

# Azithromycin Prophylaxis for Laboring Mothers

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Antimicrobial prophylaxis to prevent infection is an appealing concept. This approach is used for clinical scenarios in which the benefits have been clearly established, such as the prevention of surgical site infections, group B *Streptococcus* (GBS) sepsis in the neonate, and congenital and acquired immune deficiencies. In each case, the potential benefits of prophylaxis, including infection-associated morbidity and even mortality, must be weighed against the known risks of antimicrobial resistance and adverse drug effects. Ideally, only the highest risk patients are targeted for prophylaxis to avoid unnecessary exposure (eg, laboring mothers who are GBS positive or clean-contaminated surgical procedures) and the risk/benefit assessment is periodically reassessed over time as new data emerge.

Postpartum infections of the mother and newborn are critically important targets of preventive health efforts. Approximately 1 million neonates die each year from infection; 99% of the deaths occur in developing countries.<sup>1</sup> Because GBS is a major cause of both maternal (endometritis, chorioamnionitis, urinary tract infection) and neonatal (sepsis, pneumonia) infections, guidelines from the American Academy of Pediatrics and the Centers for Disease Control and Prevention recommend antibiotic prophylaxis with penicillin or ampicillin for laboring mothers known to be colonized with GBS through universally recommended screening during pregnancy.<sup>2</sup> This targeted approach to deliver antimicrobial prophylaxis has cut the

rate of early-onset neonatal invasive GBS infection by 80% but might not be feasible in the developing world.

In an attempt to expand the scope of peripartum prophylaxis, Oluwalana et al examined the impact of azithromycin prophylaxis given to all laboring mothers on rates of postpartum maternal and neonatal infections.<sup>3</sup> Because this was a post hoc analysis of data from a previously conducted study, it is important to describe the details of the parent study: a double-blind, placebo-controlled, randomized clinical trial designed to determine the impact of a single dose (2 g) of azithromycin given during labor on maternal (vaginal, breast milk) and neonatal (nasopharyngeal swab) colonization with *Staphylococcus aureus*, GBS, or pneumococcus.<sup>4</sup> Mothers were recruited from a government-operated health center in Western Gambia between April 2013 and April 2014. Those enrolled received azithromycin or placebo and were followed daily for 1 week postpartum and then weekly through 8 weeks for assessment of the primary outcome (colonization). The parent study found that azithromycin was associated with a reduction in maternal and infant colonization for all pathogens investigated. For the current study, the authors aimed to determine whether azithromycin prophylaxis protected against (1) postpartum infection in the mother, including mastitis, sepsis, urinary tract infection, pelvic inflammatory disease, and malaria, and (2) neonatal infection, including skin infection, umbilical infection, conjunctivitis, otitis,

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oral infection, sepsis, meningitis, pneumonia, and malaria.

Of 1061 eligible laboring women, 829 were enrolled (414 received azithromycin and 415 placebo). Although the authors accurately conclude that both mothers and infants in the treatment arm experienced fewer infections overall, these rates were entirely driven by mastitis in the mothers and skin infections in neonates, none of which were described as severe. Furthermore, based on the reported risk differences between groups, the number needed to treat to prevent a skin infection in mother or infants was 27. No significant differences in rates of sepsis, malaria, hospitalizations, or death in mothers or infants were observed; there were 3 maternal hospitalizations and 3 neonatal deaths in the azithromycin arm versus 2 maternal hospitalizations and 4 deaths in subjects receiving placebo.

Strengths of this study include the important public health topic addressed; the randomized, placebo-controlled study design; and the thorough follow-up of study subjects for 8 weeks after delivery. Some important limitations must be noted, however. Because this was a post hoc analysis of data from a study designed to evaluate a different primary outcome (colonization), the study was not powered to assess the outcomes of interest (infections). Furthermore, these outcomes were derived from adverse event reports from the parent study that were less rigorously defined (based on clinical judgment of study clinicians). Thus, it remains unclear from these data whether this approach to prophylaxis protects mothers or infants against life-threatening infections. Of note, a recent study examining the effect of azithromycin prophylaxis, albeit a lower (500 mg) dose, to prevent postoperative wound infections in mothers undergoing caesarean

delivery confirmed its lack of protection against neonatal sepsis in a secondary analysis.<sup>5</sup>

In the face of this uncertainty, we must also consider the potential downside of universal azithromycin exposure to laboring mothers. Although only a single administration, the large dose coupled with azithromycin's long half-life provide a relatively prolonged exposure. Azithromycin exposure may also facilitate the emergence of antimicrobial resistance in other antibiotic classes.<sup>6</sup> Clinically important resistance to azithromycin has been demonstrated in both maternal and neonatal infections worldwide for the pathogens targeted in this study as well as for group A *Streptococcus*, *Chlamydia*, and gonococcal infections. In addition, despite the intent to target colonization with pathogenic organisms, systemic antimicrobial exposure can alter the structure and function of the human microbiome, which has been associated with a variety of chronic health conditions in both adults and children,<sup>7</sup> and macrolide exposure has the most dramatic effects on energy metabolism and adiposity in animal models.<sup>8</sup> Early-life azithromycin exposure has also been associated with development of hypertrophic pyloric stenosis in infants.<sup>9</sup> Although maternal azithromycin use has not been directly linked to this condition, widespread exposure during labor could have unintended consequences on a population level.

In light of the small potential benefits observed in the Oluwalana study, the potential harms of azithromycin exposure likely outweigh the upside for this specific indication. If azithromycin prophylaxis in laboring mothers becomes common, however, future studies should systematically capture its effects on serious maternal and neonatal infections, as well as antimicrobial resistance,

adverse drug effects, and disruptions to the host microbiome.

#### ABBREVIATION

GBS: group B *Streptococcus*

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