 with Recommendations on the Epidemiology, Etiology, Prediction, Primary and Secondary Prevention of Preterm Birth. *Geburtshilfe Frauenheilkd* 2019; 79 (8): 800-812.
15. Morris JM, Roberts CL, Bowen JR, et al; PPROMT Collaboration. Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. *Lancet* 2016; 387 (10017): 444-52.
16. Vijgen SM, van der Ham DP, Bijlenga D, et al; PPROMEXIL study group. Economic analysis comparing induction of labor and expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks (PPROMEXIL trial). *Acta Obstet Gynecol Scand* 2014; 93 (4): 374-81.
17. van der Ham DP, van der Heyden JL, Opmeer BC, et al. Management of late-preterm premature rupture of membranes: the PPROMEXIL-2 trial. *Am J Obstet Gynecol* 2012; 207 (4): 276.e1-10.
18. Practice bulletins No. 139: premature rupture of membranes. *Obstet Gynecol* 2013; 122 (4): 918-30.
19. Choi EK, Kim SY, Heo JM, et al. Perinatal outcomes associated with latency in late preterm premature rupture of membranes. *Int J Environ Res Public Health* 2021; 18 (2): 672.
20. Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. *Cochrane Database Syst Rev* 2013; (12): CD001058.
21. Kenyon SL, Taylor DJ, Tarnow-Mordi W; ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. ORACLE Collaborative Group. *Lancet* 2001; 357 (9261): 979-88.
22. Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *JAMA* 1997; 278 (12): 989-95.
23. Liu D, Wu L, Luo J, et al. Developing a core outcome set for the evaluation of antibiotic use in prelabor rupture of membranes: a systematic review and semi-structured interview. *Front Pharmacol* 2022; 13: 915698.
24. Carlo WA, McDonald SA, Fanaroff AA, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. *JAMA* 2011; 306 (21): 2348-58.
25. Mori R, Kusuda S, Fujimura M; Neonatal Research Network Japan. Antenatal corticosteroids promote survival of extremely preterm infants born at 22 to 23 weeks of gestation. *J Pediatr* 2011; 159 (1): 110-114.e1.
26. Chawla S, Bapat R, Pappas A, Bara R, Zidan M, Natarajan G. Neurodevelopmental outcome of extremely premature infants exposed to incomplete, no or complete antenatal steroids. *J Matern Fetal Neonatal Med* 2013; 26 (15): 1542-7.
27. Gilstrap LC, Christensen R, Clewell WH, et al. Effect of corticosteroids for fetal maturation on perinatal outcomes: NIH consensus development panel on the effect of corticosteroids for fetal maturation on perinatal outcomes. *Jama* 1995; 273 (5): 413-8.
28. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane*

Database Syst Rev 2017; 3 (3): CD004454.

29. Consortium on Safe Labor; Hibbard JU, Wilkins I, Sun L, et al. Respiratory morbidity in late preterm births. *JAMA* 2010; 304 (4): 419-25.
30. Kugelman A, Colin AA. Late preterm infants: near term but still in a critical developmental time period. *Pediatrics* 2013; 132 (4): 741-51.
31. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al; NICHD Maternal–Fetal Medicine Units Network. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med* 2016; 374 (14): 1311-20.
32. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. *BMJ* 2016; 355: i5044.
33. Committee on Obstetric Practice. Committee Opinion No. 713: Antenatal Corticosteroid Therapy for Fetal Maturation. *Obstet Gynecol* 2017; 130 (2): e102-e109.
34. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery. *Am J Obstet Gynecol* 2016; 215: B13-5.
35. Mackeen AD, Seibel-Seamon J, Grimes-Dennis J, Baxter JK, Berghella V. Tocolytics for preterm premature rupture of membranes. *Cochrane Database Syst Rev* 2011; (10): CD007062.
36. Ehsanipoor RM, Shrivastava VK, Lee RM, et al. A randomized, double-masked trial of prophylactic indomethacin tocolysis versus placebo in women with premature rupture of membranes. *Am J Perinatol* 2011; 28 (6): 473-8.

The world is changed not by the self-regarding, but by men and women prepared to make fools of themselves.

Phyllis Dorothy James, Baroness James of Holland Park, OBE, FRSA, FRSL, known professionally as P. D. James (1920–2014), was an English novelist and politician. Her rise to fame came with her series of detective novels featuring Adam Dalgliesh, the police commander and poet.

Capsule

Timing in dendritic cell signaling

Dendritic cells detect pathogens through pattern recognition receptors. Watanabe et al. uncovered how two receptors for different mycobacterial components can generate distinct dendritic cell responses even though they signal through the common subunit called FcRγ. The constitutively expressed protein Dectin-2 generated strong FcRγ signaling shortly after stimulation and induced the production of the proinflammatory cytokine interleukin-2. By contrast, the protein *Mincle* did not trigger interleukin-2 production because its expression was induced after stimulation, leading to delayed FcRγ signaling.

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Capsule

Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution

Cao et al. demonstrated that convergent mutations can cause evasion of neutralizing antibody drugs and convalescent plasma, including those from BA.5 breakthrough infection, while maintaining sufficient ACE2-binding capability. BQ.1.1.10 (BQ.1.1 + Y144del), BA.4.6.3, XBB, and CH.1.1 are the most antibody-evasive strains tested. To delineate the origin of the convergent evolution, the authors determined the escape mutation profiles and neutralization activity of monoclonal antibodies isolated from individuals who had BA.2 and BA.5 breakthrough infections. Due to humoral immune imprinting, BA.2 and especially BA.5 breakthrough infection reduced the diversity of the neutralizing antibody binding sites and increased proportions of non-neutralizing antibody clones, which focused humoral immune pressure and promoted convergent evolution in the RBD. Moreover, the authors showed that the convergent RBD mutations could be accurately inferred by deep mutational scanning profiles, and the evolution trends of BA.2.75 and BA.5 subvariants could be well foreseen through constructed convergent pseudovirus mutants. These results suggest that current herd immunity and BA.5 vaccine boosters may not efficiently prevent the infection of Omicron convergent variants.

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