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Does azithromycin have a role in cesarean sections?

Yes, adding azithromycin to the usual antibiotic protocol in nonelective c-sections reduces infections. But not everyone can take advantage of it.

PRACTICE CHANGER

Prescribe a one-time dose of azithromycin 500 mg intravenously, along with standard antibiotic prophylaxis, at the time of cesarean delivery to prevent postoperative infections.¹

STRENGTH OF RECOMMENDATION

B: Based on a single good-quality, randomized controlled trial.

Tita AT, Szychowski JM, Boggess K, et al. Adjunctive azithromycin prophylaxis for cesarean delivery. *N Engl J Med*. 2016;375:1231-1241.

ILLUSTRATIVE CASE

A 26-year-old G1P0 at 40w1d presents in spontaneous labor and is dilated to 4 cm. The patient reached complete cervical dilation after artificial rupture of membranes and oxytocin augmentation. After 4 hours of pushing, there has been minimal descent of the fetal vertex beyond +1 station with significant caput succedaneum. Her physician decides to proceed with cesarean delivery.^{2,3} What antibiotics should be administered prior to incision to reduce postoperative infection?

The Centers for Disease Control and Prevention (CDC) reports that nearly 1.3 million cesarean deliveries were performed in the United States in 2015, which represents about a third of all births.⁴ C-section is the most common major surgical procedure performed in this country and is associated with an infection rate 5 to 10 times that of vaginal delivery.^{5,6} Pregnancy-associated infection, particularly during

delivery, is a significant risk and the fourth most common cause of maternal death in the United States.⁵

The current standard of care in cesarean delivery is antibiotic prophylaxis (often a first-generation cephalosporin) prior to skin incision.⁷ The majority of c-sections performed are nonelective, and of these, postoperative infections occur in 12% of women who receive standard prophylaxis.^{8,9} A small, single-center design trial suggested azithromycin adjunctive therapy expands antibiotic coverage to *Ureaplasma* species, resulting in a lower risk of postoperative infection.¹⁰

This study evaluated the use of azithromycin adjunctive therapy, in addition to standard antibiotic prophylaxis, to reduce the risk of postoperative infections in women receiving nonelective c-sections.

STUDY SUMMARY

Azithromycin reduced maternal infections up to 6 weeks post-c-section

A multicenter, randomized double-blind trial conducted in 14 hospitals in the United States evaluated the effect of a one-time dose of 500 mg intravenous (IV) azithromycin on post-cesarean infections. Women with a singleton pregnancy of at least 24 weeks' gestation were eligible for inclusion if they required nonelective cesarean delivery during labor or at least 4 hours after membrane rupture. Patients were excluded if they had a known azithromycin allergy, subsequent vaginal delivery, azithro-

mycin use within the week prior to randomization, extensive hepatic or renal dysfunction, a known history of prolonged QT interval, or substantial electrolyte abnormalities. Patients were eligible even if they were receiving other antibiotics for a positive group B *Streptococcus* screening.¹

All patients (N=2013) were treated with standard antibiotic prophylaxis, most often cefazolin, according to individual institution protocols. The women were randomized to receive either an azithromycin 500 mg/250 mL IV infusion (n=1019) or an identical placebo IV infusion (n=994) within one hour of the procedure. The primary outcome was a composite endpoint of endometritis, wound infection, or other infections occurring up to 6 weeks after the c-section. Secondary outcomes included neonatal death, sepsis, and other neonatal and maternal complications.¹

Patients in the placebo group had a higher rate of smoking during pregnancy; the researchers found no other significant differences.¹

Results. The primary composite outcome occurred less frequently in the azithromycin group than in the placebo group (6.1% vs 12.1%; relative risk [RR]=0.51; 95% confidence interval [CI], 0.38-0.68; number needed to treat [NNT]=17). When the researchers looked at the individual elements of the primary composite outcome, 2 had significant reductions vs placebo.

Endometritis (3.8% vs 6.1%; RR=0.62; 95% CI, 0.42-0.92; NNT=44) and wound infections (2.4% vs 6.6%; RR=0.35; 95% CI, 0.22-0.56; NNT=24) occurred significantly less frequently, but there was no difference for other infections (0.3% vs 0.6%; RR=0.49; 95% CI, 0.12-1.94). Serious maternal adverse events were also lower with treatment than in the control group (1.5% vs 2.9%; RR=0.5; 95% CI, 0.27-0.94; NNT=71). There was no difference in composite secondary neonatal outcomes including death and serious complications (14.3% vs 13.6%; RR=1.05; 95% CI, 0.85-1.31).¹

WHAT'S NEW

Azithromycin reduces infections without increasing adverse events

This study showed that adding azithromycin

to standard antibiotic prophylaxis within one hour of a c-section reduces post-cesarean delivery infection rates without increasing the risk of maternal or neonatal adverse events.

CAVEATS

Proceed with caution in those with prolonged QT intervals

While azithromycin was efficacious and well tolerated in the study, not every patient can take it. Patients with a previous drug reaction or allergy should avoid it, and experts advise prescribing it with caution for patients who have (or are at increased risk for) a prolonged QT interval, including those on other QT-prolonging medications.

Of note, women with scheduled c-sections and those with chorioamnionitis or another infection requiring postpartum antibiotics were excluded from this study. Thus, it is unknown if azithromycin use decreases complications in these patients.

CHALLENGES TO IMPLEMENTATION

Speed of procedure is often paramount, so drug availability is key

Nonelective c-sections occur based on many factors that include a non-reassuring fetal heart rate. In many of these cases, speed of cesarean delivery may mean the difference between positive and negative outcomes. Availability of azithromycin on labor and delivery floors for timely administration within one hour of the procedure is important.

Additionally, azithromycin has known QT prolongation risks.¹¹ While the baseline QT interval is not known for many healthy, young women, this should be considered when azithromycin is utilized in combination with other medications that may prolong the QT interval. **JFP**

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Adding azithromycin to standard antibiotic prophylaxis within one hour of a c-section reduces post-cesarean delivery infection rates without increasing the risk of adverse events.

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