Published in final edited form as:

Obstet Gynecol. 2017 March ; 129(3): 481–485. doi:10.1097/AOG.0000000000001899.

Risk Factors for Postcesarean Maternal Infection in a Trial of Extended Spectrum Antibiotic Prophylaxis

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Abstract

Objective—To identify maternal clinical risk factors for postcesarean maternal infection in a randomized clinical trial of preincision extended-spectrum antibiotic prophylaxis.

Methods—We conducted a planned secondary analysis of a randomized clinical trial. Patients were ≥ 24 weeks of gestation and delivered by cesarean delivery after a minimum of 4 hours of ruptured membranes or labor. All participants received standard preincision prophylaxis and were randomized to receive azithromycin or placebo. The primary outcome for this analysis is maternal infection: a composite outcome of endometritis, wound infection (superficial or deep), or other

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Presented in part at the 36th annual meeting of the Society for Maternal–Fetal Medicine, Atlanta, GA, February 2–7, 2016.

Financial Disclosure: The authors did not report any potential conflicts of interest.
Each author has indicated that he/she has met the journal's requirements for authorship.

Clinical Trial Registration: Study of Effectiveness and Safety of Azithromycin-based Extended-Spectrum Prophylaxis to Prevent Post Cesarean Infection https://clinicaltrials.gov/ct2/show/NCT01235546.
NCT012235546

infections occurring up to 6 weeks postpartum. Maternal clinical characteristics associated with maternal infection, after controlling for azithromycin assignment, were identified. These maternal factors were included in a multivariable logistic regression model for maternal infection.

Results—Of 2,013 patients, 1,019 were randomized to azithromycin. Overall, 177 (8.8%) had postcesarean maternal infection. In the final adjusted model, compared to the reference groups, women of Black race–ethnicity, with a nontransverse uterine incision, with duration of membrane rupture ≥ 6 hours, and surgery duration ≥ 49 minutes, were associated higher odds of maternal infection (all with adjusted odds ratios of ~2); azithromycin was associated with lower odds of maternal infection (adjusted odds ratio of 0.4, 95% confidence interval 0.3-0.6.

Conclusions—Despite preincision azithromycin-based extended spectrum antibiotic prophylaxis, postcesarean maternal infection remains a significant source of morbidity. Recognition of risk factors may help guide innovative prevention strategies.

Introduction

Cesarean delivery, the most common major U.S. surgical procedure[1] is the greatest risk factor for puerperal maternal infection. Compared to vaginal delivery, cesarean delivery is associated with at least a 5 to10 fold increase in risk for postpartum (surgical site) infections including endometritis and wound infection.[2] As many as 60-70% of all cesarean deliveries are unscheduled. Even with standard preincision prophylaxis surgical site infection occurs in 10-15% of these deliveries. [3, 4]

A systematic review of current published data concluded that among available interventions to further reduce postcesarean surgical site infections, azithromycin-based extended-spectrum prophylaxis (a single intravenous dose of azithromycin in addition to standard prophylaxis) might reduce the risk of postcesarean infection compared to standard cephalosporin alone.[5] In a randomized clinical trial of over 2000 women undergoing unscheduled and non-elective cesarean delivery, compared to placebo, we found that adding azithromycin to standard preincision prophylaxis reduced surgical site infection by 50% (12 versus 6.1%), with a relative risk (RR) of 0.51 and 95% confidence interval (CI) of 0.38 to 0.68; $p<0.001$.[6] In an effort to identify actionable prevention strategies for further clinical trials, the purpose of this secondary analysis was to identify maternal clinical risk factors for postcesarean maternal infection in the context of a trial of azithromycin-based extended spectrum antibiotic prophylaxis.

Materials and Methods

This is a planned secondary analysis of the Cesarean Section Optimal Antibiotic Prophylaxis trial (CT.gov NCT01235546), a double blind multicenter pragmatic randomized trial conducted at 9 clinical centers (14 sites) from 2011 to 2014. Each clinical site provided Institutional Review Board approval, and all participants gave written informed consent. An independent multidisciplinary Data Safety and Monitoring Board monitored the study throughout its implementation for performance and safety.

The details for the primary clinical trial have been published.[6] Briefly, women with a singleton pregnancy at ≥ 24 weeks of gestation who were undergoing a non-elective cesarean delivery (during labor, defined as ongoing contractions with documented cervical change, or at least 4 hours after membrane rupture) were eligible for randomization. Exclusion criteria were maternal medical complications precluding macrolide use; multiple gestation; known azithromycin or macrolide allergy; vaginal delivery; elective or scheduled cesarean prior to labor or membrane rupture; use of azithromycin, erythromycin or other macrolide antibiotic within 7 days of randomization; chorioamnionitis or other active bacterial infection at the time of randomization requiring antibiotic therapy, and fetal demise or known major congenital anomaly. Group B streptococci positive patients receiving intrapartum antibiotic prophylaxis for this indication were not excluded from participation.

Patients were assigned to receive standard antibiotic prophylaxis with cefazolin, given according to each study site's clinical practice, which was typically prior to incision and weight-adjusted. Patients with cephalosporin or severe penicillin allergy received the study site-specific alternative (typically clindamycin alone or clindamycin + gentamycin). Patients were randomized to either azithromycin (500mg) or identical placebo (saline). Study drug was intended to be given up to one-hour prior to skin incision, and infused over at least one hour. Clinical providers gave routine postcesarean care at each center. Study outcomes and other data were abstracted and entered by trained certified study staff.

The primary outcome for this secondary analysis is maternal puerperal infection: a composite of endometritis, wound infection (superficial or deep), or other infections (abdominopelvic abscess, maternal sepsis, pelvic septic thrombophlebitis) occurring up to 6 weeks postpartum. Endometritis was defined as the presence of two or more of the following signs with no other recognized cause: fever > 38° Centigrade (100.4° Fahrenheit), abdominal pain, uterine tenderness, or purulent drainage from uterus. Wound infection required the presence of either superficial or deep incisional surgical site infection characterized by cellulitis–erythema and induration around the incision or purulent discharge from the incision site with or without fever and included necrotizing fasciitis (wound hematoma, seroma, or breakdown alone in the absence of the preceding signs did not constitute infection). Abdominal or pelvic abscess required radiological or surgical confirmation of a purulent fluid collection.

Maternal characteristics examined included demographic, perinatal and surgical risk factors. These risk factors were collected accordingly: ethnicity was self-reported and then categorized as Hispanic, non-Hispanic Black, non-Hispanic White, or other. Body mass index, calculated by record maternal height and weight at delivery, was categorized according to the National Institute of Health/World Health Organization obesity classifications[7, 8]: body mass index < 25 kg/m^2 is underweight or normal weight, 25-29.9 kg/m^2 as overweight and ≥ 30 kg/m^2 as obese. Private pay was defined as private insurance versus those without or with government insurance. Additional maternal characteristics included maternal age at the time of screening, smoking status, primary cesarean delivery, group B streptococcus colonization status, diabetes status (further classified into pregestational and gestational diabetes), and steroid use for any reason during pregnancy. Additional perinatal characteristics included intrauterine pressure catheter use, induced labor

for any reason, and amnioinfusion. The duration of ruptured membranes was defined as the total number of hours between membrane rupture and infant delivery. Duration of rupture of membranes was further classified into 6 hours increments: ≤ 6 hours; >6-12 hours; >12-18 hours; >18-24 hours; and > 24 hours. Surgical duration was defined as time from skin incision to skin closure, and further categorized as based on quartiles, which corresponded to ≤ 38 minutes; >38-49 minutes; >49-60 minutes, and > 60 minutes.

Other surgical characteristics included skin incision (vertical or transverse), uterine incision (transverse versus non-transverse), and skin closure (staples and Dermabond [topical skin adhesive] versus sutures).

Maternal demographic, perinatal and surgical characteristics were evaluated individually using logistic regression modeling, controlling for randomization to azithromycin. Characteristics identified as statistically significant at a 0.05 level or by large effect size (odds ratio [OR], >1.5 or <0.7) were included as covariates in a multivariable logistic regression model. Interaction terms between azithromycin use and individual characteristics were evaluated for significance at the .05 level; if significant, the characteristic and its interaction term were included in the multivariable model. A parsimonious regression model was determined using backward selection, whereby statistically non-significant ($p>0.05$) characteristics were sequentially removed from the model. The characteristic with the largest p-value was eliminated in each iteration until reaching a final, reduced model where the remaining covariates were statistically significant at 0.05 level. SAS, version 9.2 (SAS Institute Inc, Cary, NC) was used for all statistical analysis.

Results

A total of 2,013 women (Table 1) were randomized to azithromycin (N=1019) or to placebo (N=994), of whom 177 (8.8%) were diagnosed with the composite outcome of maternal infection Maternal age, race–ethnicity, private pay, membrane rupture duration, surgery duration, intrauterine pressure catheter use, vertical skin incision, non-transverse uterine incision, induced labor, and staple skin closures were all significantly associated with maternal infection after controlling for azithromycin dosing at delivery (Table 2). Only staples and topical skin adhesive use had a significant interaction term, which was carried forward to the multivariable model.

In the final parsimonious logistic regression model (Table 2), maternal age, Black race–ethnicity, membrane rupture duration greater than 6 hours, surgery duration greater than 49 minutes, and non-transverse uterine incision remained as significant risk factors for maternal infection, even while controlling for azithromycin assignment. Azithromycin was protective against development of maternal infection.

Discussion

We identified maternal characteristics associated with postcesarean infection after adjusting for azithromycin extended-spectrum antibiotic prophylaxis. Specifically, Black race, duration of membrane rupture and duration of surgery were associated with increased maternal infection risk. Our findings demonstrate areas that should be studied in the future

to identify potentially modifiable risk factors remains critical for development of new prevention strategies for cesarean-associated puerperal infection.

Duration of membrane rupture[16, 17], increasing maternal body mass index[18-20], incision length and corticosteroid use[21] have been previously reported as a risk factor for postcesarean infection. Studies have reported inconsistent results on risk for maternal infection after classical compared to low-transverse uterine incisions.[22, 23] Consistent with prior studies, we found that the risk for postcesarean maternal infection was 1.9 to 3.4-fold higher as ROM increased beyond 6 hours, even after adjusting for azithromycin use. In our analysis neither incision type nor maternal obesity were independent risk factors for maternal infection.

Strengths of this secondary analysis are that the primary study was a large, double-blind multi-center randomized control trial implemented in multiple centers. Outcomes were centrally adjudicated limiting internal bias. A study limitation is that women undergoing a scheduled cesarean and those with chorioamnionitis were excluded in the parent trial; thus our findings cannot be extrapolated to these groups. In addition, we were not able to assess effect of surgical techniques (blunt versus sharp entry), surgeon experience, or type of skin disinfectant–antisepsis, as these data were not collected at the individual subject level.

Our findings of risk factors for postcesarean infection must be considered in the context of the patients enrolled in the trial. The majority of participating study sites were tertiary care training centers, and almost 50% of patients reported a BMI > 30 mg/kg^2. Thus, the risk factors for infection identified in this secondary analysis may not be generalizable to all U.S. women undergoing cesarean delivery. In addition, very few maternal infections occurred in women with a BMI < 25 mg/kg^2, which creates a wide confidence interval around the odds ratio for infection in this group.

Additional intraoperative doses of antibiotics, at intervals one or two times the half-life of the drug, are recommended to maintain adequate levels throughout the length of the procedure. [29, 30] Thus, a second dose cefazolin is recommended for surgeries greater than 3 hours.[29] However, these recommendations are not based on obstetric data. We found that the risk for maternal infection was higher despite extended spectrum prophylaxis with azithromycin for surgery duration greater than 49 minutes. Since the half-life of cefazolin is 1.8 hours and the increased plasma volume in pregnancy may result in lower drug concentrations, it may be reasonable to investigate earlier repeat dosing.

In conclusion, although extended spectrum prophylaxis as given in the primary study reduced postcesarean infections, black women, and those with ruptured membranes greater than 6 hours, or surgery duration greater than 49 minutes remained at significantly higher risk for infection. Further study and consideration is needed to determine whether alternative timing or dosing of antibiotics for patients with these risk factors can further reduce postcesarean infectious morbidity.

Acknowledgments

Supported by a grant (HD64729) from the NICHD; study medication (azithromycin) was provided by Pfizer through an investigator-initiated grant.

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Table 1

Maternal characteristics of women with and without postcesarean infection*

Maternal Characteristic	Maternal infection (n = 177)	No maternal infection (n = 1836)	P value
Azithromycin (n=1019)	60 (33.9%)	959 (52.2%)	<0.001
Years of Age, mean ± SD	26.6 ± 6.3	28.4 ± 6.3	0.001
Hispanic and Other	53 (29.9%)	570 (31.1%)	0.001
Black	81 (45.8%)	611 (33.3%)	
White	43 (24.3%)	655 (35.7%)	
Body mass index ≥ 30 kg/m^2	145 (81.9%)	1328 (73.3%)	0.020
Body mass index 25-30 kg/m^2	28 (15.8%)	410 (22.4%)	
Body mass index < 25 kg/m^2	4 (2.3%)	94 (5.1%)	
Private Pay	36 (20.7%)	593 (32.6%)	0.001
Pre-gestational diabetes	11 (6.2%)	72 (3.9%)	0.22
Gestational diabetes	14 (7.9%)	191 (10.4%)	
No diabetes	152 (85.9%)	1573 (85.7%)	
Smoker	22 (12.4%)	197 (10.7%)	0.49
Group B streptococci positive	36 (20.3%)	479 (26.1%)	0.09
Preterm < 37 weeks	19 (10.7%)	207 (11.3%)	0.83
Primary cesarean	144 (81.4%)	1379 (75.1%)	0.06
Intrauterine pressure catheter use	140 (79.1%)	1144 (62.3%)	<0.001
Non-transverse uterine incision	11 (6.3%)	70 (3.8%)	0.10
Vertical skin incision	13 (7.3%)	64 (3.5%)	0.011
Induced labor	116 (65.5%)	978 (53.4%)	0.002
Steroids for any reason	16 (9.0%)	145 (7.9%)	0.59
Steroids for lung maturity	12 (6.8%)	94 (5.1%)	0.35
Steroids for all other reasons	4 (2.3%)	56 (3.1%)	0.55
Amnioinfusion	29 (16.4%)	288 (15.7%)	0.81
Duration of membrane rupture			
≤ 6 hours	33 (18.6%)	608 (33.3%)	0.003
> 6 - 12 hours	60 (33.9%)	593 (32.5%)	
> 12 - 18 hours	43 (24.3%)	355 (19.5%)	
> 18 -24 hours	28 (15.8%)	164 (9.0%)	
> 24 hours	13 (7.3%)	105 (5.8%)	

Maternal Characteristic	Maternal infection (n = 177)	No maternal infection (n = 1836)	P value
Surgery Duration			
≤ 38 minutes	35 (19.9%)	520 (28.4%)	0.031
39 - 49 minutes	39 (22.2%)	449 (24.5%)	
> 49 - 60 minutes	50 (28.4%)	419 (22.9%)	
> 60 minutes	52 (29.6%)	445 (24.3%)	
Skin Closure			
Staples	79 (44.6%)	749 (40.8%)	0.32
Sutures/topical skin adhesive	98 (55.4%)	1087 (59.2%)	

*data presented as number (column %) except age

Table 2

Unadjusted and adjusted odds ratios (OR), 95% confidence intervals (CI) of maternal clinical factors for postcesarean maternal infection, n=2013

Maternal Characteristic	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Azithromycin assignment	0.5 (0.3-0.6)	0.4 (0.3-0.6)
Age, (years, mean ± SD)	0.95 (0.93-0.98)	0.95 (0.93-0.98)
Hispanic and Other	1.4 (0.9-2.1)	1.4 (0.9-2.2)
Black	2.0 (1.4-3.0)	1.9 (1.3-2.8)
White	Ref	Ref
Body Mass Index ≥ 30 kg/m^2	2.5 (0.9-6.9)	
Body Mass Index 25-30 kg/m^2	1.5 (0.5-4.5)	
Body Mass Index < 25 kg/m^2	Ref	-
Private Pay	0.5 (0.4-0.8)	-
Pregestational diabetes	1.6 (0.8-3.1)	
Gestational diabetes	0.7 (0.4-1.3)	
No diabetes	Ref	-
Smoker	1.1 (0.7-1.8)	-
Group B Streptococci colonization	0.7 (0.5-1.0)	-
Preterm delivery < 37 weeks	0.94 (0.57-1.6)	-
Primary cesarean	1.5 (0.97-2.1)	-
Intrauterine pressure catheter use	2.3 (1.6-3.3)	-
Nontransverse uterine incision	1.8 (0.9-3.4)	2.0 (1.03-4.0)
Vertical skin incision	2.1 (1.1-3.9)	-
Induced labor	1.6 (1.2-2.3)	-
Steroids for any reason	1.1 (0.7-2.0)	-
Steroids for lung maturity	1.4 (0.7-2.6)	-
Steroids for all other reasons	0.7 (0.2-1.9)	-
Amnioinfusion	1.0 (0.7-1.6)	-
Duration of membrane rupture		
≤ 6 hours	Ref	Ref
> 6 - 12 hours	1.9 (1.2-3.0)	1.9 (1.2-3.1)
> 12 - 18 hours	2.3 (1.4-3.7)	2.5 (1.5-4.1)

Maternal Characteristic	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
> 18 -24 hours	3.3 (2.0-5.7)	3.7 (2.1-6.4)
> 24 hours	2.4 (1.2-4.8)	2.7 (1.4-5.5)
Surgery Duration		
≤ 38 minutes	Ref	Ref
39 - 49 minutes	1.3 (0.8-2.2)	1.5 (0.9-2.5)
> 49 - 60 minutes	1.9 (1.2-2.9)	2.0 (1.3-3.2)
> 60 minutes	1.8 (1.2-2.9)	2.1 (1.3-3.4)
Skin Closure (significant interaction with treatment)		
For azithromycin group:		
Staples/topical skin adhesive	0.44 (0.3-0.8)	-
Sutures	Ref	
For placebo group:	1.48 (1.01-2.2)	
Staples/topical skin adhesive	Ref	-
Sutures		

*Adjusted for age, race/ethnicity, membrane rupture and surgery duration, non-transverse uterine incision, and assignment to azithromycin