Is azithromycin prophylaxis appropriate for vaginal delivery in low- and middle-resource populations?

Yes. In a multisite, randomized, placebo-controlled study, 29,278 patients at or beyond 28 weeks' gestation in low- or middle-resource countries received oral azithromycin 2 g or placebo during labor to evaluate whether treatment would reduce maternal and neonatal sepsis or death. Maternal sepsis or death was lower in the azithromycin group: 1.6% versus 2.4% (RR, 0.67; 95% CI, 0.56–0.79; *P*<.001), while there was no difference in the frequency of neonatal sepsis or death.

Tita ATN, Carlo WA, McClure EM, et al; for the A-PLUS Trial Group. Azithromycin to prevent sepsis or death in women planning a vaginal birth. N Engl J Med. 2023;388:1161-1170. doi:10.1056/NEJMoa2212111.

EXPERT COMMENTARY

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Maternal peripartum infection is 1 of the top 5 causes of maternal death, accounting for about 10% of cases of maternal mortality. Cesarean delivery (CD), of course, is the most important risk factor for puerperal infection. However, even vaginal delivery, particularly in low- to middle-resource countries, where deliveries often occur under less-than-optimal conditions, may be associated with a surprisingly high frequency of both maternal and neonatal infections. The beneficial effect of prophylactic antibiotics for CD is well established. An important remaining question is whether similar benefit can be achieved with prophylaxis for women planning to have a vaginal birth.

In 2017, Oluwalana and colleagues conducted a prospective, randomized, double-blind, placebo-controlled trial of a single 2-g oral dose of azithromycin in Gambian women undergoing labor.[1] During the 8 weeks after delivery, maternal infections were lower in the azithromycin group, 3.6% versus 9.2% (relative risk [RR], 0.40; 95% confidence interval [CI], 0.22–0.71; *P*=.002). Infections also were lower in the newborns, 18.1% versus 23.8% (RR, 0.76; 95% CI, 0.58–0.99; *P*=.052), delivered to mothers who received azithromycin. The greatest impact on neonatal infections was the reduced frequency of skin infections.

In 2021, Subramaniam and colleagues evaluated the effect of a single dose of oral azithromycin with, or without, amoxicillin on the prevalence of peripartum infection in laboring women in Cameroon.[2] Patients and

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FAST TRACK

While CD is the most important risk factor for puerperal infection, vaginal delivery, particularly in low- to middle-resource countries, may be associated with a surprisingly high frequency of both maternal and neonatal infections

FAST TRACK

In the study by Tita and colleagues, the incidence of maternal sepsis or death was lower in the azithromycin group (1.6% vs 2.4%; RR, 0.67; 95% CI, 0.56-0.79; P<.001), with the key effect on the frequency of maternal sepsis

their newborns were followed for 6 weeks after delivery. Unlike the previous investigation, the authors were unable to show a protective effect of prophylaxis on either maternal or neonatal infection.

Against this backdrop, Tita and colleagues conducted a remarkably large, well-designed, randomized, placebo-controlled study of azithromycin prophylaxis in women at 8 different sites in 7 low- or middle-income countries (the A-PLUS investigation).[3]

Details of the study

The investigators randomly assigned 29,278 patients at or beyond 28 weeks' gestation to receive either a 2-g oral dose of azithromycin or placebo during labor. This particular drug was chosen because it is readily available, inexpensive, well tolerated, and has a broad range of activity against many important pelvic pathogens, including genital mycoplasmas. Some patients also received other antibiotics, for example, for group B streptococcal (GBS) prophylaxis or for CD prophylaxis if abdominal delivery was indicated.

The 2 primary outcomes were a composite of maternal sepsis or death and a composite of stillbirth or neonatal death or sepsis within 4 weeks of delivery. Secondary outcomes included individual components of the primary outcomes.

Results. The results of the investigation were compelling, and the data safety monitoring committee recommended stopping the trial early because of clear maternal benefit. The groups were well balanced with respect to important characteristics, such as incidence of CD, receipt of other prophylactic antibiotics, and median time between randomization and delivery.

The incidence of maternal sepsis or death was lower in the azithromycin group (1.6% vs 2.4%; RR, 0.67; 95% CI, 0.56–0.79; *P*<.001). The key effect was on the frequency of maternal sepsis because the incidence of maternal death was very low in both groups, 0.1%. With respect to secondary outcomes, prophylaxis was effective in reducing the frequency of endometritis (RR, 0.66; 95% CI, 0.55–0.79) and perineal and incisional infection (RR, 0.71; 95% CI, 0.56–0.85).

There was no difference in the frequency of neonatal sepsis or death. There also was no difference in the frequency of adverse drug

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effects in either group. Of note, more cases of neonatal pyloric stenosis were observed in the azithromycin group, but the overall incidence was lower than the expected background rate. This possible "signal" is important because this effect has been noted with increased frequency in neonates who received this antibiotic. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

I believe that Tita and colleagues are quite correct in concluding that the simple, inexpensive intervention of azithromycin prophylaxis should be used routinely in patient populations similar to those included in this investigation and that the intervention can be invaluable in advancing the World Health Organization's campaign to reduce the rate of maternal mortality in low- and middle-resource nations.

What is not clear, however, is whether this same intervention would be effective in high-resource countries in which the level of skill of the obstetric providers is higher and more uniform; deliveries occur under more optimal sanitary conditions; treatment and prophylaxis for infections such as gonorrhea, chlamydia, chorioamnionitis, and GBS is more consistent; and early neonatal care is more robust. A similar large trial in well-resourced nations would indeed be welcome, particularly if the trial also addressed the possibility of an adverse effect on the neonatal microbiome if a policy of nearly universal antibiotic prophylaxis was adopted.

In the interim, we should focus our attention on the key interventions that are of proven value in decreasing the risk of peripartum maternal and neonatal infection:

- consistently screening for GBS colonization and administering intrapartum antibiotic prophylaxis to patients who test positive
- consistently screening for gonococcal and chlamydia infection in the antepartum period and treating infected patients with appropriate antibiotics
- minimizing the number of internal vaginal examinations during labor, particularly following rupture of membranes
- promptly identifying patients with chorioamnionitis and treating with antibiotics that specifically target GBS and *Escherichia coli,* the 2 most likely causes of neonatal sepsis, pneumonia, and meningitis
- administering preoperative prophylactic antibiotics (cefazolin plus azithromycin) to women who require CD.

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