Antibiotic prophylaxis in pregnant with premature rupture of ovular membranes: systematic review and meta-analysis

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ABSTRACT

Objective: To perform a systematic review and meta-analysis of randomized clinical trials that compared the use of antibiotics versus placebo in premature rupture of membranes preterm and evaluated maternal, fetal and neonatal outcomes in pregnant women with premature rupture of ovular membranes at a gestational age between 24 and 37 weeks.

Methods: A search was conducted using keywords in PubMed, Cochrane, Biblioteca Virtual em Saúde and Biblioteca Digital de Teses e Dissertações da USP between August 2018 and December 2021. A total of 926 articles were found. Those included were randomized clinical trials that compared the use of antibiotics versus placebo in the premature rupture of preterm membranes. Articles referring to antibiotics only for streptococcus agalactiae prophylaxis were excluded. The retrieved articles were independently and blindly analyzed by two reviewers. A total of 24 manuscripts met the inclusion criteria and 21 articles were included for quantitative analysis.

Results: Among the maternal outcomes analyzed, there was a prolongation of the latency period that was ≥7 days. In addition, we observed a reduction in chorioamnionitis in the group of pregnant women who used antibiotics. As for endometritis and other maternal outcomes, there was no statistically significant difference between the groups. Regarding fetal outcomes, antibiotic prophylaxis worked as a protective factor for neonatal sepsis. Necrotizing enterocolitis and respiratory distress syndrome showed no statistically significant differences.

Conclusion: The study showed positive results in relation to antibiotic prophylaxis to prolong the latency period, new randomized clinical trials are needed to ensure its beneficial effect.

Prospero database registration: (www.crd.york.ac.uk/prospero) under number CRD42020155315.

Keywords: Fetal membranes, premature rupture; Gestational age; Pregnant women; Antibiotic prophylaxis; Anti-bacterial agents; Infant, premature

INTRODUCTION

Premature rupture of the ovular membranes (PRPM) is defined as a spontaneous rupture of the chorionic and amniotic membranes that often occurs before the onset of labor, regardless of gestational age.1 When this rupture occurs before 37 weeks, it is called preterm PRPM, and it is an important cause of perinatal morbidity and mortality. The time elapsed between the rupture and the spontaneous onset of labor is defined as the latency period, and its duration is directly correlated with the risk of maternal infection and inversely with gestational age.2

Premature rupture of the ovular membranes occurs from 8% to 10% of pregnancies and up to 40% of preterm births result from preterm PRPM. Such
number accounts for 20% of perinatal deaths. A recent Brazilian study in a referral maternity hospitals showed that 29% of preterm births were due to preterm PRPM and they occurred in 3.5% of a total of 33,740 deliveries. There are some risk factors described for the occurrence of PRPM. Among the modifiable factors, those that stand out are cervicovaginitis, isthmocervical incompetence, smoking, amniocentesis, choriionic villus sampling, intercourse, vitamin C and mineral deficiency, as well as repeated cervical examinations.

However, the non-modifiable risk factors are history of previous surgeries, history of PRPM, vaginal bleeding, placenta previa, placental abruption, marginal insertion of the umbilical cord, and uterine hyperdistension (multiple pregnancy and polyhydramnios). The infectious process seems to be one of the most important one and this seems to lead to an inflammatory reaction, which alters the tissue structure of the membrane, weakening it and, thus, allowing its rupture. The main agents involved in this pathophysiology are *Gardnerella vaginalis*, *Neisseria gonorrhoeae*, *Streptococcus agalactiae*, *Escherichia coli*, and *Bacteroides sp.*

The diagnosis of PRPM can be extremely easy, when the anamnesis and physical examination are enough to clarify it, or extremely difficult, when not even the most advanced complementary exams are convinced of the rupture. Fortunately, anamnesis and physical examination establish the diagnosis in 90% of cases. Premature rupture of the ovular membranes is associated with important maternal and perinatal complications, and it involves more injuries when occurring far from term.

Among maternal complications, chorioamnionitis, endometritis and bacteremia are the most frequent. Maternal sepsis is rare when there is adequate obstetric care in face of maternal signs of infection. The frequency and severity of neonatal complications vary based on gestational age. Respiratory distress syndrome (RDS) is the most common complication at any gestational age as well as other morbidities, including: necrotizing enterocolitis (NEC), peri-intraventricular hemorrhage (IVH) and sepsis.

Premature rupture of the ovular membranes in women with a gestational age of less than 37 weeks remains a frequent problem in obstetric practice and there are several controversies regarding the medical management to be taken. Among the main points of disagreement are the indication of expectant management based on its diagnosis, the need for hospitalization, the use of tocolysis, and corticosteroids. In addition, there are the methods used to diagnose infection, the ideal time of delivery, and the use of antibiotics both for prophylaxis of infection by Group B *streptococcus*, as well as to increase the latency period.

Therefore, scientific research related to PRPM including the analysis of different behaviors and maternal and perinatal outcomes are of great importance for the updating and possible standardization of routines in services that is searching for benefits against the morbidity and mortality associated with its occurrence.

The aim of this study was to perform a systematic review and meta-analysis of randomized clinical trials that compared the use of antibiotic prophylaxis to increase the latency period, and evaluated the maternal, fetal and neonatal outcomes of pregnant women with PRPM at gestational age between 24 and 37 weeks.

## METHODS

**Protocol registration**

Criteria used for the search were the ones recommended by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The guidelines established by the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) tool were also followed to check whether the systematic review was done properly.

**Electronic search and search strategy**

The following keywords were used: “antibiotic”, “antibiotics”, “anti-bacterial”, “antimicrobial”, “antibiotic prophylaxis”, “antibiotics and fetal membranes”, “premature rupture of membranes”, “premature rupture of membranes”, “fetal membranes”, “fetal rupture of membranes”, “fetal membranes”, and “PRPM”.

Searches were carried out in PubMed, Cochrane, Biblioteca Virtual em Saúde and Biblioteca Digital de Teses e Dissertações da USP on August 22, 2018. There was a new search on December 2, 2021 to check whether the systematic review was done properly. All studies were included in the electronic platform Rayyan® QCRI, a web application designed to assist in the selection of articles in systematic reviews.

In PubMed search was made using the following keywords ((((antibiotic[Title/Abstract]) OR antibacterial[Title/Abstract]) OR antimicrobial[Title/Abstract]) OR antibiotic prophylaxis[Title/Abstract]) OR antibiotics[Title/Abstract]) AND (((fetal membranes[Title/Abstract]) OR premature rupture of membranes[Title/Abstract]) OR premature rupture...
of fetal membranes[Title/Abstract]) OR preterm premature rupture of fetal membranes[Title/Abstract]) OR PRPM[Title/Abstract]). However, in Cochrane the search was conducted using “antibiotic” OR “anti-bacterial”; OR “antibiotic prophylaxis”; OR “antibiotics”; OR “antimicrobial”; AND “PRPM” OR “premature rupture of membranes”; OR “premature rupture of fetal membranes”; OR “fetal membranes”.

Eligibility criteria
The evaluated criteria were study design, participants, intervention, and outcomes. We analyzed only randomized clinical trials of pregnant women with PRPM and gestational age between 24 and 37 weeks submitted to antibiotic versus placebo. Observational studies, book chapters, commentaries, literature reviews, case reports, experimental studies, or randomized clinical trials including pregnant women with PRPM and who were at gestational age below 24 weeks or above 37 weeks were excluded. Randomized clinical trials without Control Group or Placebo, and/or those that used antibiotic for *Streptococcus agalactiae* were also excluded from analysis.

Selection of studies
Authors independently assessed all selected studies in the published literature search. When articles written by the same authors were found, their contents were checked in order to establish whether the same sample had been used and, if so, the most complete sample was chosen.

Data extraction
For data extraction and management, a spreadsheet was created containing the following variables: author and year of article’s publication, gestational age of patients included in the study, number of participants, type of intervention performed, type of Control Group, duration of antibiotic use, use of corticosteroids, magnesium sulfate and tocolytics. We also considered whether the article referred to the treatment of streptococci, gestational age at which rupture membrane occurred, duration of prolonged latency period within days or hours, gestational age at delivery, cesarean delivery, chorioamnionitis, endometritis, maternal sepsis, maternal death, newborn birth weight, fetal death, perinatal death, Apgar score, RDS, NEC, neonatal sepsis, and intraventricular hemorrhage.

Assessing risk of bias
The risk of bias of studies included in this systematic review and meta-analysis was assessed by the authors in an independent and blind manner as suggested by both PRISMA protocol and Cochrane collaboration.

Statistical analysis
Meta-analyses were conducted when there were two or more studies that reported the same outcome. The fixed model was used when there was no significant heterogeneity (Cochran test > 0.10) and the random model when this heterogeneity was presented. In addition, the Higgins F test was conducted in order to define whether there was high heterogeneity (> 50%).

Subgroup meta-analyses were performed with the following variables: gestational age up to 34 weeks, the use of Ampicillin alone as an intervention, study blinding, the use of corticosteroids and tocolysis.

Funnel Plot and Deek’s test were performed to assess the risk of publication bias. The data was introduced in Review Manager version 5.3 by the Cochrane Collaboration.

RESULTS
A total of 926 manuscripts were retrieved from the search bases. In December 2021 new search, another 112 articles were found. None of the articles submitted to the meta-analysis were the result of second search. In all stages of the study, the articles were read separately by two examiners and disagreements were solved after the discussion with an expert. The flowchart of selection can be seen in figure 1 and main characteristics of included studies are shown in table 1. In total, 7,111 pregnant women and their newborns were evaluated.

The antibiotic regimens varied in the different studies, corresponding to the following therapeutic regimens: A: Ampicillin; AE: Ampicillin + Erythromycin; AM: Ampicillin + Metronidazole; AS: Ampicillin + Sulbactam; AX: Amoxicillin; AXC: Amoxicillin + Clavulanate; AGC: Ampicillin + Gentamycin + Clindamycin; AXCE: Amoxicillin + Clavulanate + Erythromycin; CG: Clindamycin + Gentamycin; E: Erythromycin; MZ: Mezlocillin; MZA: Mezlocillin + Ampicillin; P: Penicillin; PP: Piperacillin; PVM: Pivampicillin + Metronidazole.

Four articles evaluated the use of some antibiotic versus another antibiotic, however, due to the absence of a Placebo Control Group, they could not be included in the meta-analysis.
The duration of treatment was, on average, 7 days, however, some articles mentioned the use of antibiotics until delivery. The use of corticosteroids and tocolysis was not adequately reported in some studies, which impaired the assessment. The antibiotic regimen used as intervention, its duration, as well as the presence or absence of corticosteroid therapy or tocolysis, can be analyzed in table 2.

The outcomes evaluated were divided into maternal (prolonged latency period, gestational age at delivery, chorioamnionitis, endometritis and maternal death), fetal (fetal death) and neonatal (Apgar score, birth weight, RDS, NEC, neonatal sepsis and neonatal death) and they are summarized in tables 3 and 4 and in supplementary table 1.

**Extension of the latency period**

Studies were standardized in units of hours or days. The analysis showed no difference between the antibiotic and Placebo Groups (p=0.25). However, when categorized in a period greater than or equal to 7 days, there was an increase in latency time in the Antibiotic Group (p=0.03), and relative risk (RR) of 1.74 (1.06-2.85) as it can be seen in figure 2.

Regarding the latency period greater than 7 days, the funnel plot did not present adequate distribution (Supplementary figure 2.1).

**Prolongation of the latency period with corticosteroids**

The absence of corticosteroids while using antibiotic prophylaxis was correlated with an increase in the latency period in the group categorized in days.

**Gestational age at birth**

There was no statistically significant difference in terms of gestational age at delivery between the Placebo Group and the group that used antibiotics (p=0.85). This outcome was analyzed in only six studies due to the lack of data in the other manuscripts (Supplementary figure 2.2).

**Chorioamnionitis**

The use of antibiotics demonstrated protection against chorioamnionitis (p=0.03) with RR=0.71 (0.52-0.96) (Figure 3). When chorioamnionitis was evaluated along with gestational age, protection was statistically more significant in the group of pregnant women with gestational age up to 34 weeks.

Five studies used ampicillin alone. The comparison between the ampicillin Group Alone versus the Group of other Antibiotics showed no statistical difference in relation to chorioamnionitis.

The funnel plot showed an adequate distribution of studies (Supplementary figure 3.1).

**Endometritis**

There was no statistically significant difference between the Group that used Antibiotics versus the Placebo Group (p=0.49 and 95%CI: 0.39–1.56) (Supplementary figure 3.2).

**Maternal death**

There were no records of maternal deaths in the meta-analyzed studies.

**Apgar score < 7 in the fifth minute**

There was no statistically significant difference between the Groups that used Antibiotics versus Placebo (RR=0.74 and 95%CI: 0.47-1.17) supplementary figure 3.3.
Table 1. Population characteristics of included studies

| Author                  | Gestational age | Number of participants | Gestational age rupture intervention average/median | Gestational age rupture control mean/median |
|-------------------------|-----------------|------------------------|----------------------------------------------------|---------------------------------------------|
| Almeida et al.,(9)      | 37              | 106                    | 32 (±2.1)                                          | 31.7 (±4.0)                                |
| Amon et al.,(10)        | 34              | 82                     | NR                                                 | NR                                          |
| Carroli et al.,(11)     | 34              | 31                     | NR                                                 | NR                                          |
| Christmas et al.,(12)   | 34              | 94                     | 30.4                                               | 29.9                                        |
| Cox et al.,(13)         | 34              | 62                     | 26.9 (±1.9)                                        | 26.7 (±2.2)                                |
| August Fuhr et al.,(14) | 34              | 105                    | NR                                                 | NR                                          |
| Garcia-Burguillo et al.,(15) | 37           | 60                     | NR                                                 | NR                                          |
| Grable et al.,(16)      | 37              | 60                     | NR                                                 | NR                                          |
| Johnston et al.,(17)    | 34              | 85                     | 29.5 (±0.70)                                       | 30.3 (±0.5)                                |
| Kenyon et al.,(18)      | 37              | 4,809                  | E 27.5 (±6.1) AXC 28.0 (±6.0) AXCE 27.8 (±6.1)    | 27.9 (±6.1)                                |
| Kurki et al.,(19)       | 37              | 101                    | 32.4 (±2.3)                                        | 32.3 (±2.4)                                |
| Lockwood et al.,(20)    | 37              | 75                     | NR                                                 | NR                                          |
| Lovett et al.,(21)      | 37              | 102                    | ASAXC 30.17 (±0.57) AAXC 29.73 (±0.42)             | 29.58 (±0.54)                              |
| Magwali et al.,(22)     | 37              | 170                    | 32.8 (±2.7)                                        | 32.8 (±2.5)                                |
| McCaul et al.,(23)      | 34              | 37                     | NR                                                 | NR                                          |
| McGregor et al.,(24)    | 37              | 55                     | 30.5 (±3.5)                                        | 31.5 (±2.8)                                |
| Mercer et al.,(25)      | 37              | 220                    | 30.3 (±3.4)                                        | 29.8 (±3.8)                                |
| Mercer,(26)             | 34              | 614                    | 28.6 (±2.2)                                        | 28.5 (±2.4)                                |
| Morales et al.,(27)     | 34              | 78                     | 29.4 (±2.3)                                        | 29.3 (±2.7)                                |
| Ovalle et al.,(28)      | 34              | 88                     | 29.9 (±2.5)                                        | 29.3 (±2.9)                                |
| Svaere et al.,(29)      | 34              | 67                     | NR                                                 | NR                                          |

NR: not reported; E: Erythromycin; AXC: Amoxicillin + Clavulanate; AXC: Amoxicillin + Clavulanate + Erythromycin; AXCE: Amoxicillin + Clavulanate + Erythromycin; AXC: Amoxicillin + Clavulanate + Erythromycin; ASAXC: Ampicillin + Sulbactam + Amoxicillin + Clavulanate; AAXC: Ampicillin + Amoxicillin + Clavulanate.

Table 2. Characteristics of interventions of the included studies

| Author                  | Intervention | Corticosteroid | Tocolysis | Intervention duration |
|-------------------------|--------------|----------------|-----------|-----------------------|
| Almeida et al.,(9)      | AX 750mg 6/6 hours VO | NR            | NR        | NR                    |
| Amon et al.,(10)        | A 1g 6/6 hours IV for 24 hours + A 500mg 6/6 hours VO until delivery | SN | Yes | Until birth |
| Carroli et al.,(11)     | A 1g 6/6 hours IV | NR            | No        | NR                    |
| Christmas et al.,(12)   | AGC (A 2g 6/6 hours IV + G 60-90mg 8/8 hours IV + C 900mg 8/8 hours IV) 1 day, AXC 500 + 125mg 6/6 hours 7 days VO | No | No | 7 days |
| Cox et al.,(13)         | AS 1+2g 6/6 hours 4 doses IV, AXC 500 + 125mg 6/6 hours VO for 5 days | NR | No | NR |
| August Fuhr et al.,(14) | MZ 2g 8/8 hours IV 7 days | Yes | Yes | 7 days |
| Garcia-Burguillo et al.,(15) | E 500mg 6/6 hours VO until birth | No | No | Until birth |
| Grable et al.,(16)      | A 2g 6/6 hours IV (1 day) + A 500mg 6/6 hours VO until birth | NR | NR | Until birth |
| Johnston et al.,(17)    | MZ por 2 days + A VO | No | No | Until birth |
| Kenyon et al.,(18)      | AXC 250 + 125mg 6/6 hours VO + E 250mg VO | SN | SN | Until birth |
| Kurki et al.,(19)       | P 5000mIU 2 doses IV | NR | Yes | 1 day |
| Lockwood et al.,(20)    | PP 3g 6/6 hours N 72 hours | SN | SN | 3 days |
| Lovett et al.,(21)      | AS 1.5g 6/6 hours IV 72 hours + AXC 250 + 125mg 6/6 hours | SN | Yes | Until birth |
| Magwali et al.,(22)     | AXC VO 5 days | SN | NR | 5 days |
| McCaul et al.,(23)      | A 2g IV + A 500mg 6/6 hours 7 days | No | No | 7 days |
| McGregor et al.,(24)    | E 333mg 6/8 hours | No | No | NR |
| Mercer et al.,(25)      | E 333mg 6/8 hours | SN | SN | NR |
| Mercer,(26)             | A 2g 6/6 hours + E 250mg 6/6 hours IV AX 250mg 8/8 hours VO + E 333mg 8/8 hours VO 5 days | No | No | 5 days |
| Morales et al.,(27)     | A 2g 6/6 hours | No | No | NR |
| Ovalle et al.,(28)      | CG (C 600mg 6/6 hours IV + G 4mg/kg/day 48 hours) and CG (C 300mg 6/6 hours + G 2mg/kg/day 12/12 hours) IM | NR | NR | 5 days |
| Svaere et al.,(29)      | A 2g 6/6 hours IV (1 day) and M 500mg 8/8 hours IV (1 day) + PVM (PV 500mg 8/8 hours 7 days + M 400mg 8/8 hours VO) | NR | NR | 7 days |

NR: not reported; VO: orally; IV: intravenous; IM: intramuscular; SN: if necessary; AX: Amoxicillin; A: Ampicillin; AGC: Ampicillin + Gentamycin + Clindamycin; AXC: Amoxicillin + Clavulanate; AS: Ampicillin + Subactam; MZ: Mezlocillin; E: Erythromycin; P: Pencillin; PP: Pipersicillin; CG: Clindamycin + Gentamycin; C: Clindamycin; G: Gentamycin; M: Metronidazole; PV: Pivampicillin; PVM: Pivampicillin + Metronidazole.
### Table 3. Neonatal outcome data extracted from included studies

| Author | Intervention latency (≥7 days) | Control latency (≥7 days) | Chorioamnionitis Intervention | Chorioamnionitis Control | Endometritis Intervention | Endometritis Control | Maternal sepsis Intervention | Maternal sepsis Control | Maternal death Intervention | Maternal death Control |
|-------|-----------------------------|---------------------------|-------------------------------|---------------------------|--------------------------|-----------------------|-----------------------------|--------------------------|--------------------------|--------------------------|
| Almeida et al.,(9) | NR                          | NR                        | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Arnon et al.,(10) | 30/47                       | 26/58                     | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Camli et al.,(11) | NR                          | NR                        | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Christmas et al.,(12) | 20/48                     | 7/46                      | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Cox et al.,(13) | NR                          | NR                        | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| August Fuhr et al.,(14) | 10/42                       | 9/43                      | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Garcia Burguillo et al.,(15) | NR                        | NR                        | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Grable et al.,(16) | NR                          | NR                        | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Johnston et al.,(17) | 18/40                       | 8/45                      | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Kenyon et al.,(18) | 176/3,584                   | 775/1,225                 | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Kurki et al.,(19) | NR                          | NR                        | 1.50                         | 7.51                      | 0.50                     | 1.51                  | 0.50                        | 0.51                     | 0.51                    | 0.51                    |
| Lockwood et al.,(20) | 16/38                       | 4/37                      | 10/35                        | 10/35                     | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Lovett et al.,(21) | NR                          | NR                        | 11/75                        | 12/37                     | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Magvali et al.,(22) | 15/82                       | 6/66                      | 14/82                        | 20/86                     | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| McCaul et al.,(23) | NR                          | NR                        | 10/41                        | 9/43                      | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| McGregor et al.,(24) | NR                         | NR                        | 7/28                         | 6/27                      | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Mercer et al.,(25) | 23/106                      | 20/114                    | NR                           | NR                        | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Mercer,(26) | NR                          | NR                        | 69/299                       | 101/312                   | NR                      | NR                    | 0/299                       | 0/312                    | 0/299                   | 0/312                   |
| Morales et al.,(27) | NR                          | NR                        | 0.37                         | 16/41                     | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Ovalle et al.,(28) | NR                          | NR                        | 2/42                         | 11/45                     | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |
| Sivare et al.,(29) | NR                          | NR                        | 6/30                         | 5/37                      | NR                       | NR                    | NR                          | NR                       | NR                      | NR                       |

NR: not reported; SD: standard deviation; ASAXC: Ampicillin + Sulbactam + Amoxicillin + Clavulanate; AAXC: Ampicillin + Amoxicillin + Clavulanate.

### Table 4. Maternal outcome data extracted from included studies

| Author | Intervention latency (≥7 days) | Control latency (≥7 days) | Chorioamnionitis | Endometritis | Maternal sepsis | Maternal death |
|-------|-------------------------------|---------------------------|------------------|--------------|----------------|---------------|
| Almeida et al.,(9) | NR | NR | NR | NR | NR | NR |
| Arnon et al.,(10) | 31.5 (±3.3) | 30.7 (±3.2) | 2.094 (±459) | 1.742 (±402) | 15/43 | 4/39 |
| Camli et al.,(11) | 31.4 | 30.7 | 2.087 (±580) | 1.868 (±580) | 7/43 | 4/39 |
| Christmas et al.,(12) | 26.8 (±5.4) | 27.9 (±2.1) | 2.282 (±409) | 1.884 (±413) | 5/43 | 2/39 |
| Cox et al.,(13) | NR | NR | NR | NR | NR | NR |
| August Fuhr et al.,(14) | NR | NR | NR | NR | NR | NR |
| Garcia Burguillo et al.,(15) | NR | NR | NR | NR | NR | NR |
| Grable et al.,(16) | NR | NR | NR | NR | NR | NR |
| Johnston et al.,(17) | NR | NR | NR | NR | NR | NR |
| Kenyon et al.,(18) | NR | NR | NR | NR | NR | NR |
| Kurki et al.,(19) | NR | NR | NR | NR | NR | NR |
| Lockwood et al.,(20) | NR | NR | NR | NR | NR | NR |
| Lovett et al.,(21) | NR | NR | NR | NR | NR | NR |
| Magvali et al.,(22) | NR | NR | NR | NR | NR | NR |
| McCaul et al.,(23) | 30.1 (±2.7) | 31.2 (±3.9) | 1.685 (±607) | 2.072 (±799.7) | 17/43 | 7/39 |
| McGregor et al.,(24) | NR | NR | NR | NR | NR | NR |
| Mercer et al.,(25) | NR | NR | NR | NR | NR | NR |
| Mercer,(26) | NR | NR | NR | NR | NR | NR |
| Morales et al.,(27) | NR | NR | NR | NR | NR | NR |
| Ovalle et al.,(28) | NR | NR | NR | NR | NR | NR |
| Sivare et al.,(29) | NR | NR | NR | NR | NR | NR |

NR: not reported; SD: standard deviation; ASAXC: Ampicillin + Sulbactam + Amoxicillin + Clavulanate; AAXC: Ampicillin + Amoxicillin + Clavulanate.
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Supplementary table 1. Neonatal comorbidity data extracted from included studies

| Author                        | RDS Intervention | RDS Control | NEC Intervention | NEC Control | Neonatal sepsis Intervention | Neonatal sepsis Control |
|-------------------------------|------------------|-------------|------------------|-------------|-----------------------------|-------------------------|
| Almeida et al.,(9)            | NR               | NR          | NR               | NR          | NR                          | NR                      |
| Amon et al.,(10)              | 18/42            | 15/36       | 5/42             | 4/36        | 1/42                        | 6/36                    |
| Camil et al.,(11)             | NR               | NR          | NR               | NR          | NR                          | NR                      |
| Christmas et al.,(12)         | 20/48            | 21/46       | 4/48             | 2/46        | 0/46                        | 2/46                    |
| Cox et al.,(13)               | 27/31            | 21/31       | 5/31             | 0/31        | 0/31                        | 1/31                    |
| August Fuhr et al.,(14)       | 7/47             | 11/58       | 1/47             | 3/58        | 1/47                        | 7/58                    |
| Garcia-Burguillo et al.,(15)  | 7/30             | 6/30        | NR               | NR          | 4/30                        | 5/30                    |
| Grable et al.,(16)            | 6/31             | 9/29        | 1/31             | 1/29        | NR                          | NR                      |
| Johnston et al.,(17)          | 6/40             | 11/45       | 2/40             | 3/45        | 3/40                        | 11/45                   |
| Kenyon et al.,(18)            | 719/3,584        | 266/1,225   | 1171/3,584       | 33/1,225    | 233/3,584                   | 100/1,225               |
| Kurki et al.,(19)             | NR               | NR          | NR               | NR          | 0/57                        | 1/58                    |
| Lockwood et al.,(20)          | 23/37            | 20/35       | 2/37             | 0/35        | 2/37                        | 3/35                    |
| Lovett et al.,(21)            | 18/75            | 14/37       | NR               | NR          | 6/75                        | 8/37                    |
| Magwali et al.,(22)           | NR               | NR          | NR               | NR          | 13/82                       | 21/86                   |
| McCaul et al.,(23)            | 8/41             | 6/43        | NR               | NR          | 2/41                        | 3/43                    |
| McGregor et al.,(24)          | 15/26            | 15/25       | 2/26             | 4/27        | 1/24                        | 1/27                    |
| Mercer et al.,(25)            | 27/107           | 24/109      | 8/107            | 12/109      | 14/107                      | 15/109                  |
| Mercer,(26)                   | 121/299          | 152/312     | 24/299           | 27/312      | 16/299                      | 20/312                  |
| Morales et al.,(27)           | 21/37            | 20/41       | 1/37             | 3/37        | 1/37                        | 5/41                    |
| Ovalle et al.,(28)            | 5/11             | 3/13        | 0/42             | 1/43        | 7/42                        | 7/43                    |
| Svare et al.,(29)             | 3/20             | 3/37        | 0/30             | 1/37        | 7/30                        | 16/37                   |

RDS: respiratory distress syndrome; NEC: necrotizing enterocolitis; NR: not reported.

Birth weight
In the Group in which the pregnant women used Antibiotics, the newborns presented, on average, 43.38g more than in the Placebo Group (p=0.02) with a confidence interval ranging from 7.64 to 79.11g. The funnel plot showed an adequate distribution (Supplementary figure 3.4).

Respiratory distress syndrome
There was no statistically significant difference between the Groups that used Antibiotics versus Placebo (RR=0.95 and 95%CI: 0.87-1.03) supplementary figure 3.5.
Necrotizing enterocolitis

There was no statistically significant difference between the Groups that used Antibiotics versus Placebo (RR=1.02 and 95%CI: 0.79-1.33) supplementary figure 3.6.

Neonatal sepsis

The use of antibiotics reduces the risk of neonatal sepsis, with a confidence interval between 0.69 and 0.88, therefore, revealing a protective effect of 22%. The effect of antibiotic use was similar in studies that evaluated gestational age up to 34 weeks and in those that evaluated up to 37 weeks.
Supplementary figure 3.2. Forest plot of endometritis

Supplementary figure 3.3. Forest plot of Apgar < 7 fifth minute

Supplementary figure 3.4. Forest plot of birth weight
Supplementary figure 3.5. Forest plot of respiratory distress syndrome

| Study or Subgroup | Experimental Events | Control Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------|---------------------|---------------|-------|--------|-----------------------------|-----------------------------|
| **17.1.1 BLIND**  |                     |               |       |        |                             |                             |
| Cox, 1995         | 27                  | 31            | 21    | 31     | 8.7% 1.29 [0.97, 1.70]        |                             |
| August Fuhr, 2006 | 7                   | 47            | 11    | 58     | 0.9% 0.79 [0.33, 1.87]        |                             |
| Garcia-Burguilho, 1995 | 7         | 30            | 6     | 30     | 0.7% 1.17 [0.44, 3.06]        |                             |
| Gracie, 1996      | 6                   | 41            | 9     | 29     | 0.8% 0.82 [0.26, 2.53]        |                             |
| Johnson, 1998     | 6                   | 40            | 11    | 45     | 0.8% 0.81 [0.25, 2.51]        |                             |
| Kearny, 2004      | 7                   | 383           | 299   | 1225   | 43.2% 0.82 [0.82, 1.05]       |                             |
| Lockwood, 1993    | 23                  | 37            | 20    | 35     | 4.6% 1.09 [0.74, 1.59]        |                             |
| Lovett, 1997      | 18                  | 75            | 14    | 37     | 2.0% 0.83 [0.36, 1.33]        |                             |
| McCaul, 1992      | 8                   | 41            | 6     | 43     | 0.7% 1.40 [0.53, 3.69]        |                             |
| McGregor, 1992    | 15                  | 26            | 15    | 25     | 3.2% 0.96 [0.61, 1.52]        |                             |
| Mercer, 1997      | 27                  | 107           | 24    | 109    | 2.9% 1.15 [0.71, 1.85]        |                             |
| Mercer, 2002      | 121                 | 299           | 152   | 312    | 21.1% 0.83 [0.69, 0.99]       |                             |
| Ovall, 2002       | 5                   | 11            | 3     | 13     | 0.3% 1.97 [0.60, 6.44]        |                             |
| Swann, 1997       | 3                   | 30            | 3     | 37     | 0.3% 1.23 [0.27, 5.67]        |                             |
| **Total events**  | 992                 |               | 561   |        | 9.5% 0.95 [0.85, 1.05]        |                             |

Heterogeneity: Tau² = 0.00; Chi² = 14.28, df = 13 (P = 0.33); I² = 9%
Test for overall effect: Z = 0.99 (P = 0.32)

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Supplementary figure 3.6. Forest plot of necrotizing enterocolitis
Supplementary figure 3.7. Forest plot of neonatal sepsis

Supplementary figure 3.8. Forest plot of neonatal death
### Supplementary figure 3.9. Forest plot of perinatal death

| Study or Subgroup   | Experimental Events | Control Events | Total     | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---------------------|---------------------|----------------|-----------|--------|--------------------------------|--------------------------------|
| Cox, 1995           | 1                   | 31             | 5         | 31     | 0.9%                           | 0.20 [0.02, 1.61]              |
| Garcia-Burguillo, 1995 | 2                   | 30             | 5         | 30     | 1.5%                           | 0.40 [0.08, 1.90]              |
| Grabie, 1996        | 0                   | 31             | 4         | 45     | 0.5%                           | 0.16 [0.01, 2.86]              |
| Johnston, 1990      | 3                   | 40             | 4         | 45     | 1.8%                           | 0.84 [0.20, 3.54]              |
| Kenyon, 2001        | 226                 | 3584           | 82        | 1225   | 62.9%                          | 0.94 [0.74, 1.20]              |
| Kurki, 1992         | 1                   | 57             | 1         | 58     | 0.5%                           | 1.02 [0.07, 15.88]             |
| Lockwood, 1993      | 3                   | 37             | 3         | 36     | 1.6%                           | 0.95 [0.20, 4.36]              |
| Lovett, 1997        | 0                   | 38             | 0         | 37     | Not estimable                  |                               |
| McGregor, 1992      | 6                   | 28             | 0         | 27     | 0.6%                           | 12.55 [0.74, 212.62]           |
| Mercer, 1992        | 6                   | 106            | 10        | 114    | 3.9%                           | 0.66 [0.24, 1.71]              |
| Mercer, 1997        | 19                  | 299            | 18        | 312    | 9.6%                           | 1.10 [0.59, 2.06]              |
| Ovalle, 2002        | 7                   | 42             | 6         | 43     | 3.7%                           | 0.19 [0.44, 3.26]              |
| Svarre, 1997        | 2                   | 30             | 2         | 37     | 1.0%                           | 1.23 [0.18, 8.25]              |
| Subtotal (95% CI)   | 4353                |                | 2039      |        | 88.4%                          | 0.93 [0.76, 1.14]              |

**Total events:** 276

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 9.06, df = 11 (P = 0.62); I^2 = 0$

Test for overall effect: $Z = 0.70 (P = 0.48)$

### Supplementary figure 3.10. Forest plot of fetal death

| Study or Subgroup   | Experimental Events | Control Events | Total     | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---------------------|---------------------|----------------|-----------|--------|--------------------------------|--------------------------------|
| Amon, 1988          | 2                   | 43             | 6         | 39     | 1.6%                           | 0.30 [0.06, 1.41]              |
| Canni, 1997         | 3                   | 15             | 4         | 16     | 2.1%                           | 0.80 [0.21, 3.00]              |
| Christmas, 1992     | 1                   | 48             | 3         | 46     | 0.6%                           | 0.32 [0.03, 2.98]              |
| Magewali, 1999      | 8                   | 82             | 11        | 86     | 5.1%                           | 0.78 [0.32, 1.80]              |
| Morales, 1989       | 5                   | 42             | 3         | 37     | 2.0%                           | 1.47 [0.36, 5.73]              |
| Subtotal (95% CI)   | 230                 |                | 224       |        | 11.6%                          | 0.72 [0.41, 1.27]              |

**Total events:** 19

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 2.84, df = 4 (P = 0.59); I^2 = 0$

Test for overall effect: $Z = 1.14 (P = 0.25)$

### Supplementary figure 3.10. Forest plot of fetal death

| Study or Subgroup   | Experimental Events | Control Events | Total     | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---------------------|---------------------|----------------|-----------|--------|--------------------------------|--------------------------------|
| Amon, 1988          | 1                   | 43             | 3         | 39     | 24.8%                          | 0.30 [0.03, 2.79]              |
| Kurki, 1992         | 0                   | 57             | 0         | 58     | Not estimable                  |                               |
| Lockwood, 1993      | 1                   | 37             | 1         | 35     | 16.4%                          | 0.95 [0.06, 14.55]             |
| Mercer, 1992        | 2                   | 106            | 5         | 114    | 46.7%                          | 0.43 [0.09, 2.17]              |
| Subtotal (95% CI)   | 243                 |                | 246       |        | 87.9%                          | 0.45 [0.14, 1.47]              |

**Total events:** 4

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 0.41, df = 2 (P = 0.81); I^2 = 0$

Test for overall effect: $Z = 1.32 (P = 0.19)$

### Supplementary figure 3.10. Forest plot of fetal death

| Study or Subgroup   | Experimental Events | Control Events | Total     | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---------------------|---------------------|----------------|-----------|--------|--------------------------------|--------------------------------|
| Johnston, 1990      | 0                   | 40             | 1         | 45     | 12.1%                          | 0.37 [0.02, 8.93]              |
| Subtotal (95% CI)   | 40                  |                | 45        |        | 12.1%                          | 0.37 [0.02, 8.93]              |

**Total events:** 0

Heterogeneity: Not applicable

Test for overall effect: $Z = 0.61 (P = 0.54)$

### Supplementary figure 3.10. Forest plot of fetal death

| Study or Subgroup   | Experimental Events | Control Events | Total     | Weight | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|---------------------|---------------------|----------------|-----------|--------|--------------------------------|--------------------------------|
| Amon, 1988          | 1                   | 43             | 3         | 39     | 24.8%                          | 0.30 [0.03, 2.79]              |
| Kurki, 1992         | 0                   | 57             | 0         | 58     | Not estimable                  |                               |
| Lockwood, 1993      | 1                   | 37             | 1         | 35     | 16.4%                          | 0.95 [0.06, 14.55]             |
| Mercer, 1992        | 2                   | 106            | 5         | 114    | 46.7%                          | 0.43 [0.09, 2.17]              |
| Subtotal (95% CI)   | 243                 |                | 246       |        | 87.9%                          | 0.45 [0.14, 1.47]              |

**Total events:** 4

Heterogeneity: $\tau^2 = 0.00, \chi^2 = 0.42, df = 3 (P = 0.94); I^2 = 0$

Test for overall effect: $Z = 1.45 (P = 0.15)$

Test for subgroup differences: $\chi^2 = 0.01, df = 1 (P = 0.91), I^2 = 0$

### Supplementary figure 3.10. Forest plot of fetal death
When comparing the use of ampicillin versus erythromycin versus other antibiotics, the protective effect was not revealed in the erythromycin subgroup. The studies did not clarify the period of occurrence of neonatal sepsis, that is, whether early or late supplementary figure 3.7.

**Neonatal and perinatal death**
There was no statistically significant difference between the Groups of pregnant women who used Antibiotics versus Placebo (RR=0.94 and 95%CI: 0.72-1.22) supplementary figures 3.8 and 3.9.

**Fetal death**
There was no statistically significant difference between the Groups of pregnant women who used Antibiotics versus Placebo (p=0.44 and 95%CI: 0.15-1.33) supplementary figure 3.10.

## DISCUSSION
This review was prepared from randomized clinical trials, which are studies with a high degree of evidence. The first, and perhaps most important finding of this study is the publication date of the last randomized clinical trial on the subject. The most recent article found, after a comprehensive search, was published in 2013.\(^{(30)}\) Given this observation, some hypotheses can be proposed: the first would be that the medical community had lost interest in the subject, which does not seem to express the reality, since there are numerous more recent retrospective studies on the subject.\(^{(34-37)}\) Another explanation for such questioning would be that the interventions necessary to carry out clinical trials began to face ethical questions related to the use of antibiotics, since, if the use of antibiotics is beneficial in these situations, it would be unethical and iatrogenic to make a study with a Placebo Control Group. It goes without saying that some clinical trials are sponsored by pharmaceutical companies, that prohibit the publication of negative results which can also explain the lack of studies.

Regarding the selection of articles, it is pertinent to comment that only those referring to the use of broad-spectrum antibiotic therapy that increased the latency period were included in this study, as well as those that mentioned the use of antibiotics for the exclusive purpose of preventing neonatal sepsis due to streptococcal disease. Such an action may change the actual results of the study, since some studies showed the role of *Streptococcus agalactiae* as a cause of prematurity and PRPM.\(^{(37,39)}\)

The use of antibiotics seems to prolong the latency period in pregnant women with premature rupture of preterm membranes. This is a protective factor against chorioamnionitis and neonatal sepsis, in addition this seems to be beneficial for newborn weight gaining, as proposed by several authors.\(^{(30,32,34)}\) Such observation, at first, may suggest that the use of antibiotics is valid and should be incorporated into health service protocols. However, this finding should be analyzed with caution since the present study has limitations, such as lack of recent clinical trials and inconsistency regarding the dosage and antibiotic regimen.

The articles that analyzed the use of Ampicillin alone did not show statistically significant differences compared with studies that used other antibiotic prophylaxis regimens to prevent chorioamnionitis. Such finding should lead to the questioning about the real need for broad-spectrum antibiotic therapy to prevent this outcome, or whether just the use of antibiotic prophylaxis with Ampicillin is imperative.\(^{(9,10,22)}\)

Regarding the latency period due to the heterogeneity of data reporting in the different studies, it was only possible to observe the statistical difference when the latency period was categorized as < or ≥7 days. When evaluating the period of ≥7 days, a benefit was observed with the use of antibiotics. One possibility, suggested by the funnel plot, to explain different benefits in two similar groups, would be the occurrence of publication bias, which is the tendency of authors or journals to publish positive or more significant evidence, even when they are identified in studies with limited scientific evidence.

Another controversial finding was that antibiotic prophylaxis was beneficial in preventing chorioamnionitis, with no evidence of preventing endometritis. This finding contradicted the authors’ hypotheses, who expected that the use would protect against all infectious outcomes, as described in other studies.

Unfortunately, important neonatal outcomes were not verified because there were no statistically significant differences between the Group that used Antibiotics and the Control Group, including: NEC, RDS and neonatal death.\(^{(40-42)}\) If the studies had shown statistical significance in any of these variables, they could have contributed to conclusive results on the beneficial effect of antibiotics.

In the present study, the antibiotic regimens evaluated varied and it was not possible to define the most appropriate one. In addition, some of the antibiotics used, such as erythromycin orally, are not
available in the Brazilian pharmaceutical market. Thus, given the lack of consistent results in the literature, many services continue to use Ampicillin 2g intravenously every 6 hours for 48 hours, followed by amoxicillin 500mg 8/8h for 5 days, and azithromycin 1g orally, a regimen that covers Streptococcus agalactiae, Gram negative (Neisseria gonorrhoeae, Escherichia coli) and atypical bacteria such as Chlamydia e Ureaplasma, present in the vaginal flora.\(^{(39,42)}\)

Most protocols for the management of pregnancy with premature rupture of preterm membranes recommend interruption after 34 weeks.\(^{(43,44)}\) However, after reading several articles, it was evidenced that, in some studies, there is a tendency to keep the pregnancy until term with the use of antibiotic prophylaxis. Therefore, to define the ideal moment for the resolution of the pregnancy, further studies are needed to assess the risks and benefits of maintaining these pregnancies up to 37 weeks.

A major limitation of the study is related to the heterogeneity (very serious or serious concern during analysis and \(I^2\) higher than 50%) and diversity of interventions found in the articles studied, which prevented the presence of more robust results, which did not allow the conclusion of the best antibiotic therapy regimen, since different regimens were studied.

Finally, this review can benefit in the assembly of a possible guideline or protocol on the subject, given that the vast majority of published studies in this area failed to reach a consensus. As the study showed a reduction in chorioamnionitis, neonatal sepsis and an increased latency period, the use of antibiotic therapy in pregnant women with PRPM should always be considered.

**CONCLUSION**

This study showed that the use of antibiotic prophylaxis in pregnant women with premature rupture of preterm membranes is beneficial for the following variables, such as increased latency period, higher weight at birth, protective factor against chorioamnionitis, as well as neonatal sepsis. There was no statistically significant difference from the other outcomes.

After the evaluation of numerous studies, associated with the results of this review, which presented controversial outcomes, it can be concluded that new randomized clinical trials are needed to ensure the beneficial effect of antibiotic prophylaxis in prolonging the latency period.

**AUTHORS’ CONTRIBUTION**

Ana Maria Gomes Pereira: formal analysis, investigation, methodology, software, writing - review & editing. Gabriel Duque Pannain: writing - review & editing. Bruna Helena Gonçalves Esteves: methodology, writing - original draft. Maria Luiza de Lima Bacci: investigation, methodology, writing - original draft. Maria Luiza Toledo Leite Ferreira da Rocha: conceptualization, supervision, validation, visualization. Reginaldo Guedes Coelho Lopes: supervision.

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