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Original Article

Comparison of the effect of penicillins versus erythromycin in preventing neonatal group B streptococcus infection in active carriers following preterm prelabor rupture of membranes

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ABSTRACT

Objective: To compare the incidence of neonatal group B streptococcus (GBS) infection in active GBS carriers with preterm prelabor rupture of membranes (PPROMs) after penicillins and erythromycin prophylaxis.

Materials and methods: Patients diagnosed to have PPROM between 2004 and 2009 inclusive were treated using erythromycin (erythromycin group), ampicillin, amoxicillin or co-amoxiclav (penicillin group), or no antibiotics (control group) according to department protocols depending on their gestation and their GBS status at the time of presentation. Patients receiving both erythromycin and penicillins were included in the penicillin group. The incidence of neonatal GBS infection was compared between groups categorized according to the antibiotic regime received.

Results: A total of 680 women were diagnosed to have PPROM of which 85 (12.5%) were active GBS carriers. GBS isolates were 100% sensitive to penicillins but only 35% were sensitive to erythromycin. There were 16, 22, and 47 patients in the penicillin, erythromycin, and control groups, respectively. The incidence of neonatal GBS infection in the three groups was 0%, 36%, and 13%, respectively, and was statistically significant ($p = 0.023$).

Conclusion: Penicillins are more effective than erythromycin in preventing neonatal GBS infection in women with PPROM who were active GBS carriers. Because most women do not know their GBS status at the time of PPROM and it is practically difficult to identify the active carriers before delivery, ampicillin/amoxicillin should be used as a prophylactic antibiotic for active GBS carriers and women with unknown GBS carriage status to prevent neonatal GBS infection following PPROM.

Introduction

Preterm prelabor rupture of membranes (PPROMs) complicates 2–3% of pregnancy and accounts for 40% of preterm deliveries [1]. PPROM is associated with serious neonatal morbidity and mortality because of prematurity, infection, and prolonged oligohydramnios. Infection can either be the cause or a consequence of PPROM. It has been reported that positive amniotic fluid cultures are detected in 32.4% of patients and that 25–29% of patients diagnosed with PPROM developed clinical chorioamnionitis before delivery [2,3]. Chorioamnionitis itself can cause neonatal sepsis, intracranial hemorrhage, respiratory distress syndrome, and cerebral palsy [4,5]. A meta-analysis has shown that using erythromycin or penicillins as the empirical antibiotics following PPROM is associated with a significant reduction in chorioamnionitis [risk ratio (RR): 0.66; 95% confidence interval (CI): 0.46–0.96] and delivery before 48 hours (RR: 0.71; 95% CI: 0.58–0.87) and 7 days (RR: 0.79; 95% CI: 0.71–0.89) [6]. In the ORACLE I trial, erythromycin was shown to be associated with a range of health benefits for the neonate, whereas co-amoxiclav was demonstrated to be associated with increased number of necrotizing enterocolitis (NEC) [1]. Erythromycin is therefore preferred to co-amoxiclav as the first-line regime in the guidelines of some professional bodies [7,8]. However, although erythromycin is a broad-spectrum antibiotic, it is less effective at treating group B streptococcus (GBS) infections, which remains as the predominant pathogen in causing early onset neonatal sepsis, due to the insensitivity of the GBS bacterium in some patients [9].

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The prevalence of GBS is approximately 10–30% among pregnant women [10–12]. Although universal antenatal screening of GBS has been implemented in Hong Kong, it is performed at 35–37 weeks and the GBS carriage status is usually not known at the time when a woman presents with PPROM. As the bacterial culture usually takes a few days to perform, it would mean that in some pregnancies it is too late to change to an appropriate prophylactic antibiotic against GBS should the culture indicate insensitivity to erythromycin.

The aim of this study was to investigate the prevalence of GBS colonization among women presenting with PPROM, and to assess the effectiveness of different antibiotic treatments in preventing neonatal GBS infection following PPROM among the active GBS carriers.

Materials and methods

A retrospective cohort study was performed to identify women having a singleton pregnancy diagnosed with PPROM before 37 weeks of gestation and who delivered between 24 and 36^{+6} weeks from January 1, 2004, to December 31, 2009, in the Prince of Wales Hospital. Data were extracted from the patients' medical notes and institutional computerized obstetric database. The study was approved by the Institutional Investigation Ethics Review Board.

Women were diagnosed to have PPROM based on clinical history and sterile speculum examination demonstrating the presence of amniotic fluid in the vagina. If the speculum examination was equivocal, a test was performed to confirm PPROM by detecting the presence of insulin-like growth factor binding protein-1 in vaginal fluid sample using a commercial test kit (Actim PROM, Laboratorios Rubió, S.A., Barcelona, Spain). Women who were diagnosed to have PPROM before 34 weeks of gestation and who were not in active labor and showed no clinical evidence of chorioamnionitis or placental abruption were admitted for expectant management in accordance with our department protocol. Women were managed under this protocol as follows:

- Four doses of 6-mg dexamethasone to be given intramuscularly every 12 hours.
- Prophylactic antibiotic to be given for 10 days or until delivery, whichever occurred earlier.
  - ○ 250 mg erythromycin to be given orally four times daily if the patient was not known to be a GBS carrier.
  - ○ 2 g ampicillin to be given intravenously as a loading dose, followed by 250 mg oral amoxicillin, three times daily instead of giving erythromycin if the patient was known to be a GBS carrier.
  - ○ 900 mg clindamycin to be given intravenously for loading, followed by 250 mg oral erythromycin, four times daily if the patient was known to be a GBS carrier, but was allergic to penicillins.
- A high vaginal swab and midstream urine sample to be taken for bacterial culture and subsequent treatment to be given according to the culture result. Women treated by erythromycin are to be changed to amoxicillin if the GBS culture is positive and the GBS isolate is erythromycin resistant.
- The patient to be kept in hospital for observation for any clinical sign or symptom of chorioamnionitis. If chorioamnionitis is suspected, prompt delivery is advised.
- If there is no clinical evidence of chorioamnionitis or preterm labor, induction of labor is to be planned at 34 weeks by oxytocin infusion.
- Cesarean section should be performed based on obstetric indication.
- Placental swab is to be taken for bacterial culture and the placenta is to be sent for histology.
- If the patient had PPROM after 34 weeks, induction of labor is to be advised after 24 hours following the ROMs. No prophylactic antibiotic is required except in patients who are known GBS carriers who should be given 2 g ampicillin intravenously followed by 1 g every 6 hours until delivery occurs.

In this study, patients with positive maternal or neonatal GBS culture after PPROM were regarded as active GBS carriers. Women who were known to be GBS carriers with positive GBS culture in early pregnancy or previous pregnancy or history of neonatal GBS infection in the past, but were found to be GBS culture negative upon admission for PPROM were not classified as active GBS carriers.

Babies were defined as having neonatal GBS infection if they had a positive GBS culture from either blood, cerebrospinal fluid, umbilical cord, ear, eye, or nose together with raised C-reactive protein (CRP) >10 in the first 7 days of life. If CRP was not raised, it was classified as neonatal colonization.

The patients identified to be active GBS carriers were classified into three groups, namely, erythromycin, penicillin, and control (no antibiotic received) for statistical analysis. The penicillin group included women who either only received penicillins or who were switched from erythromycin to penicillins because the bacterial culture indicated that they were resistant to erythromycin. Those with PPROM who were negative for GBS cultures were not further analyzed in this study. The differences in categorical outcomes between the three groups were tested for significance using the Chi-square test for independence and Fisher's exact probability test. Difference between continuous variables was tested for significance using the independent-samples t test and one-way analysis of variance.

Statistical analysis was performed using PASW Statistic 18 (SPSS Inc, Chicago, IL, USA). All hypothesis tests were two sided and $p < 0.05$ was considered statistically significant.

Results

There were 37,138 women who had a singleton pregnancy and delivered in our unit between January 2004 and December 2009. Among these deliveries, 680 (1.8%) deliveries were from women who were confirmed to have PPROM. Table 1 summaries the maternal and clinical details of the 85 women (13%) who were found to have a positive GBS culture results after admission (active carrier), categorized according to the treatment received.

A total of 72 of the 85 women who were active carriers (85%) were only identified after delivery as the bacterial culture results were only available 2–5 days after their admission. In the remaining 13 (15%) women who were known GBS carriers before delivery, seven were newly diagnosed after PPROM, whereas six had known history of GBS carriage before PPROM. These six cases accounted for 16% of all 38 cases with a previous history of GBS colonization before PPROM (Fig. 1).

The antibiotic susceptibility test results of the GBS culture were available in 80 of the 85 cases of active carriers. The antibiotic susceptibility test results of the remaining five cases were not known as the swabs were taken in the private sector and the information about the antibiotic sensitivity was missing in the case notes. Fifty-two (65%) of the GBS isolates were resistant to erythromycin and 100% of them were sensitive to penicillins. The overall incidence of neonatal GBS infection in women diagnosed with