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Infectious Morbidity is higher after Second Stage Compared with First Stage Cesareans

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Abstract

Objective—To compare maternal and neonatal infectious morbidity following cesareans performed in the second and first stages of labor.

Study Design—We conducted a retrospective cohort study of all consecutive, singleton, term, cesarean deliveries in laboring women in a single institution from 2005 – 2012. Second stage cesareans were defined as those performed at complete cervical dilation (10 cm) and first stage cesareans were those performed before 10 cm cervical dilation. The primary outcome was endometritis. Rates of infectious morbidity were compared in the two groups. Multivariable logistic regression was used to calculate adjusted risk estimates.

Results—Of 2,505 cesareans meeting inclusion criteria, 400 (16.0%) were performed in the second stage while 2,105 (84.0%) were performed in the first stage of labor. The risk of endometritis was nearly 3-fold higher in second compared to first stage cesareans (4.25% vs 1.52%, crude OR 2.88 [95% CI 1.58, 5.23]). The risk remained significantly higher after controlling for confounders (adjusted OR 2.78 [95% CI 1.51, 5.09]).

Conclusion—Second stage cesarean is associated with increased risk of endometritis compared to first stage cesarean. Further studies will determine if different infection preventive strategies are needed at second stage cesareans to reduce endometritis.

Keywords

Cesarean; second stage; first stage; labor; infections

INTRODUCTION

Cesarean delivery is the most common major surgical procedure performed on women in the United States. In 2012, 1.3 million (32.8%) of the 4 million births in the United States were

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by cesarean (1). Infectious morbidity is one of the most common complications, affecting 2 – 20% of cesareans, depending on the population (2). While some infections are superficial, a significant proportion are more severe and involve deeper abdominal wall tissue, the peritoneal cavity or the uterus(3). These require prolonged hospitalization, readmissions or additional outpatient visits. The sheer numbers of these infections represent a substantial burden for individuals and the health care system (4). While costs vary depending on the location, depth and severity, the average attributable cost for each cesarean infection is estimated to be \$2,800 – \$3,400 (5).

Preoperative antibiotic prophylaxis has been established as an effective preventive measure for reducing postcesarean infections. The Cochrane review of randomized trials suggests a 60% decrease in postcesarean infections when antibiotic prophylaxis is used at cesarean delivery (2). In addition, pooled results from five randomized trials showed a further 50% reduction in the risk of endometritis and a trend towards lower rates of wound infections when antibiotics are administered prior to skin incision rather than after cord clamp (6). However, even with optimal use of preoperative antibiotic prophylaxis the rate of postcesarean infections remains high (7). Identifying specific subgroups at higher risk for residual infections will permit the application of tailored preventive strategies. Prior studies have compared intraoperative and postoperative complications following second stage and first stage cesarean with mixed results (8–12). A number of these studies primarily compared composite maternal and neonatal outcomes, and infectious morbidity was not the primary focus.

The objective of this study was to compare the risk of infectious morbidity following cesarean performed in the second stage to those performed in the first stage of labor. We hypothesized that women undergoing cesarean in the second stage constitute a subgroup at higher risk for postcesarean infections.

MATERIALS AND METHODS

We conducted a retrospective cohort study of all consecutive, singleton, term cesarean deliveries in the setting of labor from 2005 to 2012 at Washington University in St. Louis Medical Center. The study was approved by the Washington University School of Medicine Human Research Protection Office.

Subjects were selected from a comprehensive database of all deliveries. Trained research nurses abstracted demographic information from patients' records including medical and surgical history, obstetric and gynecologic history and prenatal history. We also obtained detailed labor and delivery information including labor duration, medications, diagnosis of chorioamnionitis and mode of delivery. For women who underwent cesarean delivery we obtained information on the stage of labor in which the cesarean was performed, indication for cesarean delivery, antibiotic administration and postoperative complications including maternal fever, endometritis, and suspected or proven neonatal sepsis. Our institutional protocol for prophylactic antibiotics at cesarean calls for administration of a single dose of antibiotics within 60 minutes prior to skin incision. However, in emergent situations the antibiotics are administered as soon as practical after skin incision. One or two grams of

cefazolin is generally used, except in women allergic to cephalosporins in which case clindamycin is given.

Women were *eligible* if they carried a term singleton fetus and underwent cesarean during labor. We *excluded* women who underwent prelabor cesarean and those carrying multiple gestations or anomalous fetuses. Term pregnancy was defined as gestational age >37 weeks. Pregnancies were dated by a woman's last menstrual period and confirmed with first or second trimester ultrasonography using standard criteria (13). Timing of cesarean in the first or second stage defined the *comparison groups*. First stage cesareans were defined as cesareans performed any time during labor, but prior to complete (10 cm) cervical dilation, while second stage cesareans were those performed after complete cervical dilation. The *primary outcome* was endometritis as diagnosed clinically by the attending physician from delivery until 6 week postpartum. An institutional standard protocol guides this clinical diagnosis, specifying: i) maternal fever (temperature >38.0°C on two occasions, 4 hours apart or >39.0°C on one occasion) >12 hours after delivery, ii) uterine tenderness, and iii) no evidence of another infection. *Secondary outcomes* were wound infection (defined clinically from delivery until 6 weeks postpartum), maternal fever (defined as maternal temperature >38.0°C after 24 hour postpartum) and suspected or confirmed neonatal sepsis. Suspected neonatal sepsis was defined neonatal clinical signs and symptoms indicative of possible sepsis and requiring laboratory work up (complete blood count, blood cultures, chest x-ray, and spinal puncture) and administration of antibiotics. Proven sepsis was defined as bacteria isolation from blood, cerebrospinal fluid, or urine cultures in addition to clinical, radiographic, or laboratory findings consistent with the diagnosis of sepsis.

We compared baseline characteristics of women who underwent first stage and second stage cesareans. Continuous variables were compared using the independent Student's t test while categorical variables were compared using the chi-square or Fisher's exact test as appropriate. Normality of distribution of the continuous variables was confirmed using the Kolmogorov-Smirnov test. We calculated rates and unadjusted odds ratios with 95% confidence (CI) intervals for endometritis and the secondary outcomes. Multivariable logistic regression was used to adjust for confounders and calculate adjusted odds ratios. Candidate variables for the logistic regression models were selected on the basis of biologic plausibility, risk factors that have been identified in prior studies for the various outcomes, and results of our univariable and stratified analyses. The number of variables in each model was reduced using backwards elimination. Differences between hierarchical explanatory models were assessed using the Wald test. Model fit for the final models was assessed with the Hosmer-Lemeshow goodness-of-fit test (14).

Because chorioamnionitis may be more common in women undergoing second stage cesarean and is also a risk factor for postpartum infectious morbidity, we repeated the analysis excluding women with chorioamnionitis. To explore whether latent or active labor influenced the risk of infectious morbidity following first stage cesarean we compared rates of endometritis in the latent (cervical dilation <6 cm) and active (6 – <10 cm) phases of labor. Finally, to explore if time in labor explained the increased risk of infectious morbidity associated with second stage cesarean we used time-to-event analysis to account for the length of labor. Cox proportional hazard model was fitted adjusting for potentially

confounding factors. The proportional hazards assumption was tested using Schoenfeld's global test (15).

We included all consecutive subjects meeting inclusion criteria; no *a priori* sample size estimation was performed. Statistical tests were all 2-tailed and $P < 0.05$ was considered significant. All statistical analyses were completed using STATA software package, version 11, Special Edition (College Station, TX).

RESULTS

Of 2,505 women meeting inclusion criteria who underwent cesarean during labor, 2,105 (84.0%) were performed during the first stage and 400 (16.0%) during the second stage (Figure 1). Maternal age, prevalence of diabetes, use of epidural anesthesia, and preoperative antibiotics prior to cord clamp were not significantly different between the two groups. Women undergoing second stage cesarean were more likely to be African American, have a higher BMI, and have been induced. They were also more likely to have been diagnosed with chorioamnionitis. Cesareans in the first stage were more likely to have been performed for the indications of non-reassuring fetal status and arrest of labor (Table 1).

Endometritis complicated 49 (1.96%) cesareans. Women undergoing second stage cesarean were significantly more likely to develop endometritis. The risk of endometritis was nearly three-fold higher in second stage compared to first stage cesareans (4.25% vs 1.52%, crude OR 2.88 [95% CI 1.58, 5.23]). The risk remained significantly higher after controlling for diabetes, obesity and maternal age (adjusted OR 2.78 [95% CI 1.51, 5.09]). After excluding women diagnosed with chorioamnionitis in labor, second stage cesarean was still associated with a significantly increased risk of endometritis (4.56% vs 1.42%, aOR 3.26, [95% CI 1.75, 6.04]). There was no significant difference in the risk of endometritis after cesarean performed in the latent and active phases of the first stage of labor (Figure 2). Cox proportional hazard's regression showed over two-fold increased risk of endometritis following second stage cesarean after accounting for time in labor and controlling for potential confounders (hazard ratio 2.44, 95% CI 1.34, 4.44). The proportional hazard assumption was not violated (Schoenfeld global test, $p = 0.57$).

Risks of wound infection (1.75% vs 2.57%, aOR 0.68 [95% CI 0.31, 1.51]) and postoperative fever (6.75% vs 5.56%, aOR 1.19, [95% CI 0.76, 1.84]) were not significantly different in the two groups (Table 2). Suspected or confirmed neonatal sepsis was also not significantly different in the two groups (0.75% vs 0.57%, crude OR 1.32 [95% CI 0.37, 4.69]).

COMMENT

We found that women who underwent cesarean delivery in the second stage of labor were at a significantly increased risk for endometritis, despite the same approach to antibiotic prophylaxis. The risk of endometritis was nearly three-fold higher in second compared to first stage cesareans after controlling for confounders. There were no differences in wound infection, postoperative maternal fever or neonatal sepsis.

A number of prior studies have compared maternal and neonatal outcomes following second stage to first stage cesarean with mixed results (8–12). However, the focus of these studies have been on composite intraoperative and postoperative outcomes and not infectious morbidity. By contrast, we specifically compared infectious morbidity in cesareans performed in the second stage to the first stages of labor, with the goal of identifying a subgroup at high risk of postcesarean infections who may benefit from additional preventive strategies. Consistent with our results, other smaller studies found significantly higher risks of endometritis with second stage cesarean (9) and no differences in wound infection (8, 9, 16) and neonatal sepsis (8, 9). The largest study to date compared composite maternal and neonatal morbidity in second and first stage cesareans and found a slightly increased risk of maternal, but not neonatal composite morbidity. They also found no significant differences in secondary outcomes including endometritis and wound infection (10). The difference in results between this study and ours may be attributable to the higher risk population in the prior study as suggested by the higher rate of endometritis in that cohort (>10% versus 2%). The lack of differences in risk of second compared to first stage cesarean may be because the impact of stage of labor during which cesarean was performed was relatively small in that higher risk cohort.

The present study is a large analysis dedicated to evaluating the risk of infectious morbidity in second stage compared to first stage cesareans. The comprehensive delivery data compiled by trained research nurses enabled us to perform detailed analysis of maternal and neonatal infectious morbidity. The inclusion of both inpatient and outpatient infections is an important feature of our study because a significant proportion of postcesarean infections occur after discharge from the hospital (3). We also used appropriate statistical tools to explore if chorioamnionitis and time in labor explained the increased risk of endometritis following second stage cesarean.

Despite these strengths there are limitations that should be considered when interpreting our results. The retrospective nature of our study makes it vulnerable to inaccuracies in data collection as well selection bias and confounding. However, this database has been well validated by ongoing quality control, increasing confidence in our findings. In addition, we included all consecutive patients meeting inclusion criteria, reducing the risk of selection bias. While we controlled for confounders, there is the potential for residual confounding by variables we did not take into account. Conducting the study in a single center may also be viewed as a limitation with regards to generalizability. However, the common institutional protocols, definitions, and clinical practice patterns increased validity of our results by minimizing both measured and unmeasured confounders.

Diagnosis of endometritis and other secondary outcomes were based on clinical diagnosis by the treating physician. While this may be considered a source of bias, we expect any bias to be minimal and non-directional because stage of labor is not generally taken into account when assessing postcesarean infections. This would tend to bias our results towards the null hypothesis of no difference rather than produce spurious associations. Finally, we did not conduct a formal sample size estimation, raising the possibility that lack of significant differences in the secondary outcomes may be due to a small sample size. However, posthoc analysis indicated that our sample size afforded 80% power to detect about a 2-fold

difference in the secondary outcomes (maternal fever and wound infection). Thus, we would offer that the results of no difference between the groups regarding the secondary outcomes demonstrate lack of clinically significant differences rather than Type II error.

There are a number of biologically plausible reasons for the higher risk of endometritis we found in women undergoing cesarean in the second stage of labor. Endometritis is a polymicrobial infection caused by mostly vaginal organisms (17), and cesarean delivery confers over 20-fold increased risk compared to vaginal delivery (18). The longer duration of labor, longer operative times and the larger cervical dilation associated with second stage cesarean are all risk factors for endometritis (8, 9, 16). The intrauterine cavity is also more likely to be invaded by vaginal flora at second stage cesareans as amniotic membranes are more likely to be ruptured for an extended period of time. The presenting fetal part is often lower in the vagina during second stage cesarean. This requires the operating hand go lower down to deliver the infant, concurrently contaminating the uterine cavity. Higher rates of chorioamnionitis at second stage cesareans may also contribute to the increased risk of endometritis. However we found persistently increased risk after excluding women diagnosed with chorioamnionitis during labor, suggesting a significant contribution by other factors.

The finding that second stage cesarean is associated with a significantly higher risk of endometritis compared to first stage cesarean in spite of current infection prevention measures has clinical and research implications. It highlights the need for tailored infection prevention strategies for specific subgroups at higher risk for postcesarean infection. Given that the etiologic agents for endometritis are largely of vaginal origin, it is plausible that vaginal preparation prior to cesarean may be an important additional preventive measure for women undergoing second stage cesarean. A recent Cochrane review showed that vaginal preparation with povidone-iodine immediately before cesarean significantly reduces the risk of postoperative endometritis (19). Of note, benefit was particularly realized in women undergoing delivery with ruptured membranes (1.4% vs 15.4%, RR 0.13, 95%CI 0.02, 0.66). We posit that women undergoing second stage cesarean will accrue similar, if not greater benefit from preoperative vaginal preparation. Broadening prophylactic antibiotic coverage may also be beneficial in reducing postcesarean endometritis (20). Tita et al. found that addition of azithromycin to the standard first or second generation cephalosporins reduced the risk of postoperative endometritis compared with the cephalosporins alone (21). Results of an ongoing multicenter trial (22) and further studies testing broader prophylactic antibiotic coverage for women undergoing cesarean during labor will determine if tailored infection prevention strategies at second stage cesareans will reduce the risk of endometritis.

In conclusion, we found that second stage cesarean is associated with a significantly increased risk of endometritis compared to first stage cesarean. This highlights the need for tailored infection prevention strategies for specific subgroups at higher risk for postcesarean infection. Further studies will determine if different infection prevention strategies such as vaginal preparation and broader antibiotic coverage should be employed at second stage cesareans to reduce the risk of endometritis. The impact of any further reduction in postcesarean infection will be magnified at the population level given the large number of cesareans performed in the United States and worldwide.

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Figure 1.
Flow chart of study subjects

Figure 2.
Rates of endometritis at cesareans performed at different cervical dilations

Table 1

Baseline characteristics of study subjects

	Second Stage Cesarean (n=400)	First Stage Cesarean (n=2105)	P
Maternal age (years), mean (sd)	24.9 (6.4)	25.4 (6.1)	0.121
African American race, n (%)	220 (55.0)	1556 (73.9)	<0.001
BMI, mean (sd)	33.2 (7.5)	35.7 (10.5)	<0.001
Nulliparous, n (%)	231 (57.8)	819 (38.9)	<0.001
Diabetes, n (%)	29 (7.3)	151 (7.2)	0.957
Chronic hypertension, n (%)	11 (2.8)	101 (4.8)	0.069
Tobacco use, n (%)	36 (9.0)	357 (17.0)	<0.001
Gestational age (weeks), mean (sd)	39.1 (1.3)	39.0 (1.3)	<0.001
Labor onset			
Spontaneous	76 (19.6)	324 (19.9)	<0.001
Augmented	144 (37.1)	425 (26.1)	
Induced	168 (43.3)	882 (54.1)	
Chorioamnionitis, n (%)	27 (6.8)	59 (2.8)	<0.001
Epidural, n (%)	162 (96.4)	618 (92.5)	0.070
Antibiotics administered prior to skin incision, n (%)	113 (77.9)	1140 (79.4)	0.680
Indication for cesarean			
Non-reassuring fetal status	235 (58.8)	1451 (68.9)	<0.001
Arrest of labor	17 (4.3)	268 (12.7)	
Maternal Exhaustion	3 (0.8)	2 (0.1)	
Failed vacuum/forceps	16 (4.0)	0 (0)	
Other	13 (3.3)	129 (6.1)	

Sd=standard deviation

Table 2

Infectious morbidities after second and first stage term cesareans

	Second stage cesarean (n=400)	First stage cesarean (n=2,105)	Crude OR (95%CI)	* Adjusted OR (95%CI)
Primary outcome				
Endometritis, n (%)	17 (4.25)	32 (1.52)	2.88 (1.58, 5.23)	2.78 (1.51, 5.09)
Secondary outcomes				
Wound infection, n (%)	7 (1.75)	54 (2.57)	0.68 (0.31, 1.50)	0.68 (0.31, 1.51)
Maternal fever, n (%)	27 (6.75)	117 (5.56)	1.23 (0.80, 1.90)	1.19 (0.76, 1.84)
Suspected or confirmed neonatal sepsis	3 (0.75)	12 (0.57)	1.32 (0.37, 4.69)	-

* Adjusted for obesity, diabetes, maternal age