

USE OF ANTIBIOTICS AND PROBIOTIC LACTOBACILLI IN THE TREATMENT OF PRETERM PREMATURE RUPTURE OF MEMBRANES: A REVIEW

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ABSTRACT

To review the current evidence of the potential use of antibiotics and probiotics Lactobacillus in preterm premature rupture of membranes cases and to see the effect on microorganism concentrations especially Streptococcus agalactiae and Lactobacillus. This review used several databases (Google Scholar, Pubmed, and Science Direct) and searched for English and Indonesian articles in the last ten years. Articles were received in the form of case reports, observational studies and clinical trials that discussed the use of antibiotics and probiotic Lactobacillus in premature rupture of membranes especially in preterm pregnancy. After searching the database and eliminating duplicates and articles unrelated to the topic, we included some articles in this review. Prophylactic antibiotics are also expected to prolong the latent phase, thereby reducing the risk of fetomaternal morbidity and mortality. Penicillin is often recommended in preterm PROM, because broad-spectrum antibiotics are better as infection prophylaxis. Providing alternative therapy with lactobacillus probiotics is believed to prevent preterm birth and has the benefit of being a safe and effective therapy in restoring normal vaginal microflora and preventing vaginal infections during pregnancy. However, further research is needed to see the effectiveness of lactobacillus probiotics and look at the concentration of microbes, especially Streptococcus agalactiae and Lactobacillus.

Keywords: Preterm Premature Rupture of Membranes, Antibiotics, Probiotics Lactobacillus, Streptococcus Agalactiae

INTRODUCTION

Premature rupture of membranes (PROM) is defined as the rupture of the amniotic membrane before labor occurs. PROM is divided into two according to the gestational age at which it occurs. If it occurs at 37 weeks of gestation or more, it is called term PROM or Premature Rupture of Membranes (PROM), where as if PROM occurs before 37 weeks of gestation it is called preterm PROM or PPRM. (Perkumpulan Obstetri Ginekologi (POGI) & Himpunan Kedokteran Feto Maternal (HKFM), 2016)

The incidence of PROM is quite high when compared with other pregnancy problems. In particular, preterm PROM is the most common cause of preterm birth, namely 3-8% worldwide. The incidence of PROM in several other countries such as Nigeria is 6.3%, Uganda 13.8%, Cameroon 7.4%, India 2.2% - 4%, Canada 2.8%, Brazil 3.1%, and Egypt 4.1%. (Endale, 2016) Meanwhile, the incidence of KPD in Indonesia varies between 6 - 19% and in preterm KPD the incidence is 2% of all pregnancies. (Pisoh et al., 2021)

In cases of PROM, the most frequent infections are ascending infections originating from lower urinary tract infections and genital tract infections. (Yudin et al., 2017) In 2014 in China, Zeng et al studied pathogenic bacteria that cause PROM in term and preterm pregnant women, and found that the bacteria that most commonly causes PROM in pregnant women is group B Streptococcus. (Zeng et al., 2014) In 2022, Brigtsen et al also examined bacterial colonization in pregnant women, especially preterm KPD at the Oslo University teaching hospital, Norway, and found that the bacteria most frequently found was group B Streptococcus. (Brigtsen et al., 2022)

Management of PROM under 37 weeks is principally antibiotics, which function to prevent increased maternal, fetal or neonatal mortality and morbidity due to infection. In addition, antibiotics can delay progression to preterm labor. (Lowing et al., 2015; POGI, 2016) The recommended antibiotic is a penicillin class antibiotic, namely ampicillin. However, due to the risk of resistance and the large risk of allergies, the Ministry of Health through Minister of Health Regulation No. 28 of 2021 recommends the second choice of antibiotic, namely cefotaxime. (POGI, 2016; Yudin et al., 2017)

In 2018, research conducted by Rasti et al at Soetomo Hospital, Surabaya regarding the comparison of the administration of cefotaxime and ceftriaxone antibiotic therapy to preterm PROM patients found that cefotaxime was able to delay labor for 52.67 hours compared to ceftriaxone 34.17 hours. Rasti et al chose these two antibiotics because they have lower side effects, minimal risk of allergies, are safe to use during pregnancy, and are more sensitive in treating bacterial infections in PROM, namely: *Staphylococcus*, *Streptococcus* dan *Escherichia coli*. (Rasti et al., 2020)

Vaginal infections are significantly reduced with the help of probiotic therapy during pregnancy. Observational research by Kavak et al in 2014 reported that the addition of probiotics with the antibiotic ampicillin in preterm PROM patients was able to delay labor for 5 days and prevent infection. (Kavak et al., 2014)

In 2023 Peng Liu et al from Shandong First Medical University, China found that *Lactobacillus* microorganisms are microorganisms that are important for women's

vaginal health, especially pregnant women. These gram-positive bacilli can maintain the acidity of the vaginal environment and inhibit the proliferation of other pathogenic microorganisms, thereby preventing preterm labor and preventing infection in pregnant women with PROM. The combination of probiotic management with antibiotics is a combination therapy that is starting to be frequently applied from various studies in the world at this time. (Liu et al., 2023) However, probiotics have different effectiveness depending on the type of probiotic and the method of administration. Probiotics given intravaginally have a faster working effect, namely 2-3 days, because intravaginal therapy directly reaches the therapeutic target. (Liu et al., 2023) based on the background we are interested to investigate the potential of utilizing antibiotics and probiotic *lactobacilli* in preterm premature rupture of membranes cases.

METHOD

This article is literature review aims to investigate how the potential use of antibiotics and probiotic *lactobacilli* affects microbial concentrations in cases of premature rupture of membranes.

The method used in this review was literature authors review for identifying, evaluating, and synthesizing research works that had been produced by reseachers dan practitioners.

The literature sources used of this review were obtained by search engines including Google Scholar, Elsevier, Wiley, Pubmed, Science Direct, and Cochrane were employed for this literature evaluation.

Preterm premature rupture of membranes or PPRM, Antibiotics,

Probiotics *Lactobacillus*, *Streptococcus agalactiae* were the keywords used.

The following criteria must be me for inclusion in the literature: (1) 10 years of publication; (2) usage of Indonesian or English; (3) complete text; and (4) articles in the form of observational studies or clinical trials. Researchers conducted the systematic selection of articles in accordance with a number of processes, including identification, screening, and adherence with inclusion criteria. Fourth articles remained in this literature study after numerous selection procedures because they were pertinent.

LITERATURE REVIEW

Premature rupture of membranes (PROM) is a rupture (breaking open) of the membranes (amniotic sac) before labor begins. If PROM occurs before 37 weeks of pregnancy, it is called preterm premature rupture of membranes (PPROM). Risk factors that are contributing to PROM include: low socioeconomic status, smokers, history of urinary tract infections, genital infections, a history of premature labor, a history of premature rupture of membranes in a previous pregnancy, or uterine distension, for example patients with multiple pregnancies and polyhydramnios (POGI & HKFM, 2016).

Rupture of the membranes during labor is generally caused by repeated contractions and stretching of the uterus. Rupture of the amniotic membrane occurs because in certain areas biochemical changes occur which cause the amniotic membrane to become fragile (Cohen et al., 2022). Patients with PROM should undergo examination to confirm the diagnosis, confirm gestational age and fetal

presentation, and assess maternal and fetal well-being (Melamed et al., 2021).

There are two types of management in KPD management, namely active and expectant management. Patients with the possibility of PROM must undergo further examination at the hospital. If the amniotic fluid stops coming out during treatment, the patient can go home for outpatient treatment. If there is deep labor in the active phase, chorioamnionitis, fetal distress, labor is terminated. If PROM is premature, comprehensive management is needed. In general, management of PROM patients who are not in labor and are infected depends on the gestational age (Cohen et al., 2022).

RESULT

After database searching and eliminating duplicates and articles unrelated to the topic, we included some articles in this review.

Observational research by Kavak et al in 2014 reported that the addition of probiotics with the antibiotic ampicillin in preterm PROM patients was able to delay labor for 5 days and prevent infection. (Kavak et al., 2014)

A prospective randomized trial by Daskalakis et al in 2017 of cases with PPRM (24-34 weeks) found 49 cases received vaginal probiotics for 10 days in combination with prophylactic antibiotics and compared with 57 others who received only antibiotics for the same period of time. that vaginal probiotics as an adjunct to antibiotic prophylaxis in women with PPRM prolong the latent period and improve perinatal outcomes. (Daskalakis & Karambelas, 2017)

Research conducted by Yadav et al 2022 Probiotics appear to

have a new role in prolonging pregnancy after PPRM. This trial compared the efficacy of vaginal probiotics combined with standard antibiotic prophylaxis versus antibiotics alone in prolonging the latent period and perinatal outcomes in cases of PPRM between 24 and 34 weeks. Although no significant differences were observed in the mean latency period ($p = 0.937$) and mean gestational age at birth ($p = 0.863$) between the two groups, the overall neonatal outcome was better in the study group. Further large-scale clinical trials are needed to demonstrate the effectiveness of probiotics. (Yadav et al., 2022)

Lorthe et al in 2022 found that in premature rupture of membranes at 24-31 weeks, antibiotic prophylaxis based on third-generation cephalosporins may be associated with improved survival without severe neonatal morbidity when compared with amoxicillin, and there was no evidence of an increase in neonatal sepsis associated with second-generation cephalosporins third-resistant pathogens. (Lorthe, Letouzey, Torchin, Foix L'Helias, et al., 2022)

The recommended antibiotic for PPRM is penicillin, because broad spectrum antibiotics are better as infection prophylaxis. Several studies have found that penicillin antibiotics (except amoxicillin-clavulonic acid) can prolong pregnancy and reduce the incidence of infection when compared with placebo. Other broad spectrum antibiotics that can be used include: ampicillin, erythromycin, clindamycin, cefotaxime, ceftriaxone. (Mercer, 2003)

Probiotics containing Lactobacillus rhamnosus, Lactobacillus gasseri, Lactobacillus plantarum as additional therapy to

standard antibiotic treatment have the benefit of being a safe and effective therapy in restoring normal

vaginal microflora and preventing vaginal infections during pregnancy, especially in PPROM.

DISCUSSION

Premature Rupture of Membranes

Premature rupture of membranes (PROM) is defined as rupture of the amniotic membranes before labor occurs. Premature rupture of membranes that occurs at or after 37 weeks of gestation is called term PROM or premature rupture of membranes, while PROM that occurs before 37 weeks of gestation is called preterm PROM or preterm premature rupture of membranes. (Perkumpulan Obstetri Ginekologi (POGI) & Himpunan Kedokteran Feto Maternal (HKFM), 2016)

Risk factors associated with PROM are patients with low socioeconomic status, smokers, a history of urinary tract infections, genital infections, a history of premature labor, a history of premature rupture of membranes in a previous pregnancy, or uterine distension, for example patients with multiple pregnancies and polyhydramnios. (POGI, 2016)

Changes in the balance between synthesis and degradation of the extracellular matrix, structure, cell number, and collagen catabolism cause collagen activity to change and cause the amniotic membrane to rupture. The amniotic membrane is very strong in early pregnancy. In the third trimester the amniotic membrane will break more easily. This is related to uterine enlargement, uterine contractions, and fetal movements. (Soewarto, 2016)

Genital infections are another factor associated with premature PROM, studies show infections can weaken the strength of the membranes, thereby leading to

rupture of the membranes. (Brown et al., 2018)

The types of microorganisms from mothers with premature PROM and PPROM are shown in Table 1. Positive cultures were observed in 76.3% of preterm PROMs, with group B Streptococcus (GBS) accounting for the majority of microorganisms (72.9%), followed by *Candida albicans* (18.6%). (Abdulaziz, 2014)

In general, there are two types of management in KPD management, namely active and expectant management. Patients with the possibility of PROM must undergo further examination at the hospital. If the amniotic fluid stops coming out during treatment, the patient can go home for outpatient treatment. If there is deep labor in the active phase, chorioamnionitis, fetal distress, labor is terminated. If PROM is premature, comprehensive management is needed. In general, management of PROM patients who are not in labor and are infected depends on the gestational age. (Cohen et al., 2022)

Antibiotic for Premature Rupture of Membranes

Antibiotics for PPROM function as prophylaxis against infections, especially chorioamnionitis. Previous studies found a significant reduction in the risk of chorioamnionitis and neonatal infection in patients treated with prophylactic antibiotics. Prophylactic antibiotics are also expected to prolong the latent phase, thereby reducing the risk of fetomaternal morbidity and mortality. (Perkumpulan Obstetri Ginekologi (POGI) & Himpunan

Kedokteran Feto Maternal (HKFM), 2016).

Table 1. The results of microbiological examination of PPRM and PROM in women.

Type of microorganism	PROM (n=591)	PPROM (n=177)	P-value
GBS	300 (50.8)	129 (72.9)	0.000*
C. albicans	181 (30.6)	33 (18.6)	0.000*
GBS & C. albicans	25 (4.2)	2 (1.1)	0.006*
CoNS	19 (3.2)	3 (1.7)	0.001*
Staphylococci saprophyticus	14 (2.4)	2 (1.1)	0.017*
Klebsiella pneumoniae	14 (2.4)	4 (2.3)	0.001*
Gardnerella vaginalis	11 (1.9)	0 (0)	-
Haemophilus influenza	11 (1.9)	1 (0.6)	0.001*
Enterococcus saprophyticus	9 (1.5)	2 (1.1)	0.036*
Pseudomonas aeruginosa	7 (1.2)	1 (0.6)	0.008*

Abbreviations, n=number; PROM = premature rupture of membrane; PPRM = preterm PROM
* Significant difference at $P < 0.05$

According to Minister of Health Regulation no. 28 of 2021, the recommended antibiotics for patients with premature rupture of membranes are intravenous ampicillin every 6 hours (option 1) and intravenous cefotaxime every 8 hours (option 2). Meanwhile, the Indonesian Obstetrics and Gynecology Association (POGI) recommends that several antibiotics be given to PROMs that last >24 hours. (Perkumpulan Obstetri Ginekologi (POGI) & Himpunan Kedokteran Feto Maternal (HKFM), 2016; *Permenkes No 28 Tahun 2021 Tentang Pedoman Penggunaan Antibiotik*, 2021) If a patient presents with PROM > 24 hours, the patient should remain in treatment until they are in the active phase. (American College of Obstetrics and Gynecology (ACOG), 2017)

Penicillin is often recommended in preterm PROM, because broad-spectrum antibiotics are better as infection prophylaxis. Several studies have found that penicillin antibiotics (except amoxicillin-clavulonic acid) can prolong pregnancy and reduce the

incidence of infection when compared with placebo. Other broad spectrum antibiotics that can be used include: ampicillin, erythromycin, clindamycin, cefotaxime, ceftriaxone. (Mercer, 2014)

A meta-analysis by Kenyon et al found that there were no significant differences between the antibiotic classes of penicillin, beta lactams, macrolides, or cephalosporins in reducing the risk of perinatal infections, gestational age, and side effects. Currently there is no consensus validating the best antibiotic for PROM. (Kenyon et al., 2013)

A prospective study by Lorthe et al in France compared the efficacy of amoxicillin, macrolides, and cephalosporins as prophylaxis in PROM. This research found that generation III cephalosporins were better at preventing morbidity when compared with amoxicillin. 93.6% of neonates from mothers treated with generation III cephalosporins were discharged home without serious complications (compared with 78.5% on amoxicillin, 83.9% on macrolides, and 86% on the combination, p value

0.04). However, this study was conducted with a limited sample size (n=492). (Lorthe, Letouzey, Torchin, Helias, et al., 2022)

Research by Rasti et al was conducted at the Regional General Hospital (RSUD) dr. Soetomo Surabaya assessed the efficacy of the third class of cephalosporin antibiotics, namely intravenous cefotaxime 3x1 gram and intravenous ceftriaxone at a dose of 2x1 gram. Both antibiotics have been proven to delay preterm labor in patients with premature rupture of membranes. (Rasti et al., 2020)

Probiotics *Lactobacillus*

In 2023 through a systematic review compiled by Peng Liu et al from Shandong First Medical University, China, stated that *Lactobacillus* is a microorganism that is important for women's vaginal health, especially pregnant women. These gram-positive bacilli can acidify the vaginal environment, and inhibit the proliferation of other pathogenic microorganisms, especially preventing preterm labor and preventing infection in pregnant women with PROM. This combination of probiotic management with antibiotics is a combination therapy that is starting to be frequently applied from various studies in the world at this time. (Liu et al., 2023)

Probiotics are often studied in gynecological infectious diseases, such as bacterial vaginosis (BV) and vulvovaginal candidiasis. BV is characterized by a decrease in *Lactobacillus* colonies, resulting in increased growth of colonies of the pathogenic bacteria *Gardnerella vaginalis*, *Mycoplasma hominis*, and other pathogens. On the other hand, *Lactobacillus* can produce lactic acid and hydrogen peroxide, maintaining vaginal pH <4.5 and inhibiting the growth of pathogens. (Buggio et al., 2019) Probiotics containing

Lactobacillus rhamnosus, *Lactobacillus gasseri*, *Lactobacillus plantarum* as additional therapy to standard antibiotic treatment have the benefit of being a safe and effective therapy in restoring normal vaginal microflora and preventing vaginal infections during pregnancy. (Husain et al., 2020)

A randomized controlled study by Daskalakis et al in Greece assessed probiotic administration in premature PROM patients. After giving vaginal probiotic supplementation for 10 days in combination with prophylactic antibiotics, it was found that the age of delivery and duration of the latent period were longer when compared with patients who were only treated with prophylactic antibiotics. (Daskalakis & Karambelas, 2017) Meanwhile, Rautava et al studied the presence of TLR in amniotic fluid after probiotic supplementation, and found an increase in TLR 1 and TLR 7 levels in amniotic fluid. This research strengthens the hypothesis that probiotics can play a role in the maturity of the immune system in pregnancy. (Rautava et al., 2012)

Meta-analysis by Baradwan et al found that the combination of probiotics and antibiotics was effective as prophylaxis for premature rupture of membranes, when compared with single antibiotic therapy. Health quality and fetomaternal complications were also found to be better in the combination group. (Baradwan et al., 2023)

CONCLUSION

General management of PPRM two types are namely active and expectant management depending on gestational age and complaints. Prophylactic antibiotics are also expected to prolong the

latent phase, thereby reducing the risk of fetomaternal morbidity and mortality. Penicillin is often recommended in preterm PROM, because broad-spectrum antibiotics are better as infection prophylaxis. Providing alternative therapy with lactobacillus probiotics is believed to prevent preterm birth and has the benefit of being a safe and effective therapy in restoring normal vaginal

microflora and preventing vaginal infections during pregnancy. Because there has not been much research regarding the effectiveness of Lactobacillus probiotics and looking at the concentration of microbes, especially Streptococcus agalctiae and Lactobacillus, this can be a suggestion for other researchers or researchers themselves to carry out further research.

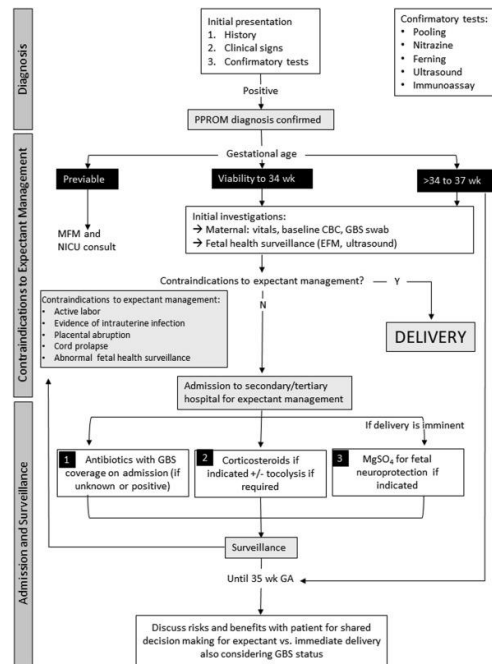


Figure 1. Preterm premature rupture of membranes algorithm (Ronzoni et al., 2022).

Conflict Of Interest

All authors has declared that there is no conflict of interest

Advice And Thanks

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