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# Antibiotic Therapy in Preterm Premature Rupture of the Membranes

This clinical practice guideline has been prepared by the Infectious Diseases Committee, reviewed by the Maternal Fetal Medicine Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Disclosure statements have been received from all members of the committees.

## Abstract

**Objective:** To review the evidence and provide recommendations on the use of antibiotics in preterm premature rupture of the membranes (PPROM).

**Outcomes:** Outcomes evaluated include the effect of antibiotic treatment on maternal infection, chorioamnionitis, and neonatal morbidity and mortality.

**Evidence:** Published literature was retrieved through searches of Medline, EMBASE, CINAHL, and The Cochrane Library, using appropriate controlled vocabulary and key words (PPROM, infection, and antibiotics). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date or language restrictions. Searches were updated on a regular basis and new material incorporated in the guideline to July 2008. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

**Values:** The evidence obtained was reviewed and evaluated by the Infectious Diseases Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) under the leadership of the principal authors, and recommendations were made according to guidelines developed by the Canadian Task Force on Preventive Health Care.

**Benefits, Harms, and Costs:** Guideline implementation should assist the practitioner in developing an approach to the use of antibiotics in women with PPROM. Patients will benefit from appropriate management of this condition.

**Validation:** This guideline has been reviewed and approved by the Infectious Diseases Committee and the Maternal Fetal Medicine Committee of the SOGC, and approved by the Executive and Council of the SOGC.

**Sponsor:** The Society of Obstetricians and Gynaecologists of Canada.

**Recommendations**

1. Following PPROM at ≤ 32 weeks' gestation, antibiotics should be administered to women who are not in labour in order to prolong pregnancy and to decrease maternal and neonatal morbidity. (I-A)
2. The use of antibiotics should be gestational-age dependent. The evidence for benefit is greater at earlier gestational ages (< 32 weeks). (I-A)

**Key Words:** Preterm premature rupture of the membranes, antibiotic therapy, maternal morbidity, neonatal morbidity

**Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care**

| Quality of Evidence Assessment* | Classification of Recommendations† |
|---|---|
| I: Evidence obtained from at least one properly randomized controlled trial | A. There is good evidence to recommend the clinical preventive action |
| II-1: Evidence from well-designed controlled trials without randomization | B. There is fair evidence to recommend the clinical preventive action |
| II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group | C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making |
| II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category | D. There is fair evidence to recommend against the clinical preventive action |
| III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees | E. There is good evidence to recommend against the clinical preventive action |
| | L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making |

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[20]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[20]

3. For women with PPROM at > 32 weeks' gestation, administration of antibiotics to prolong pregnancy is recommended if fetal lung maturity can not be proven and/or delivery is not planned. (I-A)
4. Antibiotic regimens may consist of an initial parenteral phase followed by an oral phase, or may consist of only an oral phase. (I-A)
5. Antibiotics of choice are penicillins or macrolide antibiotics (erythromycin) in parenteral and/or oral forms. (I-A) In patients allergic to penicillin, macrolide antibiotics should be used alone. (III-B)
6. The following two regimens may be used (the two regimens were used in the largest PPROM randomized controlled trials that showed a decrease in both maternal and neonatal morbidity): (1) ampicillin 2 g IV every 6 hours and erythromycin 250 mg IV every 6 hours for 48 hours followed by amoxicillin 250 mg orally every 8 hours and erythromycin 333 mg orally every 8 hours for 5 days (I-A); (2) erythromycin 250 mg orally every 6 hours for 10 days (I-A)
7. Amoxicillin/clavulanic acid should not be used because of an increased risk of necrotizing enterocolitis in neonates exposed to this antibiotic. Amoxicillin without clavulanic acid is safe. (I-A)
8. Women presenting with PPROM should be screened for urinary tract infections, sexually transmitted infections, and group B streptococcus carriage, and treated with appropriate antibiotics if positive. (II-2B)

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**ABBREVIATIONS**

| | |
|---|---|
| IUI | intrauterine infection |
| NEC | necrotizing enterocolitis |
| PPROM | preterm premature rupture of the membranes |
| RDS | respiratory distress syndrome |

## INTRODUCTION

The leading cause of perinatal death in the developed world is preterm birth (delivery occurring between 20 and 37 weeks' gestation).[1] It occurs in 7% to 8% of births in Canada, but is responsible for 60% to 80% of neonatal deaths.[2] Unfortunately, these rates have not changed significantly over the past 40 years.[2,3] Preterm premature rupture of the membranes occurs in 2.0% to 3.5% of pregnancies and is the most common cause of preterm birth, present in 30% to 40% of cases.[4] The etiology of PPROM is multifactorial, and management considerations include antibiotics, corticosteroids, and tocolytics. This guideline reviews the literature and the evidence for the use of antibiotic therapy following PPROM. The quality of evidence reported in these guidelines has been described using the evaluation of evidence criteria of the Canadian Task Force on Preventive Health Care (Table).

## PPROM AND INFECTION

There are many causes of preterm birth, although intrauterine infection is frequently associated with preterm delivery and PPROM. It has been estimated that at least 40% of all preterm births occur in mothers with IUI.[5] Microorganisms have been isolated from the amniotic fluid of women who experienced preterm labour with or without PPROM, although the rates of positive cultures are higher in women who have PPROM (approximately 32.4%) than in those with preterm labour and intact membranes (approximately 12.8%).[6] Infection can be associated with

PPROM as either a cause or a consequence. Infection preceding PPROM is often subclinical and thought to ascend from the lower genital tract.[1,5] Following rupture of the membranes, ascending bacterial invasion can lead to IUI in up to 60% of cases in the absence of antibacterial therapy.[7]

### Mechanisms of PPROM Due to Infection

The putative mechanism underlying infection and PPROM requires intrauterine bacterial invasion, which activates the decidua and fetal membranes to produce pro-inflammatory cytokines. This in turn leads to the release of prostaglandins, metalloproteases, and other bioactive substances. The prostaglandins stimulate uterine contractions, and metalloproteases soften the cervix and target the membranes, leading to rupture.[8]

### Antibiotic Therapy in PPROM

With the strong link between infection and PPROM, research has focused on the use of antibiotics following PPROM for the purpose of decreasing the complications associated with infection. Antibiotic therapy could improve outcome in two ways. First, the prevention or treatment of infection may reduce maternal or fetal/neonatal morbidity. Second, by treating or preventing ascending infection, antibiotic therapy may prolong pregnancy and delay the progression to preterm birth.[7,9]

Many studies assessing the effect of antibiotics following PPROM have been published. Most of these are small; however, there are two large randomized controlled trials. The first is the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network Trial, which enrolled 614 women with PPROM from 24 to 32 weeks' gestation.[10] The other is the ORACLE I trial, which enrolled 4826 women.[11]

In the first trial, women were randomized to receive antibiotics or placebo for a total of seven days. The antibiotic regimen used 48 hours of intravenous therapy followed by five days of oral medications. The initial phase used ampicillin 2 g IV every 6 hours and erythromycin 250 mg IV every 6 hours. After 48 hours, these medications were changed to amoxicillin 250 mg orally every 8 hours and erythromycin 333 mg orally every 8 hours. Antibiotic therapy did prolong pregnancy, with a two-fold likelihood that patients would not deliver after seven days of treatment. Treated women were more likely to remain pregnant for up to three weeks after randomization. Regarding neonatal morbidity, there was a decrease from 53% to 44% ($P < 0.05$) for one or more measures of major infant morbidity (composite morbidity defined as death, respiratory distress syndrome, early sepsis, severe intraventricular hemorrhage, severe necrotizing enterocolitis). Antibiotic therapy also significantly reduced gestational age-dependent morbidity including RDS (40.5% vs. 48.7%), stages 3 to 4 NEC (2.3% vs. 5.8%), patent ductus arteriosus (11.7% vs. 20.2%), and chronic lung disease (13.0% vs. 20.5%) ($P = 0.05$ for each). With respect to morbidity related to infection, there was a lower incidence of neonatal group B streptococcus sepsis (0% vs. 1.5%, $P = 0.03$) and amnionitis (23% vs. 32.5%, $P = 0.01$) in the antibiotic group. Neonatal sepsis (8.4% vs. 15.6%, $P = 0.009$) and pneumonia (2.9% vs. 7.0%, $P = 0.04$) were also less frequent in those who were not group B streptococcus carriers. On the basis of the results of this study, the authors recommended limited duration aggressive antibiotic therapy during conservative management of PPROM remote from term.[10]

In the ORACLE I trial, 4826 women with PPROM at < 37 weeks' gestation were enrolled and randomized into one of four oral treatment groups: (1) 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid) plus 250 mg erythromycin, (2) co-amoxiclav plus erythromycin placebo, (3) erythromycin plus co-amoxiclav placebo, or (4) co-amoxiclav placebo plus erythromycin placebo.[11] All medications were taken four times daily for 10 days or until delivery. For the composite primary outcome of death or major adverse outcome in the baby before discharge from hospital, there were no statistically significant reductions for any of the comparisons. However, oral erythromycin was associated with prolongation of pregnancy for 48 hours when erythromycin only was compared with placebo (34.8% vs. 40.7%, $P = 0.004$) and for 7 days when any erythromycin was compared with no erythromycin (57.7% vs. 60.5%, $P = 0.05$). It was also associated with a reduced need for supplemental oxygen (31.1% vs. 35.6%, $P = 0.02$) and reduced positive blood cultures (5.7% vs. 8.2%, $P = 0.02$). Subanalysis of singleton gestations revealed significant reductions in oxygen dependence at 28 days (6.9% vs. 8.9%, $P = 0.03$), positive blood cultures (5.3% vs. 7.4%, $P = 0.04$), abnormal cerebral ultrasound (3.0% vs. 4.6%, $P = 0.04$), and composite morbidity (11.2% vs. 14.4%, $P = 0.02$). Oral co-amoxiclav was associated with a prolongation of pregnancy (43.3% vs. 36.7% undelivered after 7 days, $P = 0.005$) and a reduction in the need for supplemental oxygen (30.1% vs. 35.6%, $P = 0.05$), but was also associated with a significant increase in the risk of NEC (1.9% vs. 0.5%, $P = 0.001$) without reducing other or composite neonatal morbidity. The combination of drugs (erythromycin and co-amoxiclav) led to similar findings. The authors concluded that erythromycin has a range of neonatal health benefits when administered to women with PPROM, but that co-amoxiclav should not be used because of its association with NEC.[11] The study has been criticized because there were no differences in the composite primary outcome for any of the treatment groups when compared with placebo.[12] However, there were many significant

differences in subgroup analyses (presented above). Data on long-term outcomes among children from this trial were published in 2008. After seven years of follow-up, there was no difference in the proportion of children with any functional impairment in the group born to women who received erythromycin, with or without co-amoxiclav, and in the group born to women who received no erythromycin.[13]

In addition to these two trials, many other studies have been published assessing the efficacy of antibiotics following PPROM for pregnancy prolongation and reduction of maternal and neonatal morbidity, with different regimens and duration of treatment**.** They include studies documenting an increase in the latency period in women who received imipenem/cilastatin[14] and mezlocillin.[15] In a study comparing duration of therapy, all patients received 48 hours of parenteral ampicillin and were then randomized to receive either three or seven days of oral ampicillin following PPROM. There was no difference between the two regimens in the ability to achieve a seven-day latency period, and no difference in the incidence of maternal or neonatal morbidity.[16]

Larger reviews have also been performed to assess the effects of antibiotic administration in women with PPROM on maternal and perinatal morbidity and mortality, and to attempt to identify the antibiotic(s) of choice. Kenyon and colleagues published a systematic review of 19 trials involving 6951 women, of which 14 were randomized controlled trials.[9] Participants were enrolled from 21 to 37 weeks' gestational age, and several different antibiotic regimens were used. Antibiotics were associated with a statistically significant reduction in the number of infants born within 48 hours (RR 0.71; 95% CI 0.58 to 0.87) and 7 days (RR 0.80; 95% CI 0.71 to 0.90) of PPROM. In those exposed to antibiotics, there was a decrease in chorioamnionitis (RR 0.57; 95% CI 0.37 to 0.86) and several aspects of neonatal morbidity including neonatal infection (RR 0.67; 95% CI 0.52 to 0.85), positive blood culture (RR 0.75; 95% CI 0.60 to 0.93), oxygen therapy (RR 0.88; 95% CI 0.81 to 0.96), treatment with surfactant (RR 0.83; 95% CI 0.72 to 0.96), and abnormal cerebral ultrasound (RR 0.82; 95% CI 0.68 to 0.99). Overall, the use of antibiotics was not associated with a significant reduction in neonatal mortality (RR 0.91; 95% CI 0.75 to 1.11).

In terms of specific antibiotics, benefits were seen (pregnancy prolongation and decreases in neonatal morbidity) in trials using penicillins and erythromycin. In two trials enrolling a total of 4888 women, the authors concluded that the data supported the use of antibiotics (erythromycin and penicillins) for women following PPROM to delay delivery and decrease maternal and neonatal morbidity. The strength of evidence was greater for erythromycin, as it was used in larger trials than penicillins; however, the optimal antibiotic regimen is unclear, because equivalency/superiority trials have not been done. It was recommended that amoxicillin/clavulanic acid not be used because of the increased risk of NEC (RR 4.60; 95% CI 1.98 to 10.72).[9]

Finally, in 2008, the Cochrane Collaboration published a review by Kenyon and colleagues of the use of antibiotics following PPROM.[17] This systematic review consisted of 22 trials with over 6000 women. It included the randomized controlled trials that were part of the 2004 review by Kenyon et al., and the findings therefore mirrored those of the earlier review.[9] Once again, the use of antibiotics was associated with a prolongation of pregnancy for both 48 hours (RR 0.71; 95% CI 0.58 to 0.87) and 7 days (RR 0.80; 95% CI 0.71 to 0.90), and with a decrease in chorioamnionitis and several markers of neonatal morbidity.[17] Amoxicillin/clavulanic acid was again associated with a significantly increased risk of NEC (RR 4.60; 95% CI 1.98 to 10.72).[17] The authors concluded that antibiotic administration following PPROM is associated with a delay in delivery and a reduction in markers of neonatal morbidity and that the data support the routine use of antibiotics in PPROM.[17]

The benefit of antibiotics in prolonging pregnancy after PPROM is gestational age-dependent. The risk of infection with an increasing latency period must be weighed against the risk of prematurity. It is still unclear whether induction of labour with PPROM at 32 to 35+6 weeks' gestation or expectant management with antibiotic therapy for latency results in the better outcome for both mother and newborn, although there are data to assist with management planning. At gestational ages < 32 weeks, there is good evidence that pregnancy prolongation with antibiotic therapy is beneficial.[10,11] In the Maternal-Fetal Medicine Units Network Trial, women were enrolled at < 32 weeks' gestation, and in the ORACLE I trial, although women were enrolled up to 37 weeks' gestation, the mean gestational age was 31.8 weeks. At gestational ages > 34 weeks, conservative management is associated with an increased risk of amnionitis (16% vs. 2%, $P = 0.001$), prolonged maternal hospitalization (5.2 vs. 2.6 days, $P = 0.006$), and a lower mean umbilical cord pH at delivery (7.25 vs. 7.35, $P = 0.009$) without the benefit of a significant reduction of perinatal complications related to prematurity; delivery is therefore suggested.[18] At gestational ages between 32 and 34 weeks, if fetal lung maturity can be documented, delivery is suggested, as conservative management has been shown to prolong pregnancy only briefly (36 vs. 14 hours, $P < 0.001$) and to increase the risk of amnionitis (27.7% vs. 10.9%, $P = 0.06$).[19] If fetal lung maturity can not be proven, then administration of antibiotics to prolong the latency period is

recommended. When PPROM has occurred prior to 34 weeks' gestation and antibiotic treatment has afforded latency up to 34 weeks, induction of labour may be warranted to reduce the risk of amnionitis beyond this gestational age.

For women presenting with PPROM, prenatal care providers must consider not only whether to begin antibiotic therapy, but also whether to screen for infections. As previously noted, PPROM may be preceded by infection, which most often ascends from the lower genital tract.[1,5] Screening for urinary tract infections, sexually transmitted infections, bacterial vaginosis, and group B streptococcus carriage should all be considered. In the Maternal-Fetal Medicine Units Network Trial,[10] women who screened positive for urinary tract or sexually transmitted infections were treated, although it is unclear whether all enrolled patients were screened. All women were screened for group B streptococcus and treated with oral or intravenous ampicillin if positive. In the ORACLE I trial, it is unclear whether women were screened for infections or group B streptococcus.[11]

### Recommendations

1. Following PPROM at ≤ 32 weeks' gestation, antibiotics should be administered to women who are not in labour in order to prolong pregnancy and to decrease maternal and neonatal morbidity. (I-A)

2. The use of antibiotics should be gestational-age dependent. The evidence for benefit is greater at earlier gestational ages (< 32 weeks). (I-A)

3. For women with PPROM at > 32 weeks' gestation, administration of antibiotics to prolong pregnancy is recommended if fetal lung maturity can not be proven and/or delivery is not planned. (I-A)

4. Antibiotic regimens may consist of an initial parenteral phase followed by an oral phase, or may consist of only an oral phase. (I-A)

5. Antibiotics of choice are penicillins or macrolide antibiotics (erythromycin) in parenteral and/or oral forms. (I-A) In patients allergic to penicillin, macrolide antibiotics should be used alone. (III-B)

6. The following two regimens may be used (the two regimens were used in the largest PPROM randomized controlled trials that showed a decrease in both maternal and neonatal morbidity): (1) ampicillin 2 g IV every 6 hours and erythromycin 250 mg IV every 6 hours for 48 hours followed by amoxicillin 250 mg orally every 8 hours and erythromycin 333 mg orally every 8 hours for 5 days (I-A); (2) erythromycin 250 mg orally every 6 hours for 10 days (I-A)

7. Amoxicillin/clavulanic acid should not be used because of an increased risk of necrotizing enterocolitis in neonates exposed to this antibiotic. Amoxicillin without clavulanic acid is safe. (I-A)

8. Women presenting with PPROM should be screened for urinary tract infections, sexually transmitted infections, and group B streptococcus carriage, and treated with appropriate antibiotics if positive. (II-2B)

## REFERENCES


1. Klein LL, Gibbs RS. Use of microbial cultures and antibiotics in the prevention of infection-associated preterm birth. Am J Obstet Gynecol 2004;190:1493–502.
2. Joseph KS, Kramer MS, Marcoux S, Ohlsson A, Wen SW, Allen A, et al. Determinants of preterm birth rates in Canada from 1981 to 1983 and from 1992 through 1994. N Engl J Med 1998;339:1434–9.
3. Goldenberg RL. The management of preterm labor. Obstet Gynecol 2002;100:1020–37.
4. Romero R, Athayde N, Maymon E, Pacora P, Bahado-Singh R. Premature rupture of the membranes. In: Reece A, Hobbins J, eds. Medicine of the fetus and the mother. Philadelphia:Lippincott-Raven;1999:1581–625.
5. Romero R, Espinoza J, Chaiworapongsa T, Kalache K. Infection and prematurity and the role of preventive strategies. Semin Neonatol 2002;7:259–74.
6. Goncalves LF, Chaiworapongsa T, Romero R. Intrauterine infection and prematurity. Ment Retard Dev Disabil Res Rev 2002;8:3–13.
7. Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol 2003;101:178–93.
8. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500–7.
9. Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of the membranes: a systematic review. Obstet Gynecol 2004;104:1051–7.
10. Mercer BM, Miodovnik M, Thurnau GR, Goldenberg RL, Ramsey RD, Rabello YA, 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;278:989–95.
11. 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. Lancet 2001;357:979–88.
12. Hannah M. Antibiotics for preterm prelabour rupture of membranes and preterm labour. Lancet 2001;357:973–4.
13. Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, Taylor DJ. Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial. Lancet 2008;372:1310–8.
14. Ryo E, Ikeya M, Sugimoto M. Clinical study of the effectiveness of imipenem/cilastatin sodium as the antibiotics of first choice in the expectant management of patients with preterm premature rupture of membranes. J Infect Chemother 2005;11(1):32–6.
15. August FN, Becker C, van BA, Bauer K, Hopp H. Antibiotic therapy for preterm premature rupture of membranes- results of a multicenter study. J Perinat Med 2006;34(3):203–6.
16. Segel SY, Miles AM, Clothier B, Parry S, Macones GA. Duration of antibiotic therapy after preterm premature rupture of fetal membranes. Am J Obstet Gynecol 2003;189:799–802.
17. Kenyon S, Boulvain M, Neilson J. Antibiotics for preterm rupture of membranes Cochrane Database Syst Rev 2003, Issue 2. Art. No.:CD001058. DOI: 10.1002/14651858.CD001058.
18. Naef RW 3rd, Allbert JR, Ross EL, Weber BM, Martin RW, Morrison JC. Premature rupture of membranes at 34 to 37 weeks' gestation: aggressive versus conservative management. Am J Obstet Gynecol 1998;178:126–30.
19. Mercer BM, Crocker L, Boe N. Sibai B. Induction versus expectant management in PROM with mature amniotic fluid at 32–36 weeks: a randomized trial. Am J Obstet Gynecol 1993;82:775–82.
20. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ 2003;169(3):207–8.