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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esarean 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. 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.

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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) and low-risk patients (eg, nonlaboring, intact membranes). 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. The goal of perioperative prophylaxis is to attain therapeutic levels of antibiotic agents at the tissues at the time of microbial contamination. Optionally, the agent of choice should also be long-acting, inexpensive and have a low incidence of side-effects. 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). A single preoperative antibiotic dose is recommended in abdominal or vaginal hysterectomies. 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.

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 prophy-
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 model and the random effects DerSimonian and Laird model 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 Mazumdar were carried out, and funnel plots were also created. 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 review, 5 studies included a comparison of timing of a single antibiotic prophylactic dose administration (3 RCTs and 2 nonrandomized 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 al and Cunningham et al. In 1993, Fejgin et al 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
in febrile morbidity (defined as oral temperature >38°C in 2 consecutive readings, excluding the first 24 hours). However, the duration of fever and the length of hospital stay were higher in the cord clamp group. There was no difference in the rate of endometritis, but higher rates of wound infection in the cord clamp group were found. No cases of neonatal sepsis were reported.

In 1983, Cunningham et al\textsuperscript{15} reported on 642 women who were at high risk for infection when they underwent cesarean delivery for cephalopelvic disproportion after 6 hours of rupture of membranes. Three hundred five women were given 3 doses of perioperative antibiotics (115 women received penicillin plus gentamicin, and 190 women received cefamandole). Two hundred fifty-five patients received their first dose 10-90 minutes before cord clamp, and 50 patients received their first dose within 90 minutes of cord clamp. There was no difference in the rate of uterine infection. There was a higher rate of “sepsis workup” in infants who were exposed to antibiotics in utero, but there was no difference in documented sepsis.

In the 3 RCTs, 377 women received antibiotics preoperatively, and 372 women received it at cord clamping. This resulted in 387 infants whose mothers received antibiotics preoperatively, and 384 infants whose mothers received antibiotics at cord clamping.

Preoperative administration was associated with 53% overall reduction in the risk of postpartum endometritis (RR, 0.47; 95% CI, 0.26-0.85; \( P = .012\); Figure

<table>
<thead>
<tr>
<th>Study</th>
<th>Endometritis</th>
<th>Cord clamping</th>
<th>Wound infection</th>
<th>Cord clamping</th>
<th>Total infectious morbidity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Cord clamping</td>
<td>Preoperative</td>
<td>Cord clamping</td>
<td>Preoperative</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Sullivan et al\textsuperscript{17}</td>
<td>2 (1%)</td>
<td>10 (5%)</td>
<td>5 (3%)</td>
<td>10 (5%)</td>
<td>8 (4.5%) (1 pneumonia)</td>
</tr>
<tr>
<td>Wax et al\textsuperscript{18}</td>
<td>1 (2%)</td>
<td>1 (2.4%)</td>
<td>1 (2%) (same patient with endometritis)</td>
<td>2 (4.9%)</td>
<td>1 (2%) (1 pyelonephritis)</td>
</tr>
<tr>
<td>Thigpen et al\textsuperscript{19}</td>
<td>12 (7.8%)</td>
<td>22 (14.8%)</td>
<td>6 (3.9%)</td>
<td>8 (5.4%)</td>
<td>18 (11.8%) (1 pyelonephritis)</td>
</tr>
<tr>
<td>number of cases/patients</td>
<td>15/377</td>
<td>33/372</td>
<td>12/377</td>
<td>20/372</td>
<td>27/377 (1 pneumonia)</td>
</tr>
</tbody>
</table>

1, A) and 50% reduction in the risk of total infectious morbidity (RR, 0.50; 95% CI, 0.33-0.78; \( P = .002 \); Figure 1, B). There was a trend toward a lower risk of wound infection (RR, 0.60; 95% CI, 0.30-1.21; \( P = .151 \); Figure 1, C; Table 2).

Preoperative administration of antibiotic did not significantly affect proven sepsis (RR, 0.93; 95% CI, 0.45-1.96; \( P = .86 \); Figure 2, A), suspected sepsis that required workup (RR, 1; 95% CI, 0.71-1.42; \( P = .99 \); Figure 2, B), or NICU admissions (RR, 1.07 95% CI, 0.51-2.24; \( P = .86 \); Figure 2, C; Table 3).

There was no significant heterogeneity between the RCTs. Begg’s test that was conducted for each of the outcomes (endometritis, wound infection, total infectious morbidity, and sepsis workup) did not reveal any publication bias (probability values were between 0.396 and 0.856). The funnel plots were also symmetric (Figure 3). When the nonrandomized studies were included, the benefit of preoperative antibiotics was attenuated, but the degree of heterogeneity was increased significantly.

All 3 RCTs, on the whole, had adequate allocation concealment. All of the RCTs had a central randomization process: Two trials were randomized by the pharmacy personnel (Sullivan et al\(^{17}\) and Thigpen et al\(^{18}\)), and the third trial (Wax et al\(^{19}\)) had a computer generated randomization. Details on the method of randomization were stated clearly in all 3 trials, and allocation concealment could be ensured.

**Comment**

A single dose of antibiotic that is administered after cord clamping has been the traditionally recommended prophylaxis for patients who undergo cesarean deliveries for both elective and nonelective indications.\(^2,4\) This was the result of multiple studies that showed that antibiotic prophylaxis reduces the risk of endometritis, compared placebo after cesarean delivery,\(^{20,21}\) and that single dose is as effective as multiple doses of perioperative antibiotics.\(^{22-25}\) In 1961, Burke\(^6\) demonstrated in an animal model that antibiotics that are given before contamination of the wound decrease the rate of infection. This led to the use of preoperative prophylactic antibiotics in almost all

**TABLE 3**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Neontal sepsis</th>
<th>Sepsis workup</th>
<th>NICU admission</th>
</tr>
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<tbody>
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<td></td>
<td>Preoperative (n)</td>
<td>Cord clamping (n)</td>
<td>Preoperative (n)</td>
</tr>
<tr>
<td>Sullivan et al(^{17}) (before procedure, 185; at cord clamping, 194)</td>
<td>6 (3%)</td>
<td>7 (3.6%)</td>
<td>35 (19%)</td>
</tr>
<tr>
<td>Wax et al(^{19}) (before procedure, 49; at cord clamping, 149)</td>
<td>0</td>
<td>0</td>
<td>6 (12.2%)</td>
</tr>
<tr>
<td>Thigpen et al(^{18}) (before procedure, 153; at cord clamping, 149)</td>
<td>7 (4.6%)</td>
<td>7 (4.7%)</td>
<td>11 (7.2%)</td>
</tr>
</tbody>
</table>

**Figure 3**

Begg’s funnel plot

A. Endometritis, B. wound infection, C. total infectious morbidity, and D. sepsis workup with pseudo 95% confidence limits.

s.e. of \( \log \text{RR} \) = standard error of log of RR.

surgteries that require prophylaxis. Theoretic concerns over newborn infant exposure to antibiotics pushed the obstetric community to use prophylactic antibiotics after cord clamping. Ampicillin reaches its group B streptococcus bactericidal concentrations in cord blood within 5 minutes of administration to the mother.26 Cefazolin, on the other hand, has been shown to reach its minimal inhibitory concentration for group B streptococcus in the fetal blood within 30 minutes of administration.27 Because this therapeutic drug level in the newborn infant may alter sepsis workup and potentially affect treatment, practitioners have elected to give the antibiotics after cord clamping. In addition, there was a concern that the potential selection of resistant organisms in the neonate and alteration of maternal and neonatal flora might lead to worse neonatal outcomes.10

This metaanalysis provides strong evidence that antibiotic prophylaxis for cesarean delivery that is given before skin incision, rather than after cord clamping, significantly decreases the incidence of postpartum endometritis and total infectious morbidity, without affecting neonatal outcomes. The rates of wound infection, although lower in the preparative group, did not reach statistical significance.

The National Nosocomial Infections Surveillance system reported a surgical site infection rate of 3.35% for cesarean delivery that was performed in 2000 in the absence of risk factors for infection.28 The rate of surgical site infection after a high-risk cesarean delivery was 8.11%. These rates were higher than infection rates after other surgical procedures that were collected as part of the National Nosocomial Infections Surveillance system. Given the number of operative deliveries that were performed, these rates translate into a large number of women with an infectious complication after delivery, which leads to a significant increase in cost and morbidity. One of the reasons that these rates are high, compared with other surgical procedures, may be due to the timing of prophylactic antibiotic. In fact, in a recent retrospective cohort study of 2798 term singleton cesarean deliveries from a single institution, a change of timing of prophylactic antibiotics to preoperative, rather than at cord clamping, resulted in a 60% decrease in the overall rate of surgical site infection, a 50% decrease in the rate of endometritis, and an 80% reduction in the rate of cellulitis.29

The 3 RCTs that were included in this metaanalysis had sample size calculations based on 80% power to detect a 25-50% reduction in infectious morbidity after cesarean delivery. In the study by Thigpen et al,19 the sample size was calculated after an interim analysis that showed a 50% higher than expected infection rate in both groups. This led to a smaller sample size requirement. By choosing a composite score of total infectious morbidity rather than individual infectious morbidity after cesarean delivery, a smaller sample size usually is required. However, this approach may not allow conclusions about individual outcomes to be made.

In 2 trials,18,19 only laboring women were included, whereas the study by Sullivan et al17 included both laboring and nonlaboring patients. Moreover, there was no information given on antibiotic administration for group B streptococcus prophylaxis in 2 studies,17,19 whereas group B streptococcus prophylaxis was used similarly in both groups in the study by Thigpen et al.18 Cefazolin was the antibiotic that was used in the 3 RCTs that were included in the study. It has a half-life of 1.8 hours and has been proved in a large retrospective study of 2200 patients to be effective equally to cefoxitin but 80% less expensive.30

Although this metaanalysis favors single-agent preoperative antibiotics prophylaxis, recent data suggest that the addition of azithromycin to the standard narrow-spectrum single-agent cephalosporin prophylaxis reduced the rates of endometritis and surgical wound infections after cesarean delivery.31 A large randomized trial with sufficient power to calculate differences in individual outcomes (eg, endometritis, wound infection, neonatal sepsis) with a long follow-up period is needed. Until then, individual labor and delivery suites must address the issue with their respective infection control committee and neonatology department to establish a policy that will preserve the safety of the mother and infant without increasing the cost of neonatal care.

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