Effects of Maternal Obesity on Tissue Concentrations of Prophylactic Cefazolin During Cesarean Delivery

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OBJECTIVE: To estimate the adequacy of antimicrobial activity of preoperative antibiotics at the time of cesarean delivery as a function of maternal obesity.

METHODS: Twenty-nine patients scheduled for cesarean delivery were stratified according to body mass index (BMI) category, with 10 study participants classified as lean (BMI less than 30), 10 as obese (BMI 30–39.9), and nine as extremely obese (BMI 40 or higher). All patients were given a dose of 2 g cefazolin 30–60 minutes before skin incision. Antibiotic concentrations from adipose samples, collected after skin incision and before skin closure, along with myometrial and serum samples, were analyzed with microbiological agar diffusion assay.

RESULTS: Cefazolin concentrations within adipose tissue obtained at skin incision were inversely proportional to maternal BMI ($r = -0.67$, $P < .001$). The mean adipose concentration was 9.4 plus or minus 2.7 micrograms/g in the lean group of women compared with 6.4 plus or minus 2.3 micrograms/g in the obese group ($P = .009$) and 4.4 plus or minus 1.2 micrograms/g in the extremely obese group ($P < .001$). Although all specimens demonstrated therapeutic cefazolin levels for gram-positive cocci (greater than 1 microgram/g), a considerable portion of obese and extremely obese did not achieve minimal inhibitory concentrations of greater than 4 micrograms/g for Gram-negative rods in adipose samples at skin incision (20% and 33.3%, respectively) or closure (20.0% and 44.4%, respectively). No significant difference in cefazolin concentration was observed in mean closure adipose, myometrial, or serum specimens across the BMI categories.

CONCLUSION: Pharmacokinetic analysis suggests that present antibiotic prophylaxis dosing may fail to provide adequate antimicrobial coverage in obese patients during cesarean delivery.

Patients who develop surgical infections are 60% more likely to spend time in an intensive care unit and five times more likely to be readmitted to the hospital, and are likely to have twice the mortality rate of patients without infections.[1] Perioperative antimicrobial prophylaxis has been shown to reduce the probability of postoperative surgical site infections.[2] The derived effectiveness of antimicrobial prophylaxis must incorporate three basic principles: the agent selected must cover the spectrum of anticipated microbial contamination at the surgical locus, the agent must be given in a timely fashion such that tissue concentration in the wound (tissue) exceeds the minimum inhibitory concentration of potential microbial pathogens, and a sufficient therapeutic concentration of the antimicrobial agents should persist in the tissues for the duration of the operative procedure.

The majority of information regarding pharmacokinetics and pharmacodynamics of antibiotics is based on measurements of the serum and plasma concentrations. Despite implementation of guidelines for surgical prophylaxis that have confirmed thera-

peutic antimicrobial serum levels, surgical site infections remain the most common postoperative complication, affecting up to 20% of patients undergoing intra-abdominal surgery.[3] Previous pharmacokinetic studies have demonstrated that inadequate antibiotic penetration into the tissues of the surgical site, despite therapeutic serum levels, results in an environment that is susceptible to pathogens and infection.[4] Antimicrobial tissue levels are influenced by volume of distribution, regional blood flow, and selected tissue compartment. Obesity, along with pregnancy, increases volume of distribution, thereby resulting in a greater dilution of antibiotics when compared with nonobese, nonpregnant individuals. Moreover, this change in volume of distribution is achieved primarily by increasing the relative amount of poorly perfused adipose tissue.[4]

The rate of obesity in the United States has shown a steady increase and has more than doubled in the past 25 years from 15% in 1980 to 32.9% in 2004. Moreover, nearly one-third of women of reproductive age are obese and approximately 6% are extremely obese.[5] In addition to the usual health-related concerns, obesity significantly increases the rate of pregnancy-related complications including cesarean delivery.[6] With nearly 1.2 million cesarean deliveries performed in the United States annually, the associated surgical site infections, with rates ranging from 7% to 20%, contribute significantly to maternal morbidity, mortality, and overall health care costs.[7]

Despite these alarming trends, there is a paucity of data regarding antimicrobial activity of prophylactic antibiotics in tissues and the effects of maternal obesity on these concentrations at the time of cesarean delivery. The objective of this study was to estimate the adequacy of antimicrobial activity of preoperative antibiotics at the time of cesarean delivery as a function of maternal obesity.

MATERIALS AND METHODS

This descriptive study with prospective collection of samples and data was conducted at University of California, Irvine and Long Beach Memorial Medical Center using a protocol that was reviewed and approved by the local Institutional Review Board. All participants were informed and provided written consent before participation in the study.

Individuals scheduled for cesarean delivery at term (more than 37 completed weeks of gestation) under nonemergent circumstances were eligible for participation in study. Participants were excluded in cases of known cephalosporin allergy, exposure to antibiotics within 7 days before the cesarean delivery,

need for emergent delivery, active labor, multiple gestations, suspected chorioamnionitis, and medical complications that could theoretically result in microvascular disease, which could potentially affect the pharmacokinetics and pharmacodynamics of prophylactic antibiotics. These included chronic hypertension, pregestational diabetes, and collagen vascular disease.

Maternal height and weight were collected at the time of admission to labor and delivery and used to derive the body mass index (BMI, calculated as weight (kg)/[height (m)]^2) for each participant. Maternal BMI was classified based on the World Health Organization (WHO) categories.[8] Given difficulty of finding women who at full term of pregnancy meet the criteria for "normal range" BMI (18.5–24.9), meaningful comparison could not be performed using this category as the reference group. Instead these participants were combined with the overweight (BMI 25.0–29.9) category and collectively referred to as lean or BMI less than 30. Tissue concentrations of these participants were then compared with those of obese (BMI 30–39.9) and extremely obese (BMI 40 or more) participants.

Two grams of cefazolin was parenterally administered to all study participants at least 30 minutes before but no more than 60 minutes before skin incision. At the time of cesarean delivery two samples of adipose tissue and one sample of myometrial tissue were collected in standard fashion. The first adipose sample (initial adipose) was collected after skin incision before incision of the fascia, and the second sample (closing adipose) was collected at the end of the case after the fascia was closed. A full-thickness sample of the myometrium was obtained from the superior edge of the uterine incision after delivery of the fetus. In addition, maternal blood sample was collected in the operating room after completion of the case.

Maternal blood samples were allowed to clot and centrifuged for 10 minutes at 1,500 rpm (approximately 6,000 g). Serum and tissue specimens were stored at −80°C before transport to the Surgical Microbiology Research Laboratory (Medical College of Wisconsin), where samples were processed according to previously described protocol.[9] A cefazolin microbiologic plate assay was performed by dispensing (in triplicate) 20 micrograms of serum and tissue homogenate into well cut in Antibiotic Medium #1 seeded with *Streptococcus sanguis* reference stain A597–9, on 243×243×43 mm^3 assay plates. The assay plates were incubated at 37°C for 24 hours and zones of inhibitions were measured in millimeters.

Calibration (cefazolin) standards were prepared daily in human serum, ranging from 0.25 to 128 micrograms/mL. The coefficient of linearity ranged from 0.993 to 0.997. The between-assay variation for internal controls was less than 5%.

Calculations for a priori power analysis were limited by the fact that there have been no previous investigations into tissue concentrations of cefazolin in the obstetric population. However, based on previous research involving gastric bypass patients and published linear fit calculations,[9,10] mean initial adipose concentration in the BMI 40 or greater group was estimated at 4.5 plus or minus 1.6 micrograms/g, with a difference of 1.2 micrograms/g in BMI group–specific means, alpha of 0.05 and power of 0.8. Based on these calculations, it was estimated that 10 participants in each BMI category would be sufficient to demonstrate a significant difference in initial adipose concentrations of cefazolin. Post hoc power analysis was performed and demonstrated that with significance level set at 0.05 there was 99% power to detect a statistical difference with 29 patients who were enrolled in the study.

Statistical analyses were performed using JMP 8.0 statistical software, and all tests were conducted at the 0.05 significance level. The Dunnett test was used to test differences in means from the three BMI categories with the BMI less than 30 group as the control mean. Normality of continuous data were assessed by the Shapiro-Wilk test. Continuous data that were not normally distributed were compared with the Kruskal-Wallis rank-sum test. Categorical variables were evaluated using the Fisher exact test.

RESULTS

Out of 38 individuals who were approached, 31 agreed to participate and were enrolled in the trial between July 2009 and July 2010. Two women were excluded from the study before collection of all tissue and serum specimens. One participants in the BMI 30–39.9 group required intraoperative blood transfusion and an additional dose of cefazolin, and one participant in the BMI 40 or greater group experienced a delay of more than 60 minutes from administration of cefazolin until surgery start time secondary to anesthetic complications. Demographic data for the 29 patients who completed the study protocol are presented in Table 1. Aside from weight-dependent variables (eg, maternal weight, BMI, and body surface area), there were no significant differences in baseline characteristics of study participants. Operative parameters, including duration of surgery, time from antibiotic administration to skin incision, estimated blood loss, and intraoperative fluid administration were similar between the study groups.

Table 2 demonstrates the mean serum and tissue concentrations of cefazolin in adipose and myometrial samples. The mean concentrations from initial adipose specimens were considerably higher in lean participants (9.4 plus or minus 2.7 micrograms/g) than either obese (6.4 plus or minus 2.3 micrograms/g, P=.009) or extremely obese women (4.4 plus or minus 1.2 micrograms/g, P<.001) (Figs. 1 and 2). All 10 participants with BMI less than 30 achieved concentrations above 4 micrograms/g, the theoretic breakpoint for resistance to cefazolin.[11] However, the

Table 1. Demographics and Baseline Characteristics

Characteristics	BMI Less Than 30 (n=10)	BMI 30–39.9 (n=10)	BMI 40 or Greater (n=9)	P
Maternal age (y)	28.3±5.6	32.8±7.1	28.1±4.6	.28
Race or ethnicity				.88
White	3 (30.0)	3 (30.0)	3 (33.3)	
African American	3 (30.0)	1 (10.0)	2 (22.2)	
Hispanic	3 (30.0)	5 (50.0)	4 (44.4)	
Asian	1 (10.0)	1 (10.0)	0	
Gestational age (d)	272.5±4.5	271.5±3.5	273.7±3.4	.22
Height (cm)	156.9±7.04	162.2±4.6	165.3±8.5	.1
Weight (kg)	65.7±4.8	90.0±10.8	121.8±16.1	<.001
Body mass index (kg/m²)	26.7±1.3	34.1±2.6	44.5±4.5	<.001
Body surface area (m²)	1.69±0.1	2.01±0.1	2.36±0.2	<.001
Previous cesarean delivery	8 (80.0)	9 (90.0)	8 (88.9)	.78
Preoperative hemoglobin (g/dL)	12.1±1.2	12.3±1.6	11.6±1.2	.42
Operative time (min)	60.9±14.1	56.8±21.5	56.2±11.6	.67
Estimated blood loss (mL)	800±216	790±166	805±101	.49
Fluid administration (mL)	2,330±343	2,250±327	2,200±346	.65

BMI, body mass index.
Data are mean±standard deviation or n (%) unless otherwise specified.

Table 2. Tissue and Serum Concentrations of Cefazolin

Outcome	BMI Less Than 30 (n=10)	BMI 30–39.9 (n=10)	P	BMI 40 or Greater (n=9)	P*
Adipose after skin incision (micrograms/g)	9.37±2.7	6.37±2.3	.009	4.35±1.2	<.001
Adipose before skin closure (micrograms/g)	9.07±6.4	6.61±3.5	.360	4.70±1.5	.070
Differences in adipose concentrations	−0.30±5.2	0.23±3.2	.930	0.35±0.8	.900
Myometrium (micrograms/g)	20.62±12.1	18.09±15.9	.860	13.22±6.7	.340
Serum (micrograms/mL)	65.20±30.0	54.9±41.3	.700	49.94±20.7	.490
Patients with initial or closing adipose concentration less than 4 micrograms/g	0/10	4/10	.090	4/9	.080

BMI, body mass index.
Data are mean±standard deviation or n (%) unless otherwise specified.
* Compared with BMI less than 30 group.

initial adipose samples from 2 of 10 (20%) obese and three of nine (33.3%) extremely obese participants demonstrated cefazolin concentrations below 4 micrograms/g (P=.29 and P=.14, respectively). Samples obtained before skin closure demonstrated similar mean cefazolin concentrations to those collected at the beginning of the procedure within individual BMI categories. Lean participants once again had higher mean concentration at closure (9.1 plus or minus 6.4 micrograms/g) than either obese (6.6 plus or minus 3.5 micrograms/g, P=.36) or extremely obese participants (4.7 plus or minus 1.5 micrograms/g, P=.07). All participants in the lean group had cefazolin levels above 4 micrograms/g at closure, compared with only 8 of 10 (80%) in the BMI 30–39.9 group and five of nine (55.5%) in the BMI 40 or greater group. In all, there were eight participants who did not exceed the resistance point (4 micrograms/g) on either initial or closing adipose samples. Four of these participants

belonged to the BMI 30–39.9 group and the other four to the BMI 40 or greater group. Compared with women whose samples showed therapeutic levels throughout the procedure, these participants were more likely to have higher BMI (39.7 compared with 32.9, P=.02).

Although myometrial and serum samples confirmed a similar trend in mean concentrations of cefazolin, these results were not statistically significant across BMI categories (Fig. 3). Furthermore, cefazolin tissue levels in all myometrial and serum specimens exceeded minimum inhibitory concentration for most potential wound pathogens (Table 2).

Regression analysis of initial adipose concentration of cefazolin demonstrated stronger correlation (r=−0.67, P<.001) with participant BMI (Fig. 4) compared with other weight-based models. Nevertheless, participant weight, body surface area, and dosing
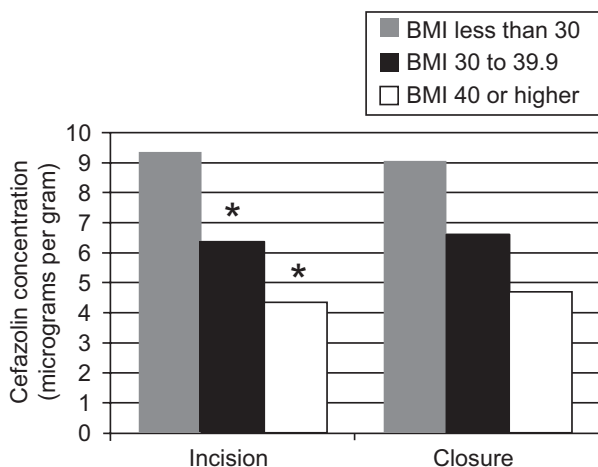

Fig. 1. Comparison of cefazolin concentrations (micrograms per gram) from initial and final adipose samples and body mass index (BMI) categories. *P<.05.

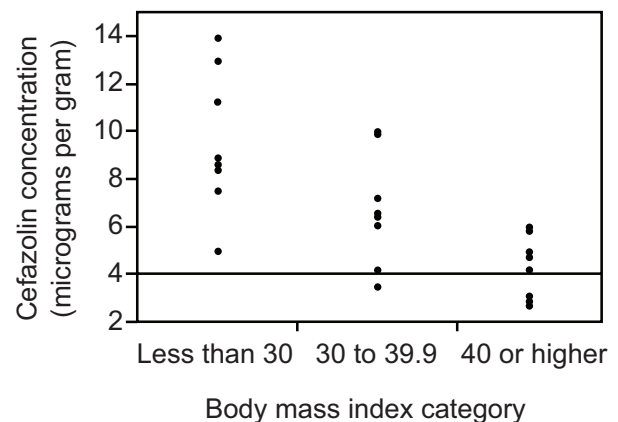*Pevzner. Cefazolin Tissue Concentrations and Obesity. Obstet Gynecol 2011.*

Fig. 2. Comparison of cefazolin concentrations (micrograms per gram) from initial adipose samples and body mass index categories. *Solid horizontal line* (4 micrograms/per gram) represents the theoretic breakpoint for resistance to cefazolin for Gram-negative isolates.

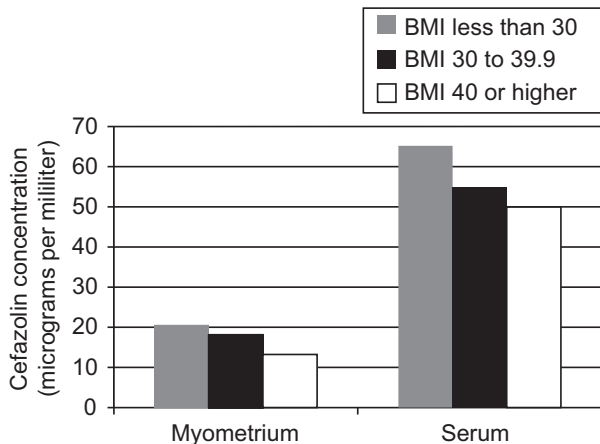*Pevzner. Cefazolin Tissue Concentrations and Obesity. Obstet Gynecol 2011.*

Fig. 3. Comparison of cefazolin concentrations (micrograms per gram) of myometrial and serum samples and body mass index (BMI) categories.

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weight all showed moderate correlation and confirmed an inverse relationship with initial concentration of cefazolin (r=−0.64, r=−0.61, and r=−0.62, respectively). Although linear fit models for weight-based variables and concentrations of cefazolin before skin closure demonstrated significant inverse relationship, the highest correlation coefficient (based on participant BMI) was −0.42, which signified a weak relationship.

The current study was not powered to demonstrate a difference in actual rates of surgical site infections across BMI categories. Nevertheless, a chart review was conducted to demonstrate the cor-
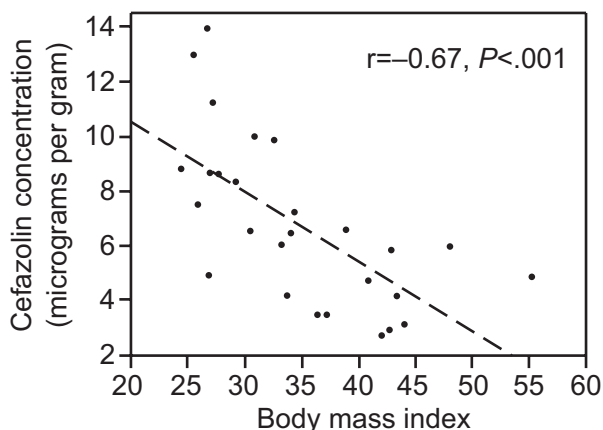

Fig. 4. Linear regression analysis comparing cefazolin concentrations (micrograms per gram) from initial adipose samples and body mass index categories.

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relation between suspected infections during a 6-week postpartum period and tissue concentrations of cefazolin. Follow-up data were available for 25 patients, with all four missing participants belonging to BMI 40 or greater group. Two participants (both with BMI 40 or greater) were noted to have wound infections and required antibiotic therapy. Adipose cefazolin concentrations from initial and closing adipose samples for these two participants were all below the 4-microgram/g resistance breakpoint (2.7 and 2.9 micrograms/g, respectively, from initial samples and 3.8 and 2.8 micrograms/g, respectively, in the final adipose samples).

DISCUSSION

Several publications have demonstrated adequate antimicrobial activity in maternal serum, amniotic fluid, and umbilical cord[12,13]; however, no previous studies in the obstetric population have examined the concentrations of cefazolin in tissues from the surgical site. An advisory statement from the National Surgical Infection Prevention Project states that antimicrobial agent "should be given in an adequate dose based on patient weight, adjusted dosing weight, or body mass index."[14] Nevertheless, the only weight-based doses are primarily from published pediatric recommendations. Due to limited existing data on appropriate antimicrobial dosing for prophylaxis, the current recommendations for adult intravenous dose for cefazolin are 1–2 g without any adjustments for weight-based variables. However, as suggested by current findings, a considerable portion of obese women undergoing cesarean delivery will not have adequate antimicrobial protection for the duration of the procedure based on these recommendations.

The majority of data regarding effects of obesity on antimicrobial concentrations in adipose tissues come from investigations involving gastric bypass patients. Forse and colleagues reported that increasing the dose of cefazolin from 1 to 2 g resulted in a 75% to 100% increase in adipose tissue concentrations. In addition, the authors reported that routine use of a 2-g dose resulted in a marked reduction in surgical site infection rate (5.6%) compared with a 1-g preoperative dose (16.5%).[10] Anaya and Dellinger have suggested that obese surgical patients may likely require a higher loading to provide consistent tissue concentrations over the duration of the surgical procedure.[15]

Additional concern comes from the recent update of cephalosporin breakpoints by the Clinical and Laboratory Standards Institute, clinical Gram-negative isolates that were fully sensitive at 8 micro-

grams/g and less are now fully resistant at 4 micrograms/g or greater, representing a significant change that will likely influence tissue therapeutic activity after perioperative antimicrobial prophylaxis.[11] Evolutionary changes in antimicrobial patterns of susceptibility and the emergence of multidrug-resistant Gram-positive and Gram-negative strains associated with postoperative surgical site infections portends a questionable utility of the existing antimicrobial prophylaxis regimens. Enhanced bacterial resistance, coupled with the current obesity trend, has the potential to drastically increase the rates of surgical site infections if no attempts are made to adjust antimicrobial dosing based on a patient's weight or BMI.

Many unanswered questions remain regarding appropriate prophylactic dose of antibiotics in the obese and obstetric population. Although currently published data are insufficient to make a recommendation regarding the weight or BMI above which antimicrobial dose should be increased, it is evident from recent human pharmacokinetic clinical studies that even 2-g dosing is at times insufficient to provide adequate intraoperative tissue concentrations in obese patients. These findings have profound implications in the practice of obstetrics and gynecology considering that practitioners are increasingly confronted with patients exhibiting increased morbidity, placing them at risk for postoperative complication. The theoretical effect of microvascular disease in patients with chronic hypertension, diabetes, and collagen vascular disease on antibiotic tissue concentrations secondary to decreased tissue perfusion also warrants further analysis.

The current investigation was not designed nor powered to demonstrate an actual difference in rates of surgical site infections after cesarean delivery. However, the significance of these results serves to provide a possible explanation and biologic plausibility for higher surgical site infection rates in obese patients. Pharmacokinetic and susceptibility limitations that exist with current prophylactic regimens suggest that a melding of traditional practices (exquisite surgical techniques, improvements in skin antisepsis, and attention to sentinel risk factors) with innovative and thoughtful strategies (alternative dosing schedules or new antiseptic agent or drug delivery techniques or both) is likely warranted in the ongoing efforts to reduce the risk of surgical site infection in the obese and other high-risk patient populations.

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