

Timing of perioperative antibiotics for cesarean delivery: a metaanalysis

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OBJECTIVE: The purpose of this study was to summarize the available evidence on timing of perioperative antibiotics for cesarean delivery.

STUDY DESIGN: We searched the literature for studies that compare prophylactic antibiotics for cesarean delivery that are given before the procedure vs at cord clamping. Only randomized controlled trials were included.

RESULTS: Preoperative administration significantly reduced the risk of postpartum endometritis (relative risk [RR], 0.47; 95% CI, 0.26-0.85; $P = .012$) and total infectious morbidity (RR, 0.50; 95% CI, 0.33-0.78; $P = .002$). There was a trend toward lower risk of wound infection (RR, 0.60; 95% CI, 0.30-1.21; $P = .15$). Preoperative administration of

antibiotics did not significantly affect suspected neonatal sepsis that requires a workup (RR, 1; 95% CI, 0.70-1.42), proven sepsis (RR, 0.93; 95% CI, 0.45-1.96), or neonatal intensive care unit admissions (RR, 1.07 95% CI, 0.51-2.24). There was no significant heterogeneity between the randomized controlled trials.

CONCLUSION: There is strong evidence that antibiotic prophylaxis for cesarean delivery that is given before skin incision, rather than after cord clamping, decreases the incidence of postpartum endometritis and total infectious morbidities, without affecting neonatal outcomes.

Key words: antibiotics, cesarean delivery, endometritis, infectious morbidity

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Cesarean delivery is the most common surgical procedure performed in the United States, with rates that have been increasing continuously since the mid 1990s. The latest estimates from the Centers for Disease Control report a 31.1% rate of cesarean deliveries in 2006, with an estimate of 1.3 million surgeries performed.¹ Infectious morbidities, such as endometritis and wound infections, constitute most of the complications after cesarean delivery, and their rates vary depending on whether the surgery was scheduled or not.

Antibiotic prophylaxis in women who undergo cesarean delivery has been proven to be beneficial in decreasing infectious morbidities both in high-risk women (eg, laboring, after rupture of membranes)^{2,3} and low-risk patients (eg, nonlaboring, intact membranes).^{2,4,5} The 60-70% reduction in endometritis and the 30-65% reduction in wound infection rate prompted the Cochrane library to recommend prophylactic antibiotics to women who undergo both elective and nonelective cesarean delivery.² The goal of perioperative prophylaxis is to attain therapeutic levels of antibiotic agents in the tissues at the time of microbial contamination.⁶ Optimally, the agent of choice should also be long-acting, inexpensive and have a low incidence of side-effects.⁴ Most obstetricians use a single agent, commonly a cephalosporin, as the prophylactic antibiotic of choice.

In a study on clean or clean-contaminated elective surgeries, 1.4% in patients who received perioperative prophylactic antibiotics (ie, within 3 hours after skin incision) had wound infection vs 0.6% in patients who were given preoperative prophylactic antibiotics (ie, in the 2 hours before skin incision), thus a relative risk (RR) of 2.4 (95% CI, 0.9-7.9).⁷ A

single preoperative antibiotic dose is recommended in abdominal or vaginal hysterectomies.⁸ However, there is a lack of consensus regarding the timing of such prophylaxis in cesarean deliveries. The usual obstetric practice so far has been to give these antibiotics at cord clamping. The concern regarding the administration of antibiotics before cord clamping traditionally has been over unnecessary fetal exposure that might mask fetal infections and increase the need for sepsis workup in the newborn infants, in addition to selection of resistant strains, thus potential adverse effects on neonates. Some have noticed a shift in early neonatal sepsis from group B streptococci to *Escherichia coli* and other Gram-negative organisms, with even change in the resistance patterns of these organisms.^{4,9,10}

The objective of this metaanalysis was to review the current evidence concerning timing of prophylactic antibiotics during cesarean deliveries.

MATERIALS AND METHODS

A literature search was conducted in PubMed (National Institutes of Health, Bethesda MD; Jan. 1960-July 2007) to identify all published studies on prophylactic

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TABLE 1
Summary of eligible studies comparing timing of antibiotics

Reference	Primary outcome	Exclusion	Inclusion	Antibiotics used
Sullivan et al ¹⁷	Total infectious morbidity	Cephalosporin allergy, age <18 years, exposure to antibiotics within 1 week of delivery, emergency c/s	> 24 wks	Cefazolin
Wax et al ¹⁸	Endometritis or wound infection	allergy, antibiotic use within 2 wks, T > 37.8 °C in labor, GBS or SBE prophylaxis, IDDM, HIV, Chronic steroid use, multiple gestation.	Labor, singleton > 37 wks	Cefazolin
Thigpen et al ¹⁹	Infectious complications	Chorioamnionitis, allergy, cesarean without labor, antibiotics within 2 wks.	Active labor, singleton pregnancy	Cefazolin
Fejgin et al ¹⁵	Febrile morbidity		Afebrile patients, emergency CD	Cefonicid or ceftriaxone preop vs. cefazolin after cord clamp.
Cunningham et al ¹⁶	Uterine infection	Chorioamnionitis	Nulliparous, CD secondary to CPD > 6h after ROM.	Penicillin + gentamicin or cefamandole

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lactic antibiotics for cesarean delivery. Keywords included: *cesarean delivery*, *antibiotics*, *prophylactic antibiotics*, and *timing of antibiotics*. The AND operator was used to combine these terms in varying combinations. Bibliographies of all relevant eligible articles were reviewed for further potential references. The search was limited to data that were published in the English language. Only studies that compared timing of prophylactic antibiotics that were given at cord clamping vs preoperatively during cesarean delivery were selected for eligibility.

Studies were included if patients were assigned randomly to either treatment groups and if they included data on any of the following outcomes: endometritis, wound infection, febrile morbidity, neonatal sepsis, and neonatal intensive care unit admissions. Only randomized controlled trials (RCT) were included in the final statistical analysis. The primary outcome was rate of postpartum endometritis. Secondary outcomes that were analyzed included wound infection, a composite postpartum infectious morbidity (that includes the previous 2 outcomes and any other postpartum infection), suspected neonatal sepsis, proven neonatal sepsis, and neonatal intensive care unit (NICU) admission. In addition, a detailed description of the antibiotic regimen that was used and definitions of the outcomes were collected.

Statistical analysis

For each study, 2-way contingency tables were constructed to calculate the treatment effects that were expressed as RRs. Separate contingency tables were made for endometritis, wound infection, total infectious morbidity, neonatal sepsis, sepsis workup, and NICU admission, if the data were available in the same article. Treatment effects were first estimated for each trial and then combined by standard metaanalytic techniques. We used both the fixed effects Mantel-Haenszel model¹¹ and the random effects DerSimonian and Laird model¹² to pool RRs from individual trials and to estimate heterogeneity. Both models yield similar results, if no heterogeneity is present. Because the random effects model is the least conservative, we report the results from this model. To detect publication bias, tests that were referred by Begg and Mazumdar¹³ were carried out, and funnel plots were also created.¹⁴ All probability values are 2-sided, and probability values <.05 were considered statistically significant. Analyses were conducted with STATA statistical software (version 9; STATA Corporation, College Station, TX).

RESULTS

Of >280 studies regarding prophylactic antibiotics for cesarean delivery that were found through the literature re-

view, 5 studies included a comparison of timing of a single antibiotic prophylactic dose administration (3 RCTs and 2 non-randomized trials). The 3 RCTs were published between 1996 and 2007, and all used cefazolin as the antibiotic of choice. The study details, which included the antibiotic regimen, are summarized in Table 1. The study outcomes definitions were somewhat similar between the individual studies. In general, *endometritis* was defined as fever >100.4 °F on 2 occasions with uterine tenderness, purulent lochia, tachycardia or leukocytosis, and *wound infection* as purulent discharge, erythema, tenderness, and induration of the incision site.

The 2 nonrandomized studies are those of Fejgin et al¹⁵ and Cunningham et al.¹⁶ In 1993, Fejgin et al¹⁵ reported on 241 patients who underwent a non-scheduled cesarean delivery who received preoperative antibiotics (125 patients received cefonicid, and 116 patients received ceftriaxone) vs 194 patients who received 3 doses of cefazolin with the first dose that was given at cord clamping. The data on the first 2 groups were collected prospectively and then pooled together and compared with the data in the third group that was collected retrospectively. The third group who received antibiotics at cord clamp had a significantly higher body mass index and operative time. There was no difference

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