A comparison of 3 antibiotic regimens for prevention of postcesarean endometritis: an historical cohort study

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BACKGROUND: Prophylactic antibiotics are of proven value in decreasing the frequency of postcesarean endometritis. The beneficial effect of prophylaxis is enhanced when the antibiotics are administered before the surgical incision as opposed to after the clamping of the umbilical cord. However, the optimal antibiotic regimen for prophylaxis has not been established firmly.

OBJECTIVE: The purpose of this study was to compare 3 different antibiotic regimens for the prevention of postcesarean endometritis.

STUDY DESIGN: This retrospective historical cohort study was conducted at the University of Florida, which is a tertiary care facility that serves a predominantly indigent patient population. In the period January 2003 to December 2007, our standard prophylactic antibiotic regimen for all women who had cesarean delivery was cefazolin (1 g) administered immediately after the baby's umbilical cord was clamped. In November 2008, we began to administer the combined regimen of cefazolin (1 g intravenously) plus azithromycin (500 mg intravenously); both were given 30-60 minutes before the skin incision. In the period of January-December 2014, we continued the dual agent regimen but based the dose of cefazolin on the patient's body mass index: 2 g intravenously if the body mass index was <30 kg/m^2 and 3 g if the body mass index was >30 kg/m^2. The surgical technique was consistent throughout all 3 time periods. Our primary endpoint was the frequency of endometritis in each time period. This diagnosis was based on fever $\geq 37.5^{\circ}$C, lower abdominal pain and tenderness, the exclusion of other localizing signs of infection, and the requirement for administration of therapeutic antibiotics. In the first year after beginning the new antibiotic regimen, we also monitored the frequency of neonatal sepsis evaluations and compared it with the frequency that was recorded during the year immediately preceding the change in antibiotic regimens.

RESULTS: During the entire period 2003-2014, 29,633 women delivered at our institution; 6455 women (22%) had a cesarean delivery. In the period January 2003 to December 2007, 1034 women had a primary or repeat cesarean delivery. One hundred seventy women (16.4%; 95% confidence interval, 14.4—18.4%) developed endometritis. In the period November 2008 to December 2013, 4484 women had a primary or repeat cesarean delivery. Fifty-nine patients (1.3%; 95% confidence interval, 1.0—1.7%) developed endometritis ($P < .0001$ compared with period 1). In the year 2014, 937 women had a cesarean delivery; 22 of them (2.3%, 95% confidence interval, 1.3—3.3%) developed endometritis ($P < .0001$ compared with period 1 and $P > .5$ and $< .10$ compared with period 2). The frequency of evaluations for suspected neonatal sepsis in infants who were delivered to mothers who had cesarean delivery was 17.6% in the period January to December 2007 and 19.3% in the period November 2008 to November 2009 (relative risk, 1.1; 95% confidence interval, 0.7—1.9). One infant had proven sepsis in the former period; 2 infants had proven sepsis in the latter period (not significant).

CONCLUSIONS: When administered before skin incision, the combination of cefazolin plus azithromycin was significantly more effective in the prevention of endometritis than the administration of cefazolin after cord clamping; the rate of endometritis was reduced to a very low level without increasing the rate of neonatal sepsis evaluations.

Key words: antibiotic, endometritis

As noted in the recent systematic review by Tita et al,[1] multiple publications have demonstrated conclusively that prophylactic antibiotics reduce the frequency of endometritis after unscheduled cesarean delivery. The report by Dinsmoor et al[2] confirmed that prophylaxis was also effective in reducing the frequency of endometritis in patients who had a scheduled cesarean delivery in the absence of labor. Recent reports have also confirmed that the preoperative administration of antibiotics is superior to the administration of antibiotics after the umbilical cord is clamped and have shown that the concern that preoperative administration would increase the number of infants who experienced proven sepsis or who required evaluations for suspected sepsis was unfounded.[3-5]

What is not so clear is the optimal antibiotic regimen to administer. Before 2008, the standard of care was to use a limited-spectrum cephalosporin, such as cefazolin, for prophylaxis.[1] In that year, 2 reports by Tita et al[6,7] demonstrated that combining cefazolin with azithromycin provided additional benefit in the reduction of the risk of both endometritis and surgical wound infection (incisional abscess and cellulitis). In these latter reports, the authors administered both drugs after the baby's umbilical cord was clamped. When we adopted this 2-drug regimen as our standard of care in 2008, we administered the drugs preoperatively. The objective of our present study was to compare the efficacy of this preoperative 2-drug regimen with our previous experience with single-dose cefazolin that was administered after cord-clamping.

Materials and Methods

This retrospective historical cohort study was conducted at the University of Florida, which is a tertiary care facility that serves a predominantly indigent patient population in the rural north central portion of the state. Approximately 80% of our obstetric patients are insured under the Florida Medicaid

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Program. Approximately 70% of the patients are white, 20% Hispanic, and 10% African American.

In the period January 2003 to December 2007, our prophylactic antibiotic regimen for all women who had cesarean delivery was cefazolin (1 g) administered intravenously, immediately after the baby's umbilical cord was clamped. This regimen was based on previous reports by Carlson and Duff[8] and Duff.[9] In November 2008, we formally implemented the combined regimen of cefazolin (1 g intravenously) plus azithromycin (500 mg intravenously) before skin incision. Cefazolin was administered as a bolus infusion within 1 hour of the start of surgery. Azithromycin was administered as a continuous infusion over 30-60 minutes before surgery. We based the decision to use 2 drugs on the reports of Tita et al[6,7] and the decision to administer the drugs preoperatively on the reports by Sullivan et al,[3] Constantine et al,[4] and Owens et al.[5] During the period January 1 to December 31, 2014, we kept the dose of azithromycin the same but modified the dose of cefazolin based on the patient's body mass index: 2 g intravenously if the body mass index was <30 kg/m^2 and 3 g intravenously if the body mass index was >30 kg/m^2. We based this decision on the report by Pevzner et al[10] who showed that, in obese and extremely obese patients, even a 2-g dose of cefazolin frequently failed to achieve therapeutic adipose tissue concentrations against Gram-negative bacilli at the time of skin incision and skin closure.

The small number of patients who had a well-documented history of an immediate hypersensitivity reaction to beta-lactam antibiotics (<2% of patients) received a single dose of clindamycin (900 mg intravenously) plus gentamicin (80 mg intravenously), both of which were administered as rapid infusions 30-60 minutes before surgery. The choice of this regimen was based on an earlier study by Gibbs and Weinstein[11] and on empiric considerations of trying to provide coverage against a reasonably broad spectrum of microorganisms, which included aerobic Gram-positive cocci (clindamycin), aerobic Gram-negative bacilli (gentamicin), and anaerobes (clindamycin).

Patients who had chorioamnionitis were the only patients specifically excluded from the study. Chorioamnionitis was diagnosed with the criteria of Gibbs and Duff[12]: temperature $\geq$37.8°C plus $\geq$2 of the following events: maternal tachycardia, fetal tachycardia, uterine tenderness, foul odor of the amniotic fluid, or maternal leukocytosis. Patients with chorioamnionitis were treated intrapartum with therapeutic antibiotics, usually ampicillin plus gentamicin. If they required cesarean delivery, they also received either clindamycin or metronidazole postoperatively in accordance with the recommendations of Edwards and Duff .[13]

All procedures were performed by resident physicians who were assisted by faculty members or by faculty members themselves. Surgical technique was relatively consistent throughout the 3 time periods.[14] The hair in the incision line was clipped, rather than shaved, just before the start of surgery, and chlorhexidine was used to wash the skin. Most procedures were performed through a transverse abdominal incision. With very few exceptions, all the uterine incisions were low transverse. Whenever possible, the placenta was extracted by exerting traction on the umbilical cord.[15] The uterus was usually closed in 2 layers with continuous sutures of 0-Vicryl (polyglactin 910, Ethicon, Somerville, NJ). The visceral and parietal peritoneums were not closed routinely. The fascia was closed with 1 or 2 continuous sutures of 0-Vicryl, and the deep subcutaneous layer was closed with a single continuous suture of 3-0 Vicryl if this layer was >2 cm in thickness. In most cases the skin was reapproximated with a single continuous subcuticular suture of 3-0 Monocryl (poliglecaprone, Ethicon, Somerville, NJ) or 4-0 Vicryl. The remaining patients had skin closure with stainless steel staples.

Our primary endpoint was the frequency of endometritis. The diagnosis of endometritis was based on the clinical findings of fever >37.5°C, tachycardia, and uterine pain and tenderness in the absence of any other localizing sign of infection.[16] A peripheral white blood cell count >15,000/mm^3 was considered corroborating evidence of endometritis but was not required absolutely to make the diagnosis. In the opinion of the attending physician, all patients had an indication for therapeutic antibiotics and usually were treated with clindamycin plus gentamicin.

Uninfected patients were discharged routinely on the second postoperative day. Patients with endometritis were treated with parenteral antibiotics until they were afebrile and asymptomatic for 24 hours. They usually were discharged on the fourth postoperative day.

During the period November 2008 through November 2009, we also monitored the frequency of sepsis evaluations in neonates who were delivered to mothers who had cesarean delivery to be certain that preoperative administration of antibiotics was not affecting the care of the neonates adversely. We compared the frequency of sepsis evaluations in this period to the frequency in the year immediately preceding the adoption of the new prophylaxis regimen. Sepsis was suspected if an infant demonstrated respiratory distress, lethargy, poor feeding, poor tone, hemodynamic instability, or thermal instability (temperature, <36°C or >38°C). The neonate then had the following laboratory tests: complete blood count; C-reactive protein; immature-to-total neutrophil ratio; blood, urine, and cerebrospinal fluid culture; and a chest x-ray. The diagnosis of proven sepsis required a positive culture or abnormal chest x-ray.

Deidentified data for the first time period were obtained from the department's computerized perinatal data base that included information about neonatal sepsis evaluations. Data for the second and third time periods were obtained from our electronic medical record research functionality. The investigation was conducted under an exempt protocol that was approved by the Institutional Review Board.

We used the uncorrected chi-square test to assess differences in the frequency of endometritis between the groups. A probability value of <.05 was considered statistically significant.