Original Research

Timing of Adjunctive Azithromycin for Unscheduled Cesarean Delivery and Postdelivery Infection

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OBJECTIVE: To estimate the association between timing of administration of adjunctive azithromycin for prophylaxis at unscheduled cesarean delivery and maternal infection and neonatal morbidity.

METHODS: We conducted a secondary analysis of a randomized trial of adjunctive azithromycin prophylaxis in patients with singleton gestations who were undergoing unscheduled cesarean delivery. The primary exposure was the timing of initiation of the study drug (after skin incision or 0–30 minutes, more than 30–60 minutes, or more than 60 minutes before skin incision). The primary outcome was a composite of endometritis, wound infection, and other maternal infections occurring up to 6 weeks after cesarean delivery. Secondary outcomes included composite neonatal morbidity, neonatal intensive care unit admission for longer than 72 hours, and neonatal sepsis. The association of azithromycin with outcomes was compared within each antibiotic timing group and presented as risk ratios (RRs) with 95% CIs. A Breslow-Day homogeneity test was applied to assess differences in association by antibiotic timing.

RESULTS: Of 2,013 participants, antibiotics were initiated after skin incision (median 3 minutes, range 0–229 minutes) in 269 (13.4%), 0–30 minutes before skin incision in 1,378 (68.5%), more than 30–60 minutes before skin incision in 270 (13.4%), and more than 60 minutes before skin incision (median 85 minutes, range 61–218 minutes) in 96 (4.8%). The RRs (95% CIs) of the infectious composite outcome for azithromycin compared with placebo were significantly lower for groups that initiated azithromycin after skin incision or within 1 hour before skin incision (after skin incision: RR 0.31, 95% CI 0.13–0.76; 0–30 minutes before: RR 0.62, 95% CI 0.44–0.89; more than 30–60 minutes before: 0.31, 95% CI 0.13–0.66). Risks were not significantly different in patients who received azithromycin more than 60 minutes before skin incision (RR 0.59, 95% CI 0.10–3.36). Results were similar when endometritis and wound infections were analyzed separately. Neonatal outcomes were not significantly different for azithromycin compared with placebo across all timing groups.

CONCLUSION: Adjunctive azithromycin administration up to 60 minutes before or at a median of 3 minutes after

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skin incision was associated with reduced risks of maternal composite postoperative infection in unscheduled cesarean deliveries.

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Cesarean delivery is the single most important risk factor for postpartum uterine infection and is associated with 5- to 10-fold higher infectious morbidity compared with vaginal delivery.[1–4] These infection risks are higher among individuals undergoing unscheduled cesarean deliveries.[5–9] To mitigate the risk of infection, preoperative antibiotic prophylaxis with a first-generation cephalosporin (cefazolin) before skin incision is recommended.[10] However, even with routine prophylaxis, up to 12% of unscheduled cesarean deliveries receiving standard preoperative antibiotic prophylaxis develop postpartum infections.[11,12] This is reduced by half with the addition of adjunctive azithromycin for surgical prophylaxis.[13] However, there are limited data on the association of the timing of azithromycin administration and postcesarean infection risk.

Time of antibiotic administration relative to skin incision is a major determinant of peak tissue antibiotic concentration.[10,14–18] Azithromycin attains peak maternal plasma concentration (exceeding the minimum inhibitory concentration [MIC] for Ureaplasma) within 1 hour and then rapidly declines over 1–2 hours to reach a steady state.[16] Thus, timing of azithromycin administration relative to skin incision is important to exceed the MIC of susceptible microorganisms implicated in postcesarean infections.

Therefore, our primary objective was to evaluate the association between timing of adjunctive azithromycin administration for prophylaxis at unscheduled cesarean delivery after labor and maternal and neonatal infectious morbidity.

METHODS

We performed a secondary analysis of a randomized controlled trial of adjunctive azithromycin prophylaxis for cesarean delivery (CSOAP trial [Cesarean Section Optimal Antibiotic Prophylaxis], NCT01235546) conducted at 14 centers in the United States. The institutional review boards at each center approved the parent trial, and the University of Alabama at Birmingham's institutional review board deemed this secondary analysis of deidentified data exempt (information was recorded in a manner that the identity of study participants could not be readily ascertained). The parent trial was funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and Pfizer donated the study medication but did not participate in the design, conduct, or reporting of either the parent trial or this secondary analysis. The inclusion and exclusion criteria and results of this trial have been previously described. Briefly, the trial included patients with singleton gestations of at least 24 weeks who were undergoing unscheduled cesarean delivery during labor or with ruptured membranes for more than 4 hours and no contraindication to azithromycin.[13]

The primary exposure for this secondary analysis was timing of study drug administration after skin incision (administered as soon as possible), or 0–30 minutes, more than 30–60 minutes, or more than 60 minutes before skin incision. Patients in the primary trial were randomly assigned to 500 mg of azithromycin in 250 mL of saline infusion or an identical-appearing saline placebo infused over 1 hour. The time of administration was defined as the time the infusion was connected to the patient. During the course of the trial, antibiotic prophylaxis, mostly with a first-generation cephalosporin (cefazolin), was administered over a 5-minute period as an intravenous push, followed by the study drug (azithromycin or placebo). Details of the timing of administration of study drug were prospectively ascertained during the course of the primary trial. Of note, only a single dose of adjunctive azithromycin was administered.

The primary outcome of this secondary analysis was a maternal postoperative infection composite of endometritis, wound infection, or other maternal infections (abdominopelvic abscess, maternal sepsis, pelvic septic thrombophlebitis, pyelonephritis, pneumonia, or meningitis) occurring within 6 weeks of cesarean delivery as defined in the primary study.[13] Maternal secondary outcomes were individual components of the primary composite outcome–endometritis and wound infection. The neonatal composite outcome included neonatal death, neonatal sepsis, other serious neonatal complications: necrotizing enterocolitis, respiratory distress syndrome, periventricular leukomalacia, grade 3 or higher intraventricular hemorrhage, and neonatal intensive care unit admission for longer than 72 hours. The primary outcome and its components were ascertained through central adjudication by investigators unaware of treatment assignments. Other maternal and infant outcomes were ascertained by trained research staff through review of the electronic medical records and direct questioning in person or by telephone. All outcomes are defined in detail in the primary

report.[13] Race and ethnicity were self-reported by study participants into prespecified categories, including "none of the above," which was also a prespecified formal category in the database. Information on race and ethnicity were collected because various studies have demonstrated racial and ethnic disparities in cesarean morbidity[19,20]; however, these ultimately were not included as covariates in our analyses.

Differences in baseline variables by azithromycin compared with placebo assignment were examined within each antibiotic timing group. Study outcomes (risk ratios [RRs] with 95% CIs) for azithromycin compared with placebo, were computed within each antibiotic timing group using placebo as the reference. A Breslow-Day test for homogeneity was applied to assess differences in associations among groups. In additional analyses, log binomial multivariable models were adjusted for characteristics identified as statistically significantly different between participants receiving azithromycin and placebo in each antibiotic timing group. All analyses were done with the SAS 9.4, and significance level was set at $P<.05$ for all analyses.

RESULTS

Of 2,013 participants from the parent trial, 269 (13.4%) received prophylactic antibiotics after skin incision (median 3 minutes, range 0–229 minutes; 250 [92.9%] of whom received antibiotics less than 60 minutes after incision), 1,378 (68.5%) received antibiotics in the 30 minutes before the skin incision, 270 (13.4%) received antibiotics in more than 30–60 minutes before skin incision, and 96 (4.8%) received antibiotics more than 60 minutes (median 85 minutes, range 61–218 minutes) before skin incision (Table 1). Only membrane status at delivery was significantly different by azithromycin (or placebo) reception status in participants who received azithromycin after skin incision.

A total of 181 (9.0%) patients met the composite primary outcome of endometritis, wound infection, or other maternal infection within 6 weeks of delivery, the majority (65.7%) of whom received antibiotics in the 30 minutes before the skin incision (Table 2). Receiving azithromycin (vs placebo) after skin incision or 0–30 minutes, more than 30–60 minutes before skin incision was associated with a significant reduction in the risk of the primary outcome. Azithromycin administered more than 60 minutes before skin incision was not significantly associated (RR 0.59, 95% CI 0.10–3.36) with a reduction in the primary outcome (Table 2). The pattern of significant risk reduction was consistent for the outcome of wound infection among patients receiving antibiotics 0–30 minutes and more than 30–60 minutes before skin incision. Further, azithromycin administration was significantly associated with a reduced risk of endometritis when administered after cesarean incision or more than 30–60 minutes before skin incision. Results were unchanged in models adjusted for membrane status at randomization.

Regardless of time of administration of azithromycin, there were no significant differences in the neonatal composite outcome, suspected or confirmed neonatal sepsis or the risk of neonatal intensive care unit admission (Table 3). The Breslow-Day test for homogeneity did not suggest any significant differences in maternal and neonatal outcomes between the antibiotic timing groups ($P>.05$).

DISCUSSION

In this secondary analysis, azithromycin administration was associated with a reduced risk of composite maternal postcesarean infection when administered within 1 hour before skin incision and when administered after (median 3 minutes, range 0–229 minutes) skin incision. Thus, administering azithromycin up to 60 minutes preincision or even after skin incision is beneficial in reducing postoperative maternal infections at unplanned cesarean deliveries. Timing of azithromycin administration, however, was not significantly associated with neonatal outcomes.

Most postpartum infections are polymicrobial (gram-positive cocci, gram-negative rods, anaerobes, Mycoplasma and Ureaplasma). Cefazolin, a commonly used first generation cephalosporin for cesarean prophylaxis, is active against many gram-positive and some gram-negative bacteria organisms. In fact, administration of 2 g of intravenous cefazolin within 1 hour before cesarean incision achieves MIC for gram-negative rods in most patients with therapeutic concentrations in umbilical cord at delivery and persisting in newborns up to 5 hours after delivery.[13,21–23] A twofold higher risk of surgical site infection (RR 2.10, 95% CI 1.20–3.80) when cefazolin only is administered more than 1 hour before skin incision, compared with administration within 1 hour before cesarean incision, is supported by these pharmacokinetic parameters.[24] Mycoplasma, Ureaplasma, and anaerobes are not effectively treated by cephalosporins but can be treated with macrolide antibiotics such as azithromycin. Evaluating placental tissue collected during the parent CSOAP trial, azithromycin was even demonstrated to have a range of antimicrobial activity beyond Mycoplasmas and Ureaplasmas.[25] In pregnant patients receiving single-dose 500 mg of azithromycin within 1 hour before skin incision, peak maternal serum concentrations are attained within 1 hour, and azithromycin is detectable in fetal compartments within 30 minutes and in sustained concentrations in breast milk up to 48 hours

Table 1. Baseline Characteristics of Patients Receiving Adjunctive Azithromycin or Placebo at Unscheduled Cesarean Delivery in the CSOAP Trial (Cesarean Section Optimal Antibiotic Prophylaxis)

	After Skin Incision (Median 3 min, Range 0–229 min) (n=269)		0–30 min Preincision (n=1,378)	
Characteristic	Azithromycin (n=135)	Placebo (n=134)	Azithromycin (n=693)	Placebo (n=685)
Maternal age (y)	28.9±6.5	27.9±6.8	28.1±6.1	28.5±6.5
Race and ethnicity				
Hispanic	19 (14.1)	11 (8.2)	128 (18.5)	138 (20.1)
Non-Hispanic Black	47 (34.8)	53 (39.6)	244 (35.2)	237 (34.6)
Non-Hispanic White	48 (35.6)	47 (35.1)	246 (35.5)	242 (35.3)
None of the above	21 (15.6)	23 (17.2)	75 (10.8)	68 (9.9)
Medicaid insurance*	82 (61.2)	84 (63.2)	424 (61.2)	412 (60.1)
Nulliparous	74 (54.8)	83 (61.9)	420 (60.6)	405 (59.1)
Comorbidities†	27 (20.0)	19 (14.2)	116 (16.7)	127 (18.5)
Substance use	13 (9.6)	16 (11.9)	90 (13.0)	109 (15.9)
Preterm birth (before 37 wk)	23 (17.0)	18 (13.4)	69 (10.0)	83 (12.1)
Group B streptococcus status	38 (28.2)	38 (28.4)	170 (24.5)	189 (27.6)
Spontaneous rupture of membranes*	56 (41.8)‡	37 (27.8)‡	247 (35.8)	229 (33.5)
BMI (kg/m^2)	34.7±7.4	34.2±7.8	35.2±7.7	35.8±7.9
Duration of ruptured membranes (h)	16.8±55.9	9.4±7.3	12.7±41.2	10.6±22.5
Standard prophylactic antibiotic§	134 (99.3)	129 (96.3)	680 (98.1)	676 (98.7)

	More Than 30–60 min Preincision (n=270)		More Than 60 min Preincision (Median 85 min, Range 61–218 min) (n=96)	
Characteristic	Azithromycin (n=140)	Placebo (n=130)	Azithromycin (n=51)	Placebo (n=45)
Maternal age (y)	27.8±5.8	28.2±6.3	29.2±6.4	28.9±6.2
Race and ethnicity				
Hispanic	39 (27.9)	41 (31.5)	17 (33.3)	18 (40.0)
Non-Hispanic Black	48 (34.3)	41 (31.5)	12 (23.5)	10 (22.2)
Non-Hispanic White	43 (30.7)	41 (31.5)	19 (37.3)	12 (26.7)
None of the above	10 (7.7)	7 (5.4)	3 (5.9)	5 (11.1)
Medicaid insurance*	84 (60.0)	76 (59.8)	32 (64.0)	28 (63.6)
Nulliparous	88 (62.9)	83 (63.8)	21 (41.2)	21 (46.7)
Comorbidities†	22 (15.7)	22 (16.9)	8 (15.7)	7 (15.6)
Substance use	28 (20.0)	29 (22.3)	12 (23.5)	10 (22.2)
Preterm birth (before 37 wk)	19 (13.6)	15 (11.5)	6 (11.8)	4 (8.9)
Group B streptococcus status	29 (20.7)	28 (21.5)	12 (23.5)	11 (24.4)
Spontaneous rupture of membranes*	49 (35.0)	50 (38.5)	21 (41.2)	11 (24.4)
BMI (kg/m^2)	36.3±8.2	35.4±7.7	36.1±7.8	35.6±7.2
Duration of ruptured membranes (h)	10.7±8.1	12.0±10.7	16.3±56.4	9.9±7.5
Standard prophylactic antibiotic§	137 (97.9)	128 (98.5)	49 (96.1)	43 (95.6)

BMI, body mass index.
Data are mean±SD or n (%).
* Column total not 100% owing to one–three participants with missing data on these variables.
† Comorbidities include pregestational diabetes, chronic hypertension, other cardiac disease, and autoimmune disease.
‡ Significantly different at $P<.05$ in azithromycin (vs placebo) status.
§ Standard prophylactic antibiotic was routinely cefazolin per protocol, except in patients with penicillin or cephalosporin allergy, who received the local alternative: clindamycin or clindamycin plus gentamicin.

after administration. Azithromycin has a considerably longer half-life (6.7 hours, 95% CI 6.4–7.6) compared with standard cephalosporins; thus, it is plausible that timing beyond the recommended 1 hour before incision could be considered.

Numerous studies have examined the timing of administration of standard cesarean prophylaxis. Most of these studies conclude that antibiotic administration before cord clamping or skin incision is associated with a lower risk of postcesarean infectious morbidity.[12,26–31] However, a more recent study among 55,901 patients in 75 Swiss hospitals between 2008 and 2019 examined the risk of surgical site infection after cesarean deliveries in which the standard antibiotic (cefuroxime, cefazolin,

Table 2. Number, Proportion, and Crude Risk Ratios Showing the Association of Adjunctive Azithromycin Compared With Placebo With the Risk of Infectious Maternal Morbidity Among Patients Undergoing Unscheduled Cesarean Delivery, by Time of Administration of Study Drug*

Outcome	After Skin Incision (Median 3 min, Range 0–229 min) (n=269)		0–30 min Preincision (n=1,378)	
	Azithromycin (n=135)	Placebo (ref) (n=134)	Azithromycin (n=693)	Placebo (ref) (n=685)
Primary composite outcome (n=181)	6 (4.4) 0.31 (0.13–0.76)	19 (14.2)	46 (6.6) 0.62 (0.44–0.89)	73 (10.7)
Endometritis (n=100)	2 (1.5) 0.16 (0.04–0.73)	12 (9.0)	32 (4.6) 0.93 (0.58–1.49)	34 (5.0)
Wound infection (n=90)	4 (3.0) 0.40 (0.13–1.23)	10 (7.5)	15 (2.2) 0.35 (0.20–0.63)	42 (6.1)

Outcome	More Than 30–60 min Preincision (n=270)		More Than 60 min Preincision (Median 85 min, Range 61–218 min) (n=96)		Interaction *P*
	Azithromycin (n=140)	Placebo (ref) (n=130)	Azithromycin (n=51)	Placebo (ref) (n=45)	
Primary composite outcome (n=181)	8 (5.7) 0.31 (0.13–0.66)	24 (18.5)	2 (3.9) 0.59 (0.10–3.36)	3 (6.7)	.18
Endometritis (n=100)	5 (3.6) 0.36 (0.13–0.97)	13 (10.0)	0 (0.0)†	2 (4.4)	.22
Wound infection (n=90)	3 (2.1) 0.23 (0.07–0.80)	12 (9.2)	2 (3.9) 0.88 (0.13–6.01)	2 (4.4)	.68

Ref, reference group.
Data are n (%) (95% CI) or crude risk ratio (95% CI) unless otherwise specified.
* Results for other infections were excluded from the table owing to nonconvergence of models from small case numbers.
† Regression model did not converge owing to small case numbers.

amoxicillin and clavulanate, ceftriaxone) was administered after umbilical cord clamping, compared with before surgical incision, and found no difference (odds ratio 1.14, 95% CI 0.96–1.36]) in the odds of surgical site infection between both groups.[32] Adjunctive azithromycin given at unscheduled cesarean delivery has been shown to lower the risk of postcesarean infectious morbidity by almost half,[13] and azithromycin prophylaxis at cesarean delivery is administered over 1 hour, as recommended by the U.S. Food and Drug Administration. Therefore, the protective association of adjunctive azithromycin in patients who receive azithromycin within 60 minutes before or after skin incision is not unexpected.

Of note, we failed to find an association between timing of administration of azithromycin and short-term neonatal outcomes, including neonatal suspected or confirmed infections. This could plausibly be due to the MIC of microorganisms implicated in neonatal infections being higher than azithromycin's concentration in the fetal compartment after single-dose administration before or as soon as possible after skin incision. However, our findings are consistent with the primary trial, which shows no safety signals or adverse outcomes in neonates exposed to adjunctive azithromycin.[13]

The strengths of this study include the relatively large number of patients recruited into the trial with rigorous exposure and outcome ascertainment and the standardized definitions of surgical site infections. Also, study outcomes, including those ascertained from interviews at the postpartum and 3-month telephone visits, were verified using medical records to reduce the risk of recall bias. Limitations include the small numbers of outcomes, especially among patients who received azithromycin more than 60 minutes before skin incision, which limits the strength of inferences that can be drawn from this group. Although we conducted multiple comparisons with the risk of false positive findings, there was a specified primary comparison to evaluate differences in association on the primary composite by timing of administration, and the findings were consistent with those of the primary paper. We do acknowledge power to detect significant interactions is likely

Table 3. Number, Proportion, and Crude Risk Ratios Showing the Association of Adjunctive Azithromycin Compared With Placebo With the Risk of Secondary Neonatal Outcomes Among Patients Undergoing Unscheduled Cesarean Delivery, by Time of Administration of Study Drug

Outcomes	After Skin Incision (Median 3 min, Range 0–229 min) (n=269)		0–30 min Preincision (n=1,378)	
	Azithromycin (n=135)	Placebo (ref) (n=134)	Azithromycin (n=693)	Placebo (ref) (n=685)
Composite neonatal outcome (n=281)*	26 (19.3) 0.96 (0.59–1.55)	27 (20.1)	95 (13.7) 1.10 (0.83–1.43)	86 (12.6)
Suspected or confirmed neonatal sepsis (n=246)	21 (15.6) 0.87 (0.51–1.48)	24 (17.9)	76 (11.0) 0.95 (0.71–1.28)	79 (11.5)
NICU admission (longer than 72 h) (n=262)	26 (19.3) 0.99 (0.61–1.62)	26 (19.4)	80 (11.5) 0.82 (0.62–1.09)	96(14.0)

Outcomes	More Than 30–60 min Preincision (n=270)		More Than 60 min Preincision (Median 85 min, Range 61–218 min) (n=96)		Interaction *P*
	Azithromycin (n=140)	Placebo (ref) (n=130)	Azithromycin (n=51)	Placebo (ref) (n=45)	
Composite neonatal outcome (n=281)*	19 (13.6) 1.26 (0.66–2.41)	14 (10.8)	6 (11.8) 0.66 (0.25–1.76)	8 (17.8)	0.75
Suspected or confirmed neonatal sepsis (n=246)	18 (12.9) 1.19 (0.62–2.30)	14 (10.8)	6 (11.8) 0.66 (0.25–1.76)	8 (17.8)	0.82
NICU admission (longer than 72 h) (n=262)	17 (12.1) 1.58 (0.75–3.32)	10 (7.7)	4 (7.8) 1.18 (0.28–4.98)	3 (6.7)	0.41

Ref, reference group; NICU, neonatal intensive care unit.
Data are n (%) (95% CI) or crude risk ratio (95% CI) unless otherwise specified.
* Composite neonatal outcome includes neonatal death, neonatal sepsis, and other serious neonatal complications (necrotizing enterocolitis, respiratory distress syndrome, periventricular leukomalacia, grade 3 or higher intraventricular hemorrhage, and NICU admission longer than 72 hours).

limited. We could not assess the association of redosing azithromycin with postcesarean infection in certain patients (eg, postpartum hemorrhage) because this was outside the scope of the original trial protocol. However, only three patients experienced postpartum hemorrhage and would not likely change our results.

In summary, this study's findings provide evidence for the beneficial association of adjunctive azithromycin when administered in the hour before skin incision or even after skin incision.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Not available.*

What other documents will be available? *Not available.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable.*

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