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Brief Original Article

Alternative antimicrobials for prophylaxis of the Group B Streptococcus maternal-fetal disease

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Abstract

Introduction: GBS colonization is an important risk factor for maternal and neonatal infection morbidity and mortality. Intrapartum antibiotics may prevent vertical transmission of GBS from colonized mothers to their babies. The objective of this study was to evaluate the effectiveness of cefazolin prophylactic regimen for GBS disease, comparing it to the established penicillin-based protocols, given the opportunity provided by the temporary unavailability of first-choice antibiotics in Brazil.

Methodology: A retrospective analysis was conducted at the Hospital Femina Obstetrics Service between January and December 2015. Ninety-eight pregnant women received standard penicillin (70 patients) or ampicillin (28 patients) antibiotic prophylaxis, and 251 pregnant women received an alternative prophylaxis with cefazolin during the study period. Risk factor, Maternal and neonatal outcomes were evaluated and compared between groups.

Results: No significant difference was found in maternal (RR = 0.71; IC 95%:0.30-1.68; p = 0.709) and neonatal (RR = 0.84; IC 95%:0.61-1.15; p = 0.271) outcomes between those patients using the alternative antibiotic prophylaxis in comparison to the standard antibiotics, with the dependent variable of maternal and neonatal outcomes grouped and controlled for potential confounding variables.

Conclusions: The antibiotics used as alternatives to penicillin and ampicillin for the prevention of maternal-fetal GBS disease are poorly studied, and this study indicate that cefazolin can be an optimal choice, offering safety in the use of this antibiotic in situations where penicillins are contraindicated or unavailable.

Key words: Group B streptococcus prophylaxis; cefazolin; penicillin; neonatal infection; maternal infection.

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Introduction

Group B Streptococcus (GBS) is a bacterium that causes maternal infections during pregnancy and the neonatal period [1,2], and is responsible for colonization of the gastrointestinal and genitourinary tracts in about 20% of pregnant women [3]. Transmission to the newborn occurs during labor or birth in around 36% of colonized mothers, causing diseases such as meningitis, sepsis and other neonatal infections [3-5].

Antimicrobial prophylaxis to prevent maternal-fetal GBS infection is recommended for pregnant women in situations such as follows: with GBS positive anal and vaginal cultures collected up to five weeks before delivery, with GBS bacteriuria in any trimester of the current pregnancy, or for those whose previous newborn was affected by invasive GBS disease. Similarly, prophylaxis is indicated for patients with unknown anal and vaginal cultures if there is a premature labor of less than 37 weeks of pregnancy, rupture of membranes duration greater than or equal to 18 hours, or intrapartum temperature greater than or equal to 38ºC [6,7]. Other factors with the potential to increase the risk of maternal-fetal infection are young mothers, black race, chorioamnionitis, and low maternal levels of GBS-specific anticapsular antibody [6,8].

The first antimicrobial prophylaxis choice for GBS disease is the use of crystalline penicillin G or ampicillin, both with already established similar efficacy [6]. For patients allergic to penicillins with a history of severe reactions, such as anaphylaxis, angioedema, respiratory distress and urticaria after administration, anal and vaginal cultures with

antimicrobial susceptibility testing are recommended. If no test is available, the use of vancomycin or clindamycin is preferable [6]. Intravenous cefazolin is recommended for patients with a history of allergy but no major risk factors for anaphylaxis [6, 9-11].

The antibiotics used as alternatives to penicillin and ampicillin for the prevention of maternal-fetal GBS disease are poorly studied. There are no randomized controlled trials within this scope, as it would be unethical to use alternatives to the standard indicated antibiotic of known efficacy and safety [6]. Therefore, the present study aimed to evaluate the effectiveness of an alternative prophylactic regimen for GBS disease, comparing it to the established penicillin-based protocols, given the opportunity provided by the temporary unavailability of first-choice antibiotics.

Methodology

A retrospective analysis was conducted at the Hospital Fêmina Obstetrics Service between January and December 2015, based on a review of medical records for patients who received prophylaxis for GBS in accordance with current recommendations [6]. This study was performed during a period of penicillin depletion in the Brazilian Unified Health System in 2015, when cefazolin was used as an alternative to penicillins for the prevention of maternal-fetal GBS infection due to its low-cost, wide availability and theoretical efficacy [12-15].

The patients were divided into two groups: standard antibiotic group, composed of patients who received standard treatment with penicillin or ampicillin prior to the aforementioned shortage; and alternative antibiotic group, composed of patients who received cefazolin as an alternative.

The variables studied were gestational age, multiparity, previous cesarean delivery, abortion, multiple birth, cervical cerclage, presence of Streptococcus sp. in anal-vaginal culture, positive Streptococcus sp. culture in current pregnancy, prelabor rupture of membranes (PROM), preterm delivery (PTD), intrapartum fever (≥ 38°C), history of neonatal GBS in previous pregnancy, penicillin allergy, prolonged membrane rupture (MR) greater than 18 hours, presence of gestational diabetes mellitus (GDM), smoking, HIV virus infection, and obesity. Adequacy of antibiotics prescribing was studied and it was considered appropriate when there was an interval greater than or equal to 4 hours between the initiation of antibiotics and infant delivery [6].

The maternal outcomes studied were postpartum endometritis, chorioamnionitis and surgical site infection (SSI); the neonatal outcomes studied were the 5-minutes APGAR score, birth weight, Intensive Care Unit hospitalization for more than 48 hours, occurrence of sepsis or meningitis, positive blood culture for any germ, need for intubation, oxygen use and death. An additional combined outcome analysis was performed in order to robustly assess the response to standard and alternative antibiotic prophylaxis: maternal (endometritis, chorioamnionitis and SSI) and neonatal (5-minutes APGAR score, need for intubation, positive blood culture, ICU hospitalization for more than 48 hours, meningitis, sepsis and death).

Categorical variables in the statistical analysis were presented as absolute frequencies and percentages, and continuous variables as mean and standard deviation. Categorical variables were compared using a chi-square test or *Fisher's* exact test, and quantitative variables using *Student's* t-test for independent samples. Adjusted residue analysis was performed to detect categories with a higher frequency than expected. Analysis of the combined outcomes was performed using the Poisson regression model with robust variance, where variables with $p < 0.2$ from bivariate analysis were included in order to adjust for potential confounders. A p value < 0.05 was considered to be of statistical significance. All analyzes were performed using the software SPSS version 20 (IBM, Armonk, NY, EUA).

This study was approved by the Research Ethics Committee of the Conceição Hospital Group on January 13, 2016, under registration no. 47914815.2.0000.5530.

Results

A total of 430 patient medical records were reviewed, with 349 participants being included in the final study sample. Eighty-one patients whose medical records were unavailable or incomplete were excluded, as well as those patients who were transferred to other hospitals before the birth of their baby or who were hospitalized for false preterm labor without a delivery.

From the sample total, 98 (28.1%) pregnant women received standard penicillin (70 patients) or ampicillin (28 patients) antibiotic prophylaxis, and 251 (71.9%) pregnant women received an alternative prophylaxis with cefazoline during the study period.

No significant difference was seen in the maternal age distribution between the groups ($25.5 \pm 8.2 \times 25.8 \pm 6.9$, $p = 0.684$). There were more individuals with a BMI greater than 30 in the group using the alternative antimicrobial prophylaxis (42.3% × 20.2%, $p < 0.001$). A significantly higher number of patients with PROM (37.8% × 25.1%, $p = 0.027$), intrapartum fever (3.1% ×

Table 1. Demographic data comparing groups of pregnant women receiving standard antimicrobial OR alternative antimicrobial prophylaxis for GBS.

Factors	Standard antimicrobial prophylaxis for GBS n = 98 (28.1%)	Alternative antimicrobial prophylaxis for GBS n = 251 (71.9%)	P value
Maternal age	25.5 ± 8.2	25.8 ± 6.9	0.684
Smoker	14 (14.3%)	31 (12.4%)	0.759
Body Mass Index >30	18 (20.2%)	90 (42.3%)	<0.001
Preterm delivery (< 34 weeks)	56 (57.1%)	133 (53%)	0.586
Multiparous pregnancy	54 (55.1%)	135 (53.8%)	0.294
Vaginal birth	68 (69.4%)	157 (62.5%)	0.323
Multiple birth	4 (4.1%)	18 (7.2%)	0.411
Gestational diabetes mellitus	18 (18.4%)	26 (10.4%)	0.06
HIV positive status	4 (4.1%)	10 (4%)	1
Vaginal/anal positive GBS colonization	24 (24.5%)	89 (35.5%)	0.066
Positive urine culture for GBS in pregnancy	2 (2%)	6 (2.4%)	1
Prelabor rupture of membranes	37 (37.8%)	63 (25.1%)	0.027
Preterm labor	56 (57.1%)	133 (53%)	0.586
Membrane rupture ≥18 hours	44 (44.9%)	49 (19.5%)	0.002
Intrapartum temperature ≥100.4°F (38.0°C)	3 (3.1%)	0 (0%)	0.022
Neonatal sepsis in previous pregnancy	1 (1%)	1 (0.4%)	0.483

GBS: Group B Streptococcus.

0%, p = 0.022) and membrane rupture greater than 18 hours (44.9% × 19.5%, p = 0.002) were seen in the group using standard antibiotics (Table 1).

Following univariate analysis, no significant difference was found in maternal and neonatal outcomes between those patients using the alternative antibiotic prophylaxis in comparison to the standard antibiotics (Table 2).

Following analysis using a Poisson regression model, with the dependent variable of maternal outcomes grouped and controlled for potential confounding variables (BMI > 30, GDM, anal and vaginal culture positive for GBS, PROM, intrapartum fever and ruptured membrane >18 hours), the comparison between standard and alternative treatment remained without significant difference (RR = 0.71; IC 95%:0.30-1.68; p = 0.709).

Similarly, in analysis of the results performed with the dependent variable of neonatal outcomes being grouped and controlled for potential confounding variables (5-minutes APGAR score less than seven, very low birth weight and neonatal death), the comparison between standard and alternative treatment remained without significant difference (RR = 0.84; IC 95%: 0.61-1.15; p = 0.271).

Discussion

GBS colonization is an important risk factor for maternal and neonatal infection morbidity and mortality. According to the literature, intrapartum antibiotics may prevent the vertical transmission of

Table 2. Outcomes of comparing groups of pregnant women receiving standard antimicrobial OR alternative antimicrobial prophylaxis for GBS.

Factors	Standard antimicrobial prophylaxis for GBS n = 98 (28.1%)	Alternative antimicrobial prophylaxis for GBS n = 251 (71.9%)	*P* value
Postpartum endometritis	4 (4.1%)	11 (4.4%)	0.999
Corioamnionitis	2 (2%)	8 (3.2%)	0.732
Surgical site infection	1 (1%)	0 (0%)	0.281
5-min Apgar score less than seven	9 (9.3%)	10 (4%)	0.094
Low birth weight infant	33 (34.4%)	77 (30.7%)	0.594
Very low birth weight infant	12 (12.4%)	17 (6.8%)	0.139
Stay of newborn for more than 48 hours in ICU	36 (36.7%)	100 (39.8%)	0.680
Newborn positive hemoculture for any germ	3 (3.1%)	10 (4%)	1.000
Neonatal sepsis	14 (14.3%)	30 (12%)	0.681
Neonatal meningitis	0 (0%)	1 (0.4%)	1.000
Neonatal death	5 (5.2%)	6 (2.4%)	0.188

n: absolute frequency; n%: relative frequency; p: statistical significance level; GBS: Group B Streptococcus; ICU: Intensive Care Unit.

GBS from colonized mothers to their babies in more than 90% of cases [5]. There is a lack of controlled studies evaluating the efficacy of penicillin alternatives used in the prevention of neonatal GBS disease, although there is a theoretical rationale for its use [4, 8, 10, 12]. The present study, conducted at a reference hospital for the care of pregnant women in southern Brazil, is the first to evaluate alternatives to penicillins in the prevention of maternal and neonatal GBS infections, during a period of penicillin shortage.

According to the data presented, no statistically significant difference was found between the standard antibiotic and alternative antibiotic prophylaxis groups for the maternal and fetal outcomes analyzed. A significantly higher percentage of pregnant women with PROM and ruptured membrane of more than 18 hours was seen in the standard antibiotic treatment group. A higher percentage of obesity was found in the alternative treatment group. However, no impact on the recorded outcomes was observed when the control of potential confounders was analyzed through logistic regression.

The study has limitations in its cross-sectional and retrospective design, the fact that it was performed over a short time period, and also in its being performed at a single hospital location. The large-scale use of cefazolin as an alternative to penicillin was justified in the present study due to the penicillins shortages that occurred in Brazil in 2015.

Conclusion

The results highlighted in this study indicate equivalence in the effectiveness of using cefazolin for preventing maternal-fetal GBS infection when compared to penicillins, offering safety in the use of this antibiotic in situations where penicillins are contraindicated or unavailable.

The search for answers in the current scenario is relevant and desirable, given there are still doubts regarding screening for GBS and its universal use. This is especially valid when considering identification of the type of patient who will benefit most from this investigation and also the best choice of treatment to be used [16, 17]. Finally, objective answers obtained from the findings of robust studies that qualify maternal-fetal assessment and care are based on exploratory researches that first consider convenient solutions to real-life care needs, such as presented in this article.

Authors' contributions

VSA, JD, FFB and MFJ participated in the revision of the manuscript. VSA, FFB and MFJ participated in the design, draft and revision of the study. ED and SPR evaluated the medical records of the case and controlpatients. VSA, JD, FFB and MFJ conceived the study and participated in its design, coordinationand the drafting of the manuscript. All authors read and approved the final manuscript.

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