REVIEW ARTICLE

Antibiotic prophylaxis in preterm rupture of membranes

Daniela Cristina Schroff Machado[1]*, Joice de Moura Dias[1], Luiza Emylce Pelá Rosado[1]

[1]Pontifícia Universidade Católica de Goiás (PUC-Goiás), Goiânia, GO, Brazil

Abstract

Preterm premature rupture of membranes (PPROM) occurs before 37 weeks of gestation, accounting for approximately one-third of cases of preterm birth and increased maternal and neonatal morbidity and mortality. Several protocols recommend expectant management between 24 and 36 weeks of gestation, in order to allow acomplishment of fetal maturation and to avoid the dramatic consequences of prematurity. Despite benefits related to gestational prolongation, the most feared risk from this protocol is the increase of maternal-fetal infection. For this reason, the use of prophylactic antibiotics is recommended, although there is no consensus regarding the best choice. The objective of the present review was to analyze the impact of antibiotic prophylaxis on maternal and neonatal outcomes in cases of PPROM. It was observed that further studies are needed with the aim of standardizing the best antibiotic regimen in PPROM, as well as defining the actual maternal and neonatal outcomes, at long term, from its use.

Keywords: premature rupture of fetal membranes; antibiotic prophylaxis; review.

Introduction

Preterm premature rupture of membranes (PPROM) is defined as the rupture that occurs before 37 weeks of gestation. It accounts for approximately one-third of cases of preterm birth and increased maternal and neonatal morbidity and mortality.[1,2] Some maternal complications can be highlighted, as intra-amniotic infection, postpartum infection and placental abruption (PA). Neonatal concerns include respiratory distress syndrome, sepsis, intraventricular hemorrhage, necrotizing enterocolitis and cerebral pausy.[3]

The conduct towards PPROM is linked to gestational age (GA), with literature differences regarding the individual best management. When GA is between 24 and 34 weeks, and more recently up to 36 weeks,[1] with no clinical evidence of infection, most protocols recommend expectant management, since the fetus needs to complete its maturation and the consequences of a preterm birth are considerable.[4]

Despite the fetal benefits related to expectant behavior, the main risk due to gestational prolongation is maternal-fetal infection.[5] For this reason, antibiotic prophylaxis is recommended for a variable period of 7 to 10 days.[2-4,6-12] Antibiotic use increases the latency period and seems to reduce the rates of neonatal infection, the need of surfactants and postnatal oxygen therapy.[4]

There are several proposed therapeutic procedures according to national and international guidelines, and the main classes of antimicrobials used are beta-lactams and macrolides, although not all of them have been tested in randomized clinical trials and there is no consensus regarding the best option in expectant management[3,9] (Table 1).

Table 1. Antibiotic prophylaxis schemes proposed by the main guidelines

INSTITUTION	SCHEME
Federação Brasileira das Associações de Ginecologia e Obstetrícia (FEBRASGO)[7]	Ampicillin 2g IV 6/6h + Erythromycin Stearate 250mg IV 6/6h for 2 days followed by Amoxicillin 500mg OM 8/8h + Erythromycin Stearate 333mg OM 8/8h for 5 days (Due to the withdrawal of the Erythromycin Stearate, an alternative medicine is azithromycin 1g OM 24/24h for 3 days)
Ministério da Saúde (MS)[2]	Azithromycin 1g OM SD + Ampicillin 2g IV 6/6h for 2 days followed by Amoxicillin 500mg OM 8/8h ou 875mg OM 12/12h for 5 days
Federación Latinoamericana de Sociedades de Obstetricia y Ginecología (FLASOG)[3]	
American College of Obstetricians and Gynecologists (ACOG)[6]	Ampicillin 2g IV 6/6h+ Erythromycin 250mg IV 6/6h for 2 days, followed by Amoxicillin 250mg OM 8/8h + Erythromycin 333mg OM 8/8h for 5 days
Society of Obstetricians and Gynaecologists of Canada (SOGC)[8]	
Sociedad Española de Ginecología y Obstetricia (SEGO)[9]	It is recommended a broad-spectrum antibiotic scheme that covers the most prevalent bacterial flora in each medical center: Ampicillin 2g IV 6/6h + Erythromycin 250mg IV 6/6h for 2 days followed by Amoxicillin + Erythromycin OM for 5 days **or** Ampicillin 1g IV 6/6h + Gentamicin 80mg IV) 8/8h + Azithromycin 1g OM 72/72h por 7 days **or** Azithromycin 1g OM SD + Ampicillin 2g IV 6/6h for 2 days followed by Amoxicillin 500mg OM 8/8h for 5 days **or** Azithromycin 1g OM SD + Cefuroxima 750 mg IV 6/6h for 2 days followed by Cefuroxima 500mg OM 12/12h for 5 days **or (in cases of allergy to penicillin)** Clindamycin 900mg IV 8/8h + Gentamicin 4,5mg/kg IV 24/24h for 2 days followed by Clindamycin 600mg OM 8/8h for 5 days
Royal College of Obstetricians and Gynaecologists (RCOG)[10]	Erythromycin for 10 days
National Institute for Health and Care Excellence (NICE)[11]	Erythromycin 250mg OM 6/6h or a maximum of 10 days or until the pregnant woman goes into labor (whichever comes first) (When there is no availability or intolerance to Erythromycin, an alternative to be considered is penicillin OM)
The Cochrane Colaboration[4]	It does not propose any scheme under the justification that there is no evidence of maternal or neonatal benefits in the routine use of antibiotics in pregnant women of early (gestacional age) gestational age in the absence of confirmed clinical infection
World Health Organization (WHO)[12]	Erythromycin 250mg OM 6/6h for 10 days (When there is no availability or intolerance to Erythromycin, an alternative to be considered is Amoxicillin)

IV: intravenous; OM: oral medication; kg: kilogram; g: gram; mg: miligram; h: hour.

The purpose of this review was to analyze studies that tested and antibiotic prophylaxis in women with PPROM and described their maternal and neonatal outcomes. Randomized or quasi-randomized trials published in Portuguese, English and Spanish in the last 20 years, which were searched in the following databases: PubMed, LILACS, Virtual Health Library of the Ministry of Health (BVS MS) and Central Cochrane were carefully analyzed. The following keywords were used: ruptura prematura de membranas fetais (premature rupture of fetal membranes or rotura prematura de membranas fetales), antibioticoprofilaxia (antibiotic prophylaxis or profilaxis antibiótica) were used.

Etiological agents in PPROM and antibiotic susceptibility profiles

In pregnancy, due to hormonal and vaginal environment changes, there is an imbalance of the flora favoring colonization by microorganisms potentially harmful to the evolution of gestation, such as *Escherichia coli*, *Streptococcus sp*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Streptococcus agalactiae*, among others.[5] Some of these have enzymes capable of degrading the chorioamniotic extracellular matrix, as well as the induction of irritability and uterine contraction by inflammatory cytokines and prostaglandins. Moreover, those enzymes could promote collagen degradation that result in premature rupture of membranes (PRM) and prematurity.

The indiscriminate use of antimicrobials has promoted the emergence of antibiotic resistant microorganisms (Table 2).

Comparison between antibiotics and antibiotic versus placebo

In the last two decades, several studies have been published with the aim of evaluating the efficacy and safety of prophylactic antibiotic regimens in PPROM (Table 3).

Mercer et al.[17] conducted a randomized, double-blind, placebo-controlled study involving university hospitals from the National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network (NICHD-MFMU) to evaluate the association of ampicillin and erythromycin vs. placebo in pregnant women with gestational age between 24 and 32 weeks. The primary outcome was fetal / neonatal death, necrotizing enterocolitis, intraventricular hemorrhage, acute respiratory distress, and sepsis in the first 72 hours. In the antibiotic group, there was a significant increase in the latency period (6.1 vs. 2.9 days, p <0.001) and a lower incidence of clinical amnionitis (23 vs. 32.5%, p = 0.01), but it was related to adverse symptoms, such as nausea, vomiting and abdominal pain (p≤0.003). The newborns had lower levels of respiratory distress syndrome (40.5 vs. 48.7%, p = 0.04), stages 2 and 3 of necrotizing enterocolitis (2.3 vs. 5.8%, p = 0.03) and bronchopulmonary dysplasia (13 vs. 20.5%, p = 0.01). In this study, corticosteroids were not administered for pulmonary maturation, allowing the exclusive evaluation of the effects of antibiotics in PPROM.

Another research, conducted by Ovalle et al.,[18] analyzed the use of clindamycin and gentamicin vs. placebo, evaluating the following variables: gestational prolongation, maternal morbidity related to infection, birth weight, neonatal morbidity and admission to the neonatal intensive care unit. The results were favorable to neonatal well-being, with a lower incidence of respiratory distress syndrome (9.5 vs. 30.2%, p <0.05) and fewer admissions in intensive care units (54.8 vs. 86 %, p <0.01). However, the number of pregnant women with intracavitary invasion by microorganisms was similar between the groups, characterized by the authors as the higher number reported in the literature up to that time. Although the study did not show sufficient statistical power to demonstrate an increase in the latency period in the subgroup of women who used antibiotics associated with amniotic cavity invasion, a significant reduction in the rate of maternal infectious morbidity was observed in this group of patients. Such findings emphasize the importance of establishing the presence of microbial invasion of the amniotic cavity in patients with PPROM. The study recommended the use of intravenous broad-spectrum antibiotics only for patients with proven genital tract infection due to the positive impact of this conduct on mother and fetus.

Lovett et al.[19] found interesting results when comparing two different schemes with placebo: ampicillin-sulbactam associated with amoxicillin-clavulanate vs. ampicillin and amoxicillin. The primary end point was an association of occurrence of neonatal sepsis, acute respiratory distress, fetal / neonatal death, and need for prolonged ventilation. Due to the low statistical power of the study, there was no difference in maternal-fetal morbidity between the groups, with a trend towards better outcomes in the group of pregnant women who used the combination of ampicillin-sulbactam and amoxicillin-clavulanate. Significant differences were seen only in the comparison of any antibiotic vs. placebo. The authors concluded that antibiotic prophylaxis would be indicated primarily in women less than 27 weeks gestation due to the increased risk of maternal infectious complications as well as those inherent in prematurity.

In 2001, it was published ORACLE I, the largest study up nowadays which also compared antibiotic regimens in PPROM. This research randomized 4826 preterm pregnant women in these groups: amoxicillin-clavulanate, erythromycin, and placebo.[20] The primary endpoint was a combination of the following variables: neonatal death, chronic lung disease or major brain abnormality on ultrasonography before discharge. The use of antibiotics in single pregnancies showed a lower need for supplemental oxygen (29.4 vs. 33.9%, p = 0.005), less need for treatment with exogenous surfactant (13.2 vs. 16.3%, p = 0.009), a lower number of ultrasonographies with abnormal brain findings (3.3 vs. 4.6%, p = 0.04), but showed a higher percentage of necrotizing enterocolitis (1.2% vs. 0.3%, p = 0.004) compared to the placebo group. There was also a lower need for oxygen therapy (7% vs. 8.6%, p = 0.05) and lower use of surfactant (12.8 vs. 15.1%, p = 0.02) in pregnant women who were recruited for the erythromycin group in relation to pregnant women who did not use this antibiotic. In women who belonged to amoxicillin-clavulanate group, there was a fourfold increased risk of necrotizing enterocolitis compared to the placebo group (24 vs. 6 patients, p = 0.001), and higher rates of newborns admitted to intensive care units (30.1 vs. 35.6%, p = 0.005). Despite this, there was no statistical significance in other maternal-fetal

Table 2. Etiological agents in PPROM and antibiotic susceptibility profiles

AUTHOR/COUNTRY	AVALIATION	GROUPS	ANTIBIOTICS	RESULTS	SENSITIVITY AND RESISTANCE	CONCLUSION
Eleje et al.[13] Nigeria	To identify the most prevalent microorganisms in pregnant women with PPROM and to evaluate the antibiotic sensitivity of microbial isolates	A: presence of PPROM B: absence of de PPROM	Beta lactams, aminoglycosides and quinolones	*Streptococcus spp* was the most frequently isolated bacterium in group A in relation to group B (p <0.001)	Ampicillin-Sulbactam, Streptomycin, Gentamicin, Cefixime, Cefuroxime, Ciprofloxacin, Ceftriaxone, Erythromycin and the association of Amoxicillin-clavulanate had better sensitivity	Use of Ampicillin-sulbactam or Erythromycin would be good options for the conservative management of PPROM
Sáez-López et al.[14] Spain	To evaluate the sensitivity of several subtypes of *Escherichia coli (E. coli)*	A: women with signs of infection B: women with no signs of infection	Beta-lactams, Aminoglycosides, Carbapenems, Tetracyclines and Quinolones	Groups A: PPROM was the most prevalent risk factor in pregnant women with *E. coli* infection B: 13% culture positive for *E. coli*	65.5% of the samples of pregnant women with *E. coli* infection were resistant to Ampicillin and there was a greater tendency to resistance to all antibiotics in women in group A, especially in relation to the use of Gentamicin (p = 0.001)	The use of Cephalosporins as first-line therapy for the treatment of mothers and newborns is indicated because of the high percentage of sensitivity
Lee et al.[15] South Korea	To investigate the prevalence, effects and antimicrobial susceptibility of *Mycoplasma hominis (M. Hominis)* and *Ureaplasma urealyticum (U. urealyticum)* in pregnant women	A: pregnant women in general B: pregnant women with PPROM	Azithromycin, Ciprofloxacin, Clarithromycin, Doxycycline, Erythromycin, Fosfomycin, Ofloxacin, Pristinamycin and Tetracycline	Groups A: 82.7% infection by *U. urealyticum* alone, 0.3% infection by *M. hominis* alone and 17.0% infection by both agents B: 21.2% infection by *U. urealyticum* alone, 12.4% infection by both agents and 18.8% mycoplasma negative	*M. hominis* isolates: resistant to Azithromycin, Clarithromycin and Erythromycin *U. urealyticum* isolates: sensitivity of 86.0%, 75.2% and 64.0% for Clarithromycin, Azithromycin and Erythromycin Mixed infections: high level of resistance to most antibiotics except Tetracycline	High frequency of *U. urealyticum* infection in pregnant women with PPROM and good sensitivities to Clarithromycin, Azithromycin and Erythromycin
Melo et al.[16] Brazil	To evaluate the antimicrobial susceptibility of *Streptococcus agalactiae* isolates (*Streptococcus group B; GBS*) in pregnant women	Pregnant women in general	Penicillin, Vancomycin and Cefotaxime, Erythromycin, Clindamycin, Chloramphenicol and Tetracycline	25% women infected with GBS	All isolates were susceptible to Penicillin, Vancomycin and Cefotaxime, 8.1% resistant to Erythromycin, 2.2% and 4.4% with intermediate resistance to Clindamycin and Chloramphenicole 82.3% resistant to Tetracycline	Due to the potential resistance of GBS to Erythromycin and Clindamycin, caution is advised when using these antimicrobials

Table 3. Studies comparing antibiotic or antibiotic regimens with placebo

AUTHOR/COUNTRY/DESIGN	PARTICIPANTS	SCHEMES	RESULTS	LOSSES
Mercer et al.[17] USA (RCT)	N=614 ATB (N=300) vs. Placebo (N=314)	Ampicillin 2g IV 6/6h + Erythromycin 250mg IV 6/6h for 2 days→ Amoxicillin 250mg OM 8/8h + Erythromycin 333mg OM 8/8h for 5 days vs. Placebo	Increased birth weight, lower levels of acute respiratory distress (40.5 vs. 48.7%, p = 0.04) and lower rates of necrotizing enterocolitis stages 2 and 3 (2.3 vs. 5.8%; p = 0.03) in infants exposed to ATB	No losses after randomization
Ovalle et al.[18] Chile (RPS)	N=88 ATB (N=42) vs. Placebo (N=46)	Clindamycin 600mg IV 6/6h + Gentaminicin 4mg/kg/day IV for 2 days→ Clindamycin 300mg OM 6/6h + Gentamicin 2mg/kg/day IM 12/12h for 5 days vs. Placebo	Increased birth weight (1849 vs. 1645 grams, p = 0.05), reduction in neonatal ICU admission lVels (54.8 vs. 86%, p <0.01) and fewer cases of acute respiratory distress syndrome (9.5 vs 30.2%, p <0.05) in infants exposed to ATB	7 losses after randomization ATB: 4 Placebo: 3
Lovett et al.[19] USA (RCT)	N=164 Ampicillin-sulbactam (N=38) vs. Ampicillin (N=37) vs. Placebo (N=37)	Ampicillin-sulbactam 1,5g IV 6/6h for 3 days→ Amoxicillin-clavulanate 500mg OM 8/8h until delivery vs. Ampicillin 2g IV 6/6h for 3 days→ Amoxicillin 500mg OM 8/8h until delivery vs. Placebo	a) Ampicillin-sulbactam + Amoxicillin-clavulanate and Ampicillin + Amoxicillin vs. Placebo: less need for mechanical ventilation > 72h (5.26 vs. 8.11%, p <0.05) in infants exposed to ATB b) Ampicillin-sulbactam + Amoxicillin-clavulanate vs. Placebo: Lower rates of sepsis (7.9 vs. 16.2%, p <0.05) and lower levels of acute respiratory distress (21 vs. 37.8%, p <0.05) in infants exposed to ATB	52 losses after randomization (There is no discrimination of the amount of women lost in each group)
Kenyon et al.[20] USA (RCT)	N=4826 Erythromycin (N=1190) vs. Amoxicillin-clavulanate (N=1205) vs. Erythromycin + Amoxicillin-clavulanate (N=1189) vs. Placebo (N=1225)	Erythromycin 250mg vs. Amoxicillin-clavulanate 325mg (250-125) vs. Erythromycin 250mg + Amoxicillin-clavulanate 325mg vs. Placebo OM 6/6h for 10 days or until delivery	a) Any antibiotic vs. placebo: lower number of ultrasonographies with abnormal brain findings (p = 0.04) b) Any Erythromycin vs. no Erythromycin: reduction primary outcome (11.2 vs. 14.4%, p = 0.02)	17 losses after randomization Erythromycin: 7 Amoxicillin-clavulanate: 7 protocol violations in the Erythromycin + Amoxicillin-clavulanate group: 3
Ryo et al.[21] Japan (CC)	N=140 Imipenem-cilastatin (N=100) vs. Control group* (N=40) *Penicillin or cephalosporin (N=38) and no ATB (N=2)	Imipenem-cilastatin 0,5g IV 12/12h for 3 days→ Other ATB (according to the sensitivity profile in culture) vs. Penicillin or cephalosporin or no antibiotic	Increase of number of deaths in the first year of life in infants of control group (p = 0.002 vs. study group)	No losses after randomization

ATB: antibiotic; IV: intravenous; OM: oral medication; IM: intramuscular; kg: kilogram; g: gram; mg: miligram; h: hour; SD: single dose; vs.: *versus*; IMP-CS: imipenem-cilastatin; RCT: randomized clinical trial; RPS: randomized prospective study; CC: case-control; RR: retrospective review; RC: retrospective cohort.

Table 3. Continued...

AUTHOR/ COUNTRY/ DESIGN	PARTICIPANTS	SCHEMES	RESULTS	LOSSES
Fuhr et al.[22] USA (RCT)	N=105 ATB (N=47) vs. Placebo (N=58)	Mezlocilin 2g IV 8/8h for 7 days vs. Placebo	Maternal: increased latency period over 7 days (63.8 vs. 44.8%, p <0.05) in the group of pregnant women receiving ATB Neonatal: lower overall neonatal morbidity (measured by levels of sepsis, acute respiratory distress and intraventricular hemorrhage in infants exposed to ATB	No losses after randomization
Ehsanipoor et al.[23] USA (RR)	N=147 Ampicillin-sulbactam (N=88) vs. Cefazolin + Erythromycin (N=59)	Ampicillin-sulbactam 300mg 6/6h IV for 2 days→ Amoxicillin-clavulanate 500mg OM 8/8h for 5 days vs. Cefazolin 200mg IV 8/8h + Erythromycin 250mg IV 6/6h for 2 days→ Cefalexin 500mg OM (6/6h + Erythromycin 250mg OM 6/6h for 5 days	There was no increased risk of necrotizing enterocolitis in infants exposed to Amoxicillin-clavulanate (8 vs. 10.2%, p = 0.64)	No losses after randomization
Hernández y Ballinas et al.[24] Mexico (RPS)	N=40 Erythromycin (N=20) vs. Clindamycin (N=20)	Erythromycin 250mg OM 6/6h vs. Clindamycin 600mg IV 8/8h (There is no description of treatment time)	There were no significant differences in any of the maternal or neonatal outcomes	No losses after randomization
Kwak et al.[25] South Korea (RPS)	N=102 Cefazolin + Placebo (N=35) vs. Cefazolin + Erythromycin (N=31) vs. Cefazolin + Clarithromycin (N=36)	Cefazolin 1g IV 6/6h + Placebo vs. Cefazolin 1g IV 6/6h + Erythromycin 250mg OM 6/6h vs. Cefazolin 1g IV 6/6h + Clarithromycin 500mg OM 12/12h (For 7 days or until delivery – whichever occurred first)	There was no significant difference related to neonatal morbidity (respiratory stress syndrome, pulmonary bronchodysplasia, intraventricular hemorrhage grades 3 and 4, retinopathy of prematurity, necrotizing enterocolitis stages 2 and 3 and congenital neonatal sepsis) between the groups analyzed	No losses after randomization
Nabhan et al.[26] Egypt (RCT)	N=1640 ATB (N=820) vs. Placebo (N=820)	Ampicillin-sulbactam 1,5g IV SD vs.Placebo	There was no significant difference related to early or probable neonatal sepsis between groups analyzed	No losses after randomization

ATB: antibiotic; IV: intravenous; IM: intramuscular; kg: kilogram; g: gram; mg: miligram; h: hour; SD: single dose; vs.: versus; IMP-CS: imipenem-cilastatin; RCT: randomized clinical trial; RPS: randomized prospective study; CC: case-control; RR: retrospective review; RC: retrospective cohort.

Table 3. Continued...

AUTHOR/ COUNTRY/ DESIGN	PARTICIPANTS	SCHEMES	RESULTS	LOSSES
Pierson et al.[27] USA (RC)	N=168 Ampilicina + Erythromycin (N=75) vs. Ampicillin + Azithromycin (N=93)	Ampillicin + Erythromycin → Amoxicillin + Erythromycin vs. Ampicillin + Azithromycin *(There is no description of dosages, route of administration and treatment time)*	There were no significant differences in any of the maternal or neonatal outcomes	No losses after randomization
Navathe et al.[28] USA (RC)	N=68 Ampicillin + Erythromycin (N=37) vs. Ampicillin + Azithromycin (N=31)	Ampicillin IV + Erythromycin IV for 2 days→ Amoxicillin OM + Erythromycin OM for 5 days vs. Ampicillin IV for 2 days+ Azithromycin 1g OM SD→ Amoxicillin OM for 5 days *(There is no full description of the dosages)*	There were no significant differences in any of the maternal or neonatal outcomes	No losses after randomization
Finneran et al.[29] USA (RC)	N=162 Ampicillin + Erythromycin (N=84) vs. Ampicillin + Azithromycin (N=78)	Ampicillin + Erythromycin → Amoxicillin + Erythromycin vs. Ampicillin + Azithromycin OM 1g SD → Amoxicillin *(There is no description of dosages, route of administration and treatment time)*	There were no significant differences in any of the maternal or neonatal outcomes	No losses after randomization

ATB: antibiotic; IV: intravenous; OM: oral medication; IM: intramuscular; kg: kilogram; g: gram; mg: miligram; h: hour; SD: single dose; vs.: *versus*; IMP-CS: imipenem-cilastatin; RCT: randomized clinical trial; RPS: randomized prospective study; CC: case-control; RR: retrospective review; RC: retrospective cohort.

parameters. Because of this study, the use of erythromycin in PPROM is suggested, on the contrary, the association of amoxicillin-clavulanate which was discouraged.

According to a prospective cohort of children evaluated in the previous study, there was no significant differences between antibiotic or placebo groups regarding the impact of antibiotic exposure in relation to functional impairment and outcomes related to behavior, learning and health problems of children at 7 years[30] and also in relation to schooling at age 11.[31]

Ryo et al.[21] performed a study that included pregnant women with PPROM between 24 and 31 weeks and 6 days and compared the use of imipenem-cilastatin followed by antibiotic suggested by the result of the culture vs. ampicillin or cephalosporin. The reserach evaluated the latency period, neonatal deaths and the presence of sequels in patients. There was a significant increase in latency time in the group that used imipenem-cilastatin in relation to the control group (11 vs. 6 days, p = 0.016). In the newborns followed up for 1 year, 5 children (12.5%) included in the control group died in this period (p = 0.002). Of the remaining 35 patients, four had sequelae but there was no difference between the two groups (p = 0.327). The authors suggest that the use of imipenem-cilastatin (combined with betamethasone) has the potential to be used as the first-choice antibiotic in the expectant management of patients with PPROM, especially in extremely premature infants who are considered to be at high risk for developing infections.

Fuhr et al.[22] prospectively evaluated the use of mezlocillin vs. placebo in women with PPROM between 24 and 32 gestational weeks. Gestational prolongation and the presence of sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and acute respiratory distress in newborns were observed, showing similar results to other previously published studies regarding increased latency and reduction of neonatal infection. At that time, the prescription of mezlocillin associated with sulbactam for 7 days was a routine for women with PPROM in the absence of infectious symptoms, and erythromycin was prescribed when the latter could not be used.

The combination ampilicillin-sulbactam followed by amoxicillin-clavulanate vs. cefazolin-cephalexin associated with erythromycin was evaluated retrospectively by Ehsanipoor et al.[23] The main objective of the study was to determine whether the use of amoxicillin-clavulanate was associated with increased cases of necrotizing enterocolitis. In contrast to previous results,[16] they showed no increased risk in infants exposed to amoxicillin-clavulanate (8 vs. 10.2%, p = 0.64) and no other findings related to maternal or neonatal morbidity. Even with their reduced sampling, the authors suggest that ampicillin-sulbactam associated with amoxicillin-clavulanate and a cephalosporin associated with erythromycin are safe and effective antibiotic regimens for patients with PPROM. Thus, in hospitals with high levels of ampicillin resistance, replacement with cephalosporin together with erythromycin could be an alternative.

Erythromycin and clindamycin were compared for the first time by Hernández y Ballinas et al.[24] in 40 patients with PPROM. As a primary endpoint, the authors evaluated the presence of chorioamnionitis, respiratory distress syndrome, sepsis and necrotizing enterocolitis. Unfortunately, due to the small sample size, the results of maternal-fetal outcomes did not show significant differences, although a trend better maternal and neonatal outcomes, and in the prevention of chorioamnionitis and necrotizing enterocolitis in the group of pregnant women who used erythromycin.

Kwak et al.[25] conducted a randomized clinical trial comparing three groups: cefazolin associated with erythromycin, cefazolin associated with clarithromycin and cefazolin alone. The primary endpoint was the neonatal complications: respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage grade 3 and 4, retinopathy of prematurity, necrotizing enterocolitis stages 2 and 3 and congenital neonatal sepsis. Although there was no significant differences regarding such outcomes, interestingly, the presence of funisitis and its degree of staging showed differences when comparing cefazolin associated with clarithromycin with isolated cefazolin, revealing greater funisitis items in stages 1 and 3 in the group that used cefazolin alone and inverting these findings when treating stage 2 (stage 1: 26.5 vs. 5.9%; stage 2: 35.3 vs. 55.9%; stage 3: 17.7 vs. 2.9%, p = 0.023). It was not found no difference when erythromycin was used. Despite the limitations of the study compared to the sampling and little accuracy of the inclusion criteria, Kwak et al.[25] suggest that clarithromycin can be an alternative to erythromycin, since it has higher bioavailability, tissue penetration and transplacental passage.

Nabhan et al.[26] conducted a randomized, double-blind, controlled clinical trial comparing the parenteral single-dose ampicillin-sulbactam use with placebo in patients in spontaneous labor associated with PPROM in preterm or borderline fetuses (36 weeks or more of gestation). The pre-specified primary outcome was early or probable neonatal sepsis. Early sepsis occurred in 34 (4.1%) and 24 (2.9%) neonates in the antibiotic and placebo groups, respectively, but without statistical significance. Despite this, an increased rate of cesarean section (20.1 vs. 14.9%, p = 0.006), longer post-partum hospital stay (8.28 ± 8.50 days vs. 8.24 ± 7.47 days, p = 0.05) and higher frequency of postpartum haemorrhage (4.3 vs. 2.0%, p = 0.009). After subgroup analysis, the postpartum haemorrhage remained significant only among women who had normal birth (3.5 vs. 1.7%, p = 0.042). It was also observed a longer stay of infants in intensive care unit (0.30 ± 1.51 days vs. 0.25 ± 1.31 days, p = 0.05) and longer duration of mechanical ventilation (0.04 ± 0.43 days vs. 0.03 ± 0.41 days, p = 0.01). However, the study had some limitations such as absence of analysis of subgroups of women at higher risk of infection, non-follow-up of newborns in relation to late neonatal sepsis,

non-reporting of drug-resistant infections among newborns, inclusion of pregnancies with 36 weeks or more, which could change some results. Anyway, Nabhan et al.[26] conclude that routine prophylactic use of antibiotics near term does not provide maternal and neonatal benefits.

Pierson et al.,[27] in a retrospectively research, compared ampicillin associated with erythromycin and ampicillin associated with azithromycin in patients with PPROM. The primary endpoint was the latency period and secondary endpoints were chorioamnionitis rate, cesarean rate, Apgar score, birth weight, neonatal death, neonatal sepsis and neonatal respiratory distress syndrome. They found no significant difference in any of the maternal or neonatal outcomes. Although, it is not specified in the study the medicine dose and the treatment duration. Despite its various limitations, such as small sample of participants, irregular identification of patients with PPROM, inclusion of women with genito-urinary infections, and the use of tocolytic or magnesium sulfate therapy in pregnant women (who could influence the latency period). Besides the addition of antibiotics for other reasons, the study concludes that azithromycin would be an equivalent option to erythromycin, with potentially decreased costs and ease of administration.

Recently two other studies have compared the use of erythromycin or azithromycin associated with ampicillin followed by amoxicillin, primarily by assessing the latency period.[28,29] Both researches did not reveal significant differences in relation to the latency period, as well as maternal and neonatal morbidities, thus suggesting that the use of azithromycin could be an option in the management of PPROM.

Evaluation of amniotic fluid and placental histological findings after antibiotic prophylaxis

Despite the evidence regarding antibiotic prophylaxis in cases of PPROM, it is not clear whether its effects are attributable to the eradication of intrauterine infection or to the reduction of the intensity of the inflammatory process present in the microbial invasion of the amniotic cavity or even to the prevention of infection OF uterine cervix and vagina[32] (Table 4).

Final considerations

After reviewing the studies, it was observed that despite the consensus regarding the increase in the latency period, there is no compliance with the most appropriate scheme to be used in the management of PPROM, although the drugs tested correspond to the current sensitivity profiles of the main microorganisms involved. It was noted that most studies comparing erythromycin and azithromycin did not detect significant differences in maternal and neonatal outcomes, suggesting azithromycin as a drug option with greater ease of administration and lower cost. In addition, due to the association between the use of amoxicillin-clavulanate and the occurrence of necrotizing enterocolitis, it is recommended to avoid its routine use.

It has also been found that both amniotic fluid and placental histology analyzes do not appear to be good parameters for predicting clinical outcomes and possible eradication of the microorganism or inflammatory process associated with PPROM, since this inflammatory process may already been stablished before the membranes rupture.

It was also observed that there are some doubts regarding the maternal and neonatal outcomes when using antibiotics. There are many confounding factors present in the literature, such as the inclusion of women with near-term PPROM or long-term fetal viability that impairs identification of the potential benefits of antibiotic use; several maternal and neonatal outcomes are less frequently diagnosed after the early use of antibiotics, eg, masking a febrile process in a pregnant woman with chorioamnionitis or even a false negative culture in a neonate with suspected neonatal sepsis; and the small sampling of a good part of the studies does not have the statistical power to reach significant results, being necessary larger samples.

The 20 years of article analysis comprises a transitional period about the recommendations of corticotherapy in PPROM, therefore, some studies have associated the use of corticoids and others haven't, which may mask the real effects of isolated antibiotic prophylaxis.

It is also not possible to generalize the results observed for the different populations since the bacterial colonization and antimicrobial susceptibility profile may vary according to the place and type of service.

Considering these points, it is possible to conclude that more randomized and controlled trials with a good casuistry are necessary, in order to analyze the actual maternal and neonatal outcomes of the use of antibiotics in PPROM and, if the results are positive, to standardize the best therapeutic scheme according to the profile of each institution.

Table 4. Studies evaluating amniotic fluid and placental histological findings after antibiotic prophylaxis

AUTHOR	AVALIATION	ANTIBIOTICS	RESULTS	CONCLUSION
Bendon et al.[32]	To identify differences in the histology of membranes between patients with PPROM treated with ATB or placebo	Ampicillin e Erythromycin vs. Placebo	The analysis did not reveal differences in the histological characteristics between the patients	Retrospective histologic examination of placental membranes cannot be used to assess the effectiveness of ATB use (they may have preceded the RPM and did not regress with treatment or the histology did not reveal the potential effects of the drugs)
Ovalle et al.[33]	Analyze whether the administration of antibiotics vs. placebo in patients with PPROM would be associated with lower rates of histological chorioamnionitis and funisitis	Clindamycin e Gentamicin vs. Placebo	No significant differences were found in the microbiological findings of the amniotic fluid between the studied groups *Ureaplasma urealyticum* was the most isolated microorganism, followed by *Gardnerella vaginalis, Mycoplasma hominis, S. agalactiae and Streptococcus viridans* Patients receiving ATB had a lower frequency of histological chorioamnionitis than those receiving placebo (45.7 vs. 69.4%, p <0.05) and a higher percentage of placentas without pathological findings (28.6 vs. 5, 6%, p <0.01) There were no differences between patients who received or not ATB in relation to: funisitis, villous, trophoblastic hyperplasia and fetal placental vascular lesions The administration of ATB among fetuses presenting funnels did not change the frequency of neonatal infection (27.3 vs. 30.8%),	The inability of ATB to improve fetal or neonatal survival is probably the result of pathophysiological derangement that should have been in place at the time when antimicrobial therapy is instituted, since a systemic fetal inflammatory response may be present before the rupture of the membranes in some fetuses and, consequently, subsequent antibiotic administration would be late to modify the course of the disease

In this same study, in order to verify the existence of placental findings characteristic of PPROM, a blind analysis of 15 placenta samples by four different pathologists, using a provisional list of criteria to be filled, was performed. After analyzing the data, it was determined that 29 histological characteristics could be objectively described with good agreement among the investigators: coagulation necrosis without inflammation, separation of the chorionic epithelium of connective tissue, mononuclear and eosinophilic infiltrate, recent hemorrhage, among others.

PPROM: preterm premature rupture of membranes; ATB: antibiotic; *vs: versus*; PRM: premature rupture of membranes.

Table 4. Continued...

AUTHOR	AVALIATION	ANTIBIOTICS	RESULTS	CONCLUSION
Mercer et al.[34]	To review the placental histological findings of 79% of participants in the NICHD-MFMU[17] comparing the use of ATB vs. placebo (no significant differences in relation to placental or membrane inflammation between groups)	Ampicillin e Erythromycin vs. Placebo	The latency period was lower in pregnant women who presented membrane inflammation (6.7 vs. 14.6 days, p <0.001), and there was no correlation with placental histology Clinical amnionitis was five times more frequent in women with membrane and placental inflammation (p = 0.0009) After controlling for exposure to drugs in the study, latency period, presence of Streptococcus agalactiae and gestational age at delivery, there was no association between placental or membrane inflammation to composite fetal morbidity, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis or perinatal death	Treatment with ATB possibly does not reverse the progression of the cascade of histopathological inflammation in the PPROM environment, and does not reduce the probability of fetal exposure to the intrauterine inflammatory medium Although such exposure may predispose to long-term neurological sequelae, the lack of correlation between acute inflammation and the duration of membrane rupture suggests that early delivery after PPROM does not necessarily prevent exposure to this environment or these results
Gomez et al.[35]	Verify that the administration of ATB to 46 pregnant women with PPROM eradicates the intra-amniotic infection and / or reduces the frequency of intra-amniotic inflammation	Ampicillin and Erythromycin for 7 days in patients with no evidence of microbial invasion of the amniotic cavity or intra-amniotic inflammation Ceftriaxone, Clindamycin and Erythromycin for 10-14 days in patients with any of these positive findings	Intra-amniotic inflammation: 39% without use of ATB and 53% after administration of ATB Positive culture of amniotic fluid: 15% in the first amniocentesis and 28% in the second amniocentesis after completion of treatment 83% or more of patients with PPROM and intra-amniotic inflammation or culture of positive amniotic fluid maintained the same microbiological and inflammatory states after the use of the drug	The treatment with ATB rarely eradicates the microbial invasion of the amniotic cavity in patients with PPROM, thus, this would not be the mechanism by which the ATB exert their beneficial effect

In this same study, 29 placentas were studied histologically. In general, the prevalence of histological chorioamnionitis was 59%, while funnitis was present in 52% of the cases. Patients with persistent intra-amniotic inflammation had histological chorioamnionitis and funneling in 67% and 58% of cases, respectively. Cases without intra-amniotic inflammation or those that changed their inflammatory state in the amniotic fluid from positive to negative presented a lower prevalence of histological chorioamnionitis in 23%.

PPROM: preterm premature rupture of membranes; ATB: antibiotic; vs: versus; PRM: premature rupture of membranes.

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*Correspondence

Daniela Cristina Schroff Machado
Pontifícia Universidade Católica de Goiás (PUC-Goiás)
Rua 145, 500, Setor Marista
CEP 74170-080, Goiânia, GO, Brazil
Tel.: +55 (62) 98221-6185
E-mail: danielaschroff@hotmail.com

Authors information

DCSM - Physician graduated at Pontifícia Universidade Católica de Goiás. JMD - Physician graduated at Pontifícia Universidade Católica de Goiás. LEPR - Master in Epidemiology and Teacher in Human Reproduction for Pontifícia Universidade Católica de Goiás.

Authors contribution
DCSM: research, discussion and writing of the text. JMD: research, discussion and writing of the text.

LEPR: orientation of the study, discussion and review of the text.