OBSTETRICS

Intrapartum antibiotic prophylaxis for Group B Streptococcus: has the time come to wait more than 4 hours?

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Despite progress in preventing infant group B streptococcal disease, group B streptococcus remains the leading cause of early-onset neonatal sepsis in the United States. Fortunately, most women who are colonized with group B streptococcus receive therapy and antibiotic prophylaxis is effective. However, the only factor associated with missed chemoprophylaxis is the short duration of time between hospital admission and delivery. Although antibiotic prophylaxis given for at least 2 hours shows some pharmacological benefit, the most effective method of preventing early-onset group B streptococcus disease is 4 hours of therapy. Intrapartum management strategies might be modified to improve the efficacy of antibiotic exposure. Obstetricians should consider strengthening the beneficial effect of intrapartum antibiotic prophylaxis for infants exposed to group B streptococcus by providing at least 4 hours of treatment coverage.

Key word: group B streptococcus

Approximately 30% of women in the antepartum period are colonized with group B Streptococcus (GBS).[1] Prior to routine screening and treatment for intrapartum maternal GBS colonization, rates of early-onset GBS sepsis were 1.7 per 1000 births.[1] After the implementation of intrapartum antibiotic chemoprophylaxis, the estimated rates of early GBS infection were reduced by 83%; the risk ratio, 0.17; the 95% confidence interval (CI), 0.04−0.74.[2]

Current GBS screening guidelines indicate that there is insufficient evidence to suggest that management of maternal GBS colonization should have an impact on obstetric procedures such as labor induction.[1] Recently, 4 or more hours of intrapartum antibiotic prophylaxis prior to delivery has been shown to be the most effective treatment for preventing early-onset GBS disease.[3,4] Although chemoprophylaxis is administered to 87-99% of women who are positive for GBS at term, as much as one quarter will receive less than 4 hours of intrapartum antibiotic therapy.[4,5]

The only factor associated with missed opportunities for chemoprophylaxis in term pregnancies colonized with GBS is an interval between hospital admission and delivery of less than 4 hours.[5] Although not all women arrive in time for 4 hours of antibiotic prophylaxis, the median period between entry and delivery for term births receiving intrapartum antibiotic prophylaxis is 7.8 hours (range, 3.8−13.1 hours).[5] Despite adequate time, at least 14% of lost opportunities for prevention were the result of failure to dispense ample lengths of intrapartum antibiotic prophylaxis.[3] If antibiotic therapy is shown to be effective for these women, then promoting the advantages of treatment is paramount. As obstetricians, we need to consider whether we should optimize fetal exposure to intrapartum GBS antibiotic prophylaxis to achieve maximum neonatal benefit.

Biological plausibility

It is unclear whether antepartum antibiotic prophylaxis for GBS reduces neonatal infection by decreasing the microbiological load of vaginal GBS, achieving bactericidal antibiotic levels in the fetus and amniotic fluid, or some combination thereof. GBS vaginal colony counts decrease by 5-fold within administering 2 hours of intravenous penicillin G and by 50-fold within 4 hours.[6]

Pharmacokinetic studies of β-lactam antibiotics utilized for maternal prophylaxis for intrapartum GBS suggest that bactericidal levels in fetal blood are achieved as early as 3 minutes, with higher levels persisting for up to 2 hours, and the lowest fetal concentration in mothers who fail to receive their additional dose at the 4 hour time point.[7,8] However, in women receiving maintenance doses every 4 hours, fetal antibiotic levels are consistently above the minimal inhibitory concentration for GBS.[8]

The paradox that maximal clinical benefit occurs when fetal blood levels are at their lowest may be a function of the in vivo effectiveness of β-lactam antibiotics. β-Lactam antibiotics exhibit time-dependent bactericidal activity, in which the antibiotic concentration in fluids and tissues may not represent the time course of antibacterial effects exerted by levels in blood and at the site of infection.[9] The predominant determinant of bacteriological response to the antibiotic is the time that the blood level of the antibiotic exceeds the minimal inhibitory concentration. However, despite adequate bactericidal levels in fetal cord blood, 15% of their mothers will have amniotic fluid antibiotic concentrations below the minimal inhibitory concentration for GBS.[7] Cases of neonatal GBS sepsis that occur with short durations of maternal antibiotic prophylaxis (ie, <4 hours) may either be the result of the following: (1) fetal

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exposure to GBS in utero prior to antibiotic administration when tissue injury by GBS may not be quickly reversible or (2) inadequate time for antibiotics to decrease vaginal GBS colony counts.[6,7]

What is the optimal antibiotic exposure?

Most published medical literature on intrapartum antibiotic prophylaxis for GBS suggest a 4 hour time threshold for antibiotic exposure. Because of the rare outcome of neonatal GBS sepsis, neonatal GBS colonization was utilized as a surrogate. Thus, studies that performed neonatal cultures after delivery may reflect contamination with vaginal flora. Small observational studies assessing the optimal timing of intrapartum antibiotic prophylaxis for maternal colonization with GBS noted increased rates of neonatal GBS colonization in women who received less than 4 hours of antibiotic therapy.[10-12] No infants whose mothers received intrapartum antibiotics developed neonatal sepsis.

Recently, 2 large cohort trials evaluated the effectiveness of intrapartum antibiotic prophylaxis in GBS colonized women for the prevention of neonatal sepsis.[3,4] A population-based surveillance program for invasive GBS disease in more than 7600 women in selected counties in 10 states demonstrated that 4 or more hours of intrapartum prophylaxis with penicillin or ampicillin was 91% effective in the prevention of early-onset GBS disease compared with women receiving no treatment ($P < .001$),[3] whereas prophylaxis of shorter durations of either less than 2 or between 2 and 4 hours before delivery had some effectiveness (47% and 38%, respectively). These brief durations of antibiotics were not statistically different from women who received no intrapartum antibiotic prophylaxis ($P = .11$ and $P = .14$, respectively).

A study of a single institution with more than 4700 low-risk women at a gestation of 37 weeks or longer showed that intrapartum antibiotic prophylaxis for GBS of 4 hours or longer reduced the risk of infants being diagnosed with clinical sepsis by 65% (relative risk [RR], 0.35; 95% CI, 0.16−0.79; $P = .01$).[4] The duration of intrapartum antibiotic administration had an impact on the diagnosis of neonatal clinical sepsis, with the diagnosis decreasing the longer the mother received intrapartum antibiotics: 1.6% for less than 2 hours, 0.9% for 2 to less than 4 hours, and 0.4% for 4 hours or longer. However, the only significant difference for the risk of diagnosis of neonatal clinical sepsis was for women who received less than 2 hours ($P = .02$) but not at 2 to less than 4 hours ($P = .12$) when compared with 4 hours or longer.[4]

When utilizing alternative antibiotics, such as with penicillin-allergic women, the period of therapy for optimal neonatal outcome is unknown. It appears that 4 or more hours of intrapartum β-lactam antibiotic prophylaxis is most effective, resulting in the lowest rate of early-onset GBS disease.

What might be done?

The simple strategy is to begin intrapartum antibiotic prophylaxis as soon as technically possible. Because the most common reason for missed intrapartum chemoprophylaxis in GBS colonized, term pregnancies is the time period between hospital admission and delivery of less than 4 hours, this should be a priority.

Improving clinical processes to optimize intrapartum therapy may be beneficial such as triage tools to ensure that patients requiring therapy receive priority treatment and setting a standard of initiating antibiotic therapy within a short period of time from admission. Although medically necessary procedures should not be delayed to provide 4 hours of antibiotic administration, variations in practice may be warranted based on the needs of individual patients to optimize intrapartum antibiotic exposure. First, for women who present in spontaneous labor, postponing techniques of augmentation, either artificial rupture of membranes or administration of oxytocin, until 4 hours of antibiotic administration is completed, would be of neonatal benefit (if maternal and neonatal status were stable, and a 4 hour delay would not have an impact on the mother-infant condition). A policy of early amniotomy and prompt utilization of oxytocin for either the prevention of, or therapy for a delayed labor, has shown only modest reductions for both cesarean delivery (RR, 0.89; 95% CI, 0.79−1.01) and the admission to delivery time (mean decrease, −1.28 hours; 95% CI, −1.97 to −0.59).[13] Obstetricians will need to balance the small increase in an admission to delivery interval against the benefit of lowering the risk of neonatal infection.

Second, for women admitted for induction of labor, GBS prophylaxis should begin first, even prior to initiating uterotonic agents. With the capriciousness of the labor process, waiting until the active phase of labor to initiate antibiotic prophylaxis for GBS might result in suboptimal chemoprophylaxis.

Third, women with premature rupture of membranes at term who are colonized with GBS and not in labor may have optimal neonatal benefit if given 4 hours of antibiotic prophylaxis prior to the induction of the labor. Although it has been suggested that immediate induction with intravenous oxytocin is associated with a lower rate of neonatal infection in GBS colonized mothers with term premature rupture of membranes, this difference is not significant (odds ratio, 0.29; 95% CI, 0.08−1.05).[14] Depending on a patient's cervical examination at hospital admission, clinical judgment to initiate uterotonic agents immediately or after giving 4 hours of intrapartum antibiotic prophylaxis might be considered.

Conclusion

Pharmacokinetic and microbiologic data suggest that a 2-hour duration of intrapartum maternal antibiotic prophylaxis for GBS provides some protective benefits to the infant. However, studies that correlate duration of prophylaxis with clinical outcomes suggest that at least 4 hours of antibiotic therapy is needed for maximum advantage. Obstetricians should consider improving the therapeutic effect of intrapartum antibiotic prophylaxis for women-infant pairs colonized with GBS by providing at least 4 hours of treatment exposure. ■

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