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Association between antibiotic prophylaxis and adverse perinatal outcomes in premature rupture of membranes

Thaísa de Souza Lima[1], Flávia Mariane Pagani[2], Carolina Bianchini Borges[1], Caetano Galvão Petrini[1,2], Marina Carvalho Paschoini[1], Edward Araújo Júnior[3*], Alberto Borges Peixoto[4]

SUMMARY

OBJECTIVE: The aim of this study was to evaluate the association between antibiotic prophylaxis and adverse perinatal outcomes in premature rupture of membranes.

METHODS: This retrospective cohort included pregnant women with premature rupture of membranes (between 24 and 33+6 weeks) who used or did not use prophylactic antibiotics. Pearson's chi-square (χ^2) test, Student's t-test, and binary logistic regression were used for statistical analysis.

RESULTS: A significant effect was observed in patients with premature rupture of membranes using prophylactic antibiotics regarding amniotic fluid index (p=0.007), deepest vertical pocket (p=0.049), duration of antibiotic therapy (p≤0.001), C-reactive protein level upon admission (p≤0.001), leukocyte count upon admission (p=0.007), and length of stay in neonatal intensive care (p=0.047). A significant association was observed between the abovementioned patients and surfactant use during the neonatal period (p=0.04). A higher prevalence of surfactant use was noted in these patients (20.0 vs. 8.7%; p=0.04).

CONCLUSION: No association was found between antibiotic prophylaxis and the presence of adverse perinatal outcomes in pregnant women with premature rupture of membranes between 24 and 33+6 weeks of gestation.

KEYWORDS: Pregnancy. Premature rupture of membrane (pregnancy). Antibiotic prophylaxis. Morbidity.

INTRODUCTION

Premature rupture of membranes (PROM) is defined as spontaneous rupture of membranes before the onset of labor. The incidence rate of PROM is approximately 10%, with 7% in full-term and 3% in preterm pregnancies. Approximately 60–95% of PROM cases progress to labor in the next 24–48 hours, which is associated with one-third of preterm deliveries[1,2].

PROM is associated with adverse perinatal outcomes. Sim et al.[3] highlighted chorioamnionitis, cesarean section rates, and maternal sepsis as the primary adverse maternal outcomes and respiratory distress syndrome (RDS), bronchopulmonary dysplasia, and neonatal sepsis as the primary neonatal morbidities.

Previous studies have shown that antibiotic prophylaxis in PROM is associated with pregnancy prolongation as well as a reduction in the number of maternal and neonatal infections and morbidities[4,5]. Thus, the use of antibiotics increases the latency period, improving perinatal conditions and problems associated with prematurity, such as RDS and neonatal sepsis.

However, some researchers have raised concerns regarding the benefits of the routine use of antibiotics, from the diagnosis of PROM to birth, as unnecessary administration has been linked with an increased rate of necrotizing enterocolitis and predisposition to antibiotic resistance. Therefore, they suggest that antibiotics should be administered only to pregnant women with clinical or laboratory signs of infection[6-8].

This study aimed to evaluate the relationship between antibiotic prophylaxis and adverse perinatal outcomes in pregnant women with PROM between 24 and 33+6 weeks of gestation.

METHODS

This was a retrospective cohort study conducted at the Clinic Hospital of the Federal University of Triângulo Mineiro (UFTM) and Mário Palmério University Hospital of the University of Uberaba (UNIUBE) between January 2014 and April 2019. The study was approved by the ethics committee (CAAE:10374919700005154) of both institutions.

[1]Universidade Federal do Triângulo Mineiro, Department of Obstetrics and Gynecology – Uberaba (MG), Brazil.
[2]Universidade de Uberaba, Mário Palmério University Hospital – Uberaba (MG), Brazil.
[3]Universidade Federal de São Paulo, Paulista School of Medicine, Department of Obstetrics – São Paulo (SP), Brazil.
[4]Sabin Medicina Diagnóstica, Ultracron – Osasco (SP), Brazil.
*Corresponding author: araujojred@terra.com.br
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The patients included were divided into two groups: PROM with the use of antibiotics at the time of diagnosis and PROM without the use of antibiotics. All patients with single or multiple pregnancies with spontaneous PROM, as confirmed by clinical examination and/or additional tests, and gestational age between 24 and 33+6 weeks, as dated by the ultrasound of the first trimester, were included. All pregnancies with fetal malformations, as evidenced by obstetric ultrasound, and chromosomal anomalies, as confirmed by fetal karyotyping, were excluded.

The patients using antibiotics at the time of diagnosis were selected at UNIUBE, whereas those not using antibiotics were selected at UFTM. The reason for this selection was based on the institutional protocols in force at each hospital.

According to UNIUBE's protocol, the patients diagnosed with PROM were hospitalized and followed expectantly. After hospitalization, betamethasone was administered (12 mg every 24 hours for two days) to accelerate fetal lung maturity. Maternal monitoring was performed by clinical (daily) and laboratory (every three days) evaluations. For maternal infection screening, the following tests were requested: blood count, C-reactive protein level (PCR), urinalysis, urine culture, beta-hemolytic streptococci culture (rectal and vaginal swabs), and vaginal wet mount. Fetal monitoring was performed by cardiotocography (daily) and obstetric Doppler ultrasound (weekly). Prophylactic antibiotics were always administered upon admission, shortly after the PROM diagnosis. In the absence of maternal hypersensitivity, penicillin G was prescribed as a 5,000,000 IU loading dose, followed by 2,500,000 IU every four hours for seven days. Pregnancies were terminated upon obstetric indication at 34 weeks or immediately in case of clinical or laboratory signs of maternal and/or fetal infection. Magnesium sulfate was used for neuroprotection in all births with gestational age <32 weeks.

According to the UFTM protocol, the patients with PROM were also followed expectantly. For maternal infection screening, the following laboratory tests were performed every three days: complete blood count, PCR, complements C3 and C4, urinalysis, and urine culture. Fetal monitoring was performed by cardiotocography (every three days) and Doppler obstetric ultrasound (weekly). Corticotherapy was administered with betamethasone (4 mg every eight hours for 48 hours), and magnesium sulfate if gestational age <32 weeks, for fetal neuroprotection. Prophylactic antibiotics were not administered at the time of PROM diagnosis. Penicillin G at a dose of 5,000,000 IU was used every four hours, until birth, only in the presence of uterine contractions and possibility of delivery in the next few hours. Pregnancy termination was performed according to obstetric indication at 34 weeks or whenever there were clinical or laboratory signs of maternal and/or fetal infection.

In both hospitals, PROM was diagnosed in the presence of typical history of vaginal fluid leakage with characteristic odor, and clinical presence of moistened vulva associated with the visualization of clear fluid in the posterior vaginal fornix during speculum examination or a positive fern test. In some cases, diagnosis could also be performed through diagnostic amnioinfusion (observing the output of contrast, vitamin B12, through the vagina, approximately 30–60 minutes after its injection). Ultrasound was not used for the diagnosis of PROM in either hospital; however, in the presence of oligohydramnios associated with suggestive and/or doubtful clinical signs, patients were followed as if diagnosed with PROM.

The following variables were evaluated: 1- and 5-minutes Apgar score, birth weight, length of stay in neonatal intensive care unit (ICU), presence of neonatal infection (neonatal sepsis), need for oxygen therapy, use of surfactant, presence of maternal chorioamnionitis and sepsis, maternal PCR levels, duration of latency period, and type of delivery.

Data were entered and analyzed using spreadsheets in the software programs SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and MedCalc (Ostend, Belgium). Quantitative variables were subjected to the Kolmogorov–Smirnov test. The variables showing a normal distribution were presented as mean and standard deviation. To study their differences, the unpaired t-test was used. The variables that presented nonnormal distribution were demonstrated as median, and minimum and maximum values. The Mann–Whitney U test was used to study their differences. Categorical variables were described based on absolute and percentage frequencies and are presented in tables and graphs. Pearson's chi-square test (χ^2) was used to study the difference between categorical variables and their proportions. Binary logistic regression was performed to determine the best predictors of perinatal adverse outcomes and the composite perinatal outcomes between groups. Through logistic regression, the odds ratio (OR) of the development of adverse maternal and perinatal outcomes was estimated for the variables that presented statistical differences. The receiver operating characteristics (ROC) curve was used to determine the best cutoff value for the predictor variables of composite perinatal outcomes. Significance was set at $p<0.05$ for all tests.

RESULTS

In total, 1,136 pregnant women (>24 weeks) were diagnosed with PROM in both hospitals. Of them, 14.9% (169) were between 24 and 33+6 weeks of gestation. Of these 169 women, five were excluded due to fetal malformations. For the final

statistical analysis, 164 women were included and divided into two groups based on antibiotic prophylaxis (group I, n=58, and group II, n=106).

A significant effect was noted in group I regarding the number of pregnancies (p=0.018), parity (p=0.038), amniotic fluid index (AFI) (p=0.007), measurement of the largest vertical pocket (LVP) (p=0.049), duration of antibiotic therapy (p≤0.001), PCR level upon admission (p=0.001), last PCR level (p≤0.001), leukocyte count upon admission (p=0.007), and length of stay in neonatal ICU (p=0.047). However, no significant difference was observed regarding the duration of the latency period (p=0.659; Table 1).

A significant association was observed between group I and surfactant use during the neonatal period (p=0.04). A higher prevalence of surfactant use was noted in these patients (20.0 vs. 8.7%; p=0.04). No significant association was observed among antibiotic prophylaxis=0.057), oxygen use (p=0.072), and composite adverse perinatal outcomes (p=0.058; Table 2).

The following were significant predictors of adverse perinatal outcomes: gestational age at delivery [$\chi^2(1)=12.5$; p=0.002; R^2Nagelkerke=0.110; OR 1.35; 95%CI 1.170–1.165], AFI [$\chi^2(1)=5.4$; p=0.022; R^2Nagelkerke=0.081; OR 1.12; 95%CI 1.018–1.253], LVP [$\chi^2(1)=7.03$; p=0.015; R^2Nagelkerke=0.192; OR 1.65; 95%CI 1.104–2.481], and birth weight [$\chi^2(1)=23.3$; p<0.0001; R^2Nagelkerke=0.20; OR 1.0; 95%CI 1.001–1.003]. Contrastingly, maternal age (p=0.285), antibiotic prophylaxis (p=0.191), PCR level upon admission (p=0.747), last PCR level (p=0.393), leukocyte count upon admission (p=0.304),

Table 1. Clinical characteristics of the studied population.

	Group I (n=58) median (min–max)	Group II (n=106) median (min–max)	χ^2	p-value
Maternal age (years)	26 (15–41)	25 (14–43)	0.26	0.608†
GA at delivery (weeks)	32 (24.8–35.5)	32.4 (24.3–34.3)	0.03	0.859†
Number of pregnancies	1 (1–6)	2 (1–9)	5.60	0.018†
Parity	0 (0–5)	1 (0–7)	4.13	0.038†
AFI (cm)	5 (0–18.7)	2.5 (0–18)	7.18	0.007†
LVP (cm)	3.6 (0–7.6)	1.95 (0–6)	3.88	0.049†
Antibiotic prophylaxis time (hours)	72 (1–240)	6.5 (1–72)	34.6	<0.001†
PCR level on admission (mg/dL)	1.95 (0.5–23.2)	0.8 (0–36.7)	24.6	<0.001†
PCR level last (mg/dL)	2.2 (1.1–20.9)	0.4 (0–7.1)	21.2	<0.001†
Leukocyte count on admission (cells/mm^3)	10,050 (4910–21,940)	11,800 (5,980–28,700)	7.20	0.007†
Leukocyte count last (cells/mm^3)	12,055 (5,250–21,660)	13920 (3257–23,140)	0.78	0.376†
Birth weight (grams)	1,890 (940–3,570)	1,775 (630–2,955)	2.60	0.107†
Apgar score at 1st min	8 (1–10)	8 (0–9)	0.40	0.527†
Apgar score at 5th min	9 (3–10)	9 (1–10)	0.74	0.389†
Length of stay in the neonatal ICU (hours)	504 (10–2,208)	768 (3–5,520)	3.95	0.047†
Latency period (hours)	48 (4–1,560)	48 (3–620)	0.19	0.659†
Ethnicity			0.308	0.857§
White	53.6 (30/56)	49.21 (52/106)		
Black	12.5 (7/56)	13.2 (14/106)		
Mixed	33.9 (19/56)	33.7 (40/106)		
Smoking	13 (7/54)	18.1 (17/94)	0.662	0.416§
Alcoholism	5.6 (3/54)	6.4 (6/94)	0.041	0.839§
Type of delivery			2.45	0.180§
Cesarean	44.6 (25/56)	57.5 (61/106)		
Vaginal	55.4 (31/56)	42.5 (45/106)		

GA: gestational age; AFI: amniotic fluid index; LVP: largest vertical pocket; PCR: C-reactive protein; ICU: intensive care unit. †Mann-Whitney: median (minimum–maximum); χ^2: chi-square; §: percentage (absolute number/total number of cases per group); p-value: p<0.05.

Table 2. Association between use or not of prophylactic antibiotics on the premature rupture of membranes and adverse perinatal outcomes.

	Group I (n=58)			Group II (n=106)			χ^2	p-value
	n	N	%	n	N	%		
Apgar score at 1st minute <7	8	57	14	27	102	26.5	3.3	0.070
Admission at neonatal ICU	41	57	71.9	59	104	56.7	3.61	0.057
Surfactant use	11	55	20	9	104	8.7	4.21	0.040
Oxygen use	39	57	68.4	67	104	64.4	0.26	0.609
Fetal death	0	55	0	5	106	4.7	2.68	0.102
Neonatal death	5	55	9.1	12	106	11.3	0.19	0.662
Maternal death	0	0	0	0	0	0		
Neonatal sepsis	17	55	30.9	21	105	20	2.37	0.124
Maternal sepsis	0	0	0	0	0	0		
Chorioamnionitis	13	56	23.2	39	105	37.1	3.24	0.072
Composite perinatal outcomes	38	56	67.9	86	106	81.1	3.60	0.058

n: absolute number; ICU: intensive care unit; N: total number of cases per group; %: percentage; χ^2: chi-square; p-value: p<0.05.

last leukocyte count (p=0.914), and latency period (p=953) were not statically significant (Table 1).

Using ROC curves, the best cutoff value was determined for the predictor variables of composite perinatal outcomes. Table 2 presents the cutoff values for sensitivity, specificity, positive likelihood ratio (LR+), and negative LR (LR–) to better predict composite perinatal outcomes. LVP (≤3.6 cm; AUC 0.728; 95%CI 0.581–0.847; p=0.0006) and estimated fetal weight (≤1,735 grams; AUC 0.739; 95%CI 0.665–0.805; p≤0.0001) performed moderately in the prediction of composite adverse perinatal outcomes. Gestational age at delivery (≤31.9 weeks; AUC 0.652; 95%CI 0.573–0.725; p=0.0006) performed poorly, whereas AFI showed no significant performance (p=0.073) in this prediction (Figure 1).

DISCUSSION

Preterm PROM is associated with several obstetric complications, such as placental abruption, prematurity, intrapartum fetal distress, and umbilical cord prolapse[2]. Regardless of gestational age at the time of diagnosis of PROM, the risk of intrauterine infection is the most relevant complication; the earlier and longer the rupture time of membranes, the more frequent it is[4]. Antibiotic prophylaxis prolongs pregnancy and reduces maternal and neonatal morbidity. In their systematic review, Kenyon et al.[4] reported the highest frequency of antibiotic prophylaxis, showing an association with increased latency period, reduced chorioamnionitis and postpartum endometritis, and decreased neonatal morbidity. Thus, antibiotic prophylaxis has been recommended in preterm PROM cases[9]. However, in this study, no significant difference was observed in the latency period between the groups. In addition, no significant difference was noted in the reduction of maternal and neonatal morbidity.

According to Sim et al.[3], the primary predictors of neonatal survival after gestational age at PROM diagnosis and at birth were prolonged latency period, AFI, leukocyte count, and PCR levels <1 mg/dL in the first 24 hours of hospitalization. Serum PCR levels ≥1 mg/dL upon admission correlated positively with clinical signs of chorioamnionitis[7]. In a study carried out by our group in patients with PROM between 34 and 36.9weeks, patients with expectant management had a higher PCR level than those with an active conduct (5.2 vs. 1.5 mg/dL)[10]. However, similar to the results of a study by Çetin et al.[1], our study results did not find a significant association between antibiotic prophylaxis and PCR levels in predicting neonatal survival in PROM.

Gasparović et al.[11] compared two groups of pregnant women with PROM who used (n=190) and did not use (n=134) prophylactic antibiotics. They found significant differences in gestational age, birth weight, Apgar scores, maternal PCR levels, and latency period between the groups. Histological chorioamnionitis was more frequent in the group receiving prophylactic antibiotics. Dannapaneni et al.[12] observed that women with PROM <33 weeks who used prophylactic antibiotics had perinatal outcomes similar to those without PROM.

Gestational age at the time of PROM diagnosis, AFI and LVP measurements, and fetal weight at birth were the predictors for adverse perinatal outcomes. According to Esteves et al.[13], one of the primary predictors of survival was birth weight,

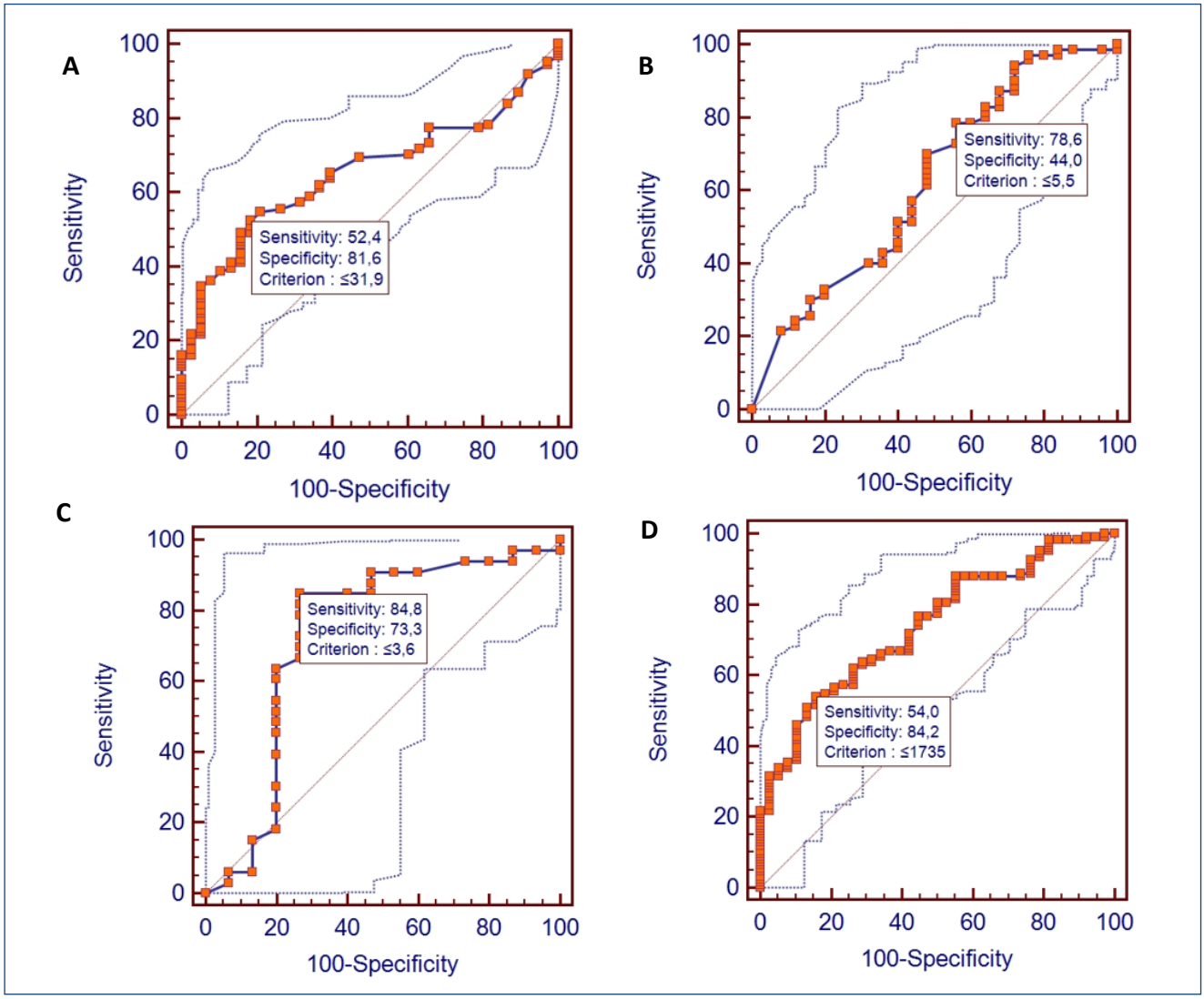

Figure 1. Receiver operating characteristics curve to establish the cutoffs for gestational age at delivery **(A)**, amniotic fluid index measurement **(B)**, largest vertical pocket measurement **(C)**, and estimated fetal weight **(D)** to predict adverse perinatal outcomes in pregnant women with premature rupture of membranes between 24 and 33+6 weeks of gestation.

and they recommended efforts to increase latency, aiming for older gestational age at delivery and birth weight >960 grams. Sayed Ahmed et al.[14] evaluated the maternal serum level of interleukin-6 (IL-6) in pregnant women with PROM between 24 and 34 weeks. Considering the IL-6 level cutoff point of 8.5 pg/mL, histological chorioamnionitis and admission to neonatal ICU were significantly higher, whereas birth weight and 1- and 5-minutes Apgar scores were significantly lower.

CONCLUSION

In conclusion, no association was found between antibiotic prophylaxis and the presence of adverse perinatal outcomes in pregnant women with PROM between 24 and 33+6 weeks of gestation.

AUTHORS' CONTRIBUTIONS

TSL: Data curation, Writing – review & editing, Visualization. **FMP:** Data curation, Writing – review & editing, Visualization. **CBB:** Methodology, Writing – review & editing, Visualization. **CGP:** Investigation, Writing – review & editing, Visualization. **MCP:** Project administration, Supervision, Writing – review & editing, Visualization. **EAJ:** Writing – original draft, Writing – review & editing, Visualization. **ABP:** Conceptualization, Formal Analysis, Visualization.

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