**Antimicrobial prophylaxis within 30 minutes versus 30 to 60 minutes before cesarean delivery and surgical site infection rate**

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**Condensation:** Rate of infectious morbidity is comparable when antibiotic prophylaxis is given within 30 minutes or between 30 and 60 minutes before cesarean delivery incision.

**AJOG at a Glance**

1. To examine the effect of prophylactic antibiotic timing (up to 30 minutes vs 30 to 60 minutes) before cesarean section skin incision on the rate of infectious morbidity.
2. Incidence of infectious morbidity was comparable between women who received prophylactic antibiotic within 30 minutes or from 30 to 60 minutes before skin incision.
3. Compared to other nonobstetric surgical procedures where the optimal window is best when restricted to 30 minutes, the results of the current study may ease adherence and lead to a higher compliance rate.

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**Abstract**

**Objective:**

Based on prior studies, antimicrobial prophylaxis (AP) administered within 60 minutes before skin incision is recommended for all cesarean deliveries (CDs). A number of reports have shown a higher rate of surgical site infection (SSI) when AP is administered more than 1 hour before incision or after cord clamping. Nevertheless, the optimal timing within this range and its effect on SSI are unknown. This study aimed to examine the effect on the rate of SSI when AP was administered within 30 minutes compared to 30 to 60 minutes before skin incision.

**Study Design:**

A retrospective cohort study was conducted at a single teaching hospital on data from January 2014 to March 2018. Women who delivered by CD were divided into 2 groups according to AP timing before skin incision: group 1 within 30 minutes and group 2 from 30 to 60 minutes. The primary outcome was the rate of any infectious morbidity including SSI. In order to detect a decrease from 5% to 3% in SSI rate, with α = 0.05 and β = 80%, a sample size of 3200 was needed.

**Results:**

Of 3202 women who had a CD during the study period, 2989 were eligible to be included in the final analysis: 2791 in group 1 and 198 in group 2. The mean time from AP to skin incision was 14.37±7.92 minutes in group 1 and 43.41±37.40 minutes in group 2 (*P* < .001). The primary composite outcome occurred in 125 women (4.48%) in group 1 and 8 women (4.04%) in group 2 (OR, 1.114; 95% CI, 0.537–2.310; *P* = .7726). The incidence of SSI was 1.08% in group 1 and 0.51% in group 2 (OR, 2.130; 95% CI, 0.289–15.704; *P* = .7189). The difference did not change significantly after adjusting for variables that differed significantly between the groups or in a separate subanalysis restricted to intrapartum CDs and to obese women.

**Conclusion:**

The incidence of infectious morbidity was comparable between women who received AP within 30 minutes and from 30 to 60 minutes before skin incision.

**Key words:** cesarean delivery; surgical site infection, timing of antimicrobial prophylaxis.

**Introduction**

A major risk factor for postpartum infection is cesarean delivery (CD).1 The impact is substantial, because the CD rate has increased greatly in the past 2 decades, and in several countries, nearly 1 in 3 pregnant women are delivered by CD.2,3 Maternal infection is associated with increased perioperative mortality and morbidity that may lead to an increase in readmissions, prolonged hospital stays, and health care costs.4,5

Several studies from various populations have shown that nearly 3% to12% of all CDs were complicated by surgical site infection (SSI).1,2,6,7 The beneficial effect of prophylactic antibiotics in reducing the occurrence of infectious morbidity related to CD, whether elective or emergency, is also well established.8

The effectiveness of prophylactic antibiotics depends on their presence in effective concentrations throughout the operative period.9 A number of meta-analyses concluded that antibiotic administration up to 60 minutes before skin incision, compared to after cord clamping, reduces the infection rate significantly.10–12 Likewise, administering antibiotic prophylaxis more than 1 hour before incision in CDs was associated with double the rate of SSI compared to 1 hour before incision.13

Within the range of 1 hour before incision, administering antimicrobial prophylaxis as close as possible to the incision time may not suffice to guarantee appropriate antimicrobial levels in tissue at the surgical site.14 On the other hand, an increased interval may not compensate for the accelerated elimination present in pregnancy.15,16 The aim of the current study was to examine the effect of prophylactic antibiotic timing (up to 30 minutes vs 30 to 60 minutes before surgery) on the rate of SSI.

**Patients and Methods**

A retrospective cohort study was conducted at a single university teaching hospital with approximately 4400 annual deliveries. The study protocol was approved by the local institutional review board at Emek Medical Center. The study consisted of all women who underwent cesarean delivery at a gestational age of 24 weeks or more between January 2014 and March 2018. Women who received antibiotic prophylaxis after skin incision due to the urgency of the procedure or had missing data regarding the exact timing of prophylaxis administration were excluded.

Women were identified by using the computerized labor charts and electronic medical records at admission and discharge. Data were extracted from labor, anesthesia, and postpartum hospitalization charts as well as computerized outpatient diagnosis and clinic records including visits to a physician, laboratory results, and visits to any gynecologic emergency unit up to 3 months after discharge. The computerized system in hospitals and outpatient clinics in Israel is a common, secure, web-based system that allows the medical staff in a hospital to view outpatients’ data and visits and vice versa. Trained research staff members ascertained all medical files of individual cases manually for validation.

*Surgical site infection* was defined according to the US Centers for Disease Control and Prevention criteria.17,18 Women who had a superficial incisional infection, deep incisional infection, or endometritis were categorized as having SSI. Endometritis was defined as the presence of temperature ≥38°C on 2 separate occasions, or temperature ≥39°C and at least 1 of the following signs with no other recognized cause: abdominal pain, uterine tenderness, or purulent discharge. Wound infection was defined as the presence of either superficial or deep incisional SSI characterized by cellulitis or erythema and localized swelling around the incision or purulent discharge from the incision site regardless of fever. Wound hematoma, seroma, or separation alone was not considered as an infection. Diagnosis of abdominal or pelvic abscess required radiologic or surgical confirmation. Other infections included urinary tract infection with the presence of culture-positive urine and pneumonia in the presence of clinical and radiological confirmation.

Each CD was categorized as planned, unplanned but not in labor and with intact membranes, or intrapartum. The cesarean surgical approach was standardized during the study period.

All participants received chlorhexidine skin preparation unless there was a documented allergy, in which case, povidone-iodine was used. Standard sterile draping of participants was performed. Intravenous 1 g cefazolin was administered prior to skin incision. In women with a body mass index (BMI) of 35 kg/m2 or more, 2 g was given. Clindamycin was given in cases of allergy to cefazolin. A Pfannenstiel incision was the preferred skin incision. Surgical dressings were removed within 24 hours postoperatively. Women were examined daily in the hospital by a physician and the registered nurses.

Women were divided into 2 groups according to the time of antimicrobial prophylaxis administration before skin incision: group 1 received prophylaxis up to 30 minutes before skin incision and group 2 from 30 to 60 minutes before skin incision.

The primary outcome was a composite of SSI (endometritis, wound infection) or other infections including abdominal pelvic abscess, maternal sepsis, urinary tract infection, or pneumonia occurring up to 3 months after surgery.

We assumed that antimicrobial prophylaxis given 30 to 60 minutes before incision would result in more effective concentrations throughout the operative period and may lead to a reduced infection rate compared to antimicrobial prophylaxis given up to 30 minutes before skin incision. Accordingly, in order to detect a decrease in the rate of the primary outcome from 5% observed previously at our institution19 to 3% between the groups, 3200 women were needed to achieve 80% power with α = 0.05. Based on sample-size calculation, the retrospective data were collecting began from 2018 and ended in 2014 to obtain an appropriate sample size.

**Statistical analysis**

To analyze the differences between the 2 groups as a function of the administering time of the antimicrobial prophylaxis before skin incision (up to 30 minutes vs 30 to 60 minutes before skin incision) adjusted to the selected set of categorical variables, a series of $χ^{2}$ tests or Fisher exact tests (when the assumptions of the parametric $χ^{2}$ test were not met) were conducted. The odds ratio (OR) with its corresponding 95% confidence interval (CI) was computed. For the empty cells in the contingency tables, a factor of 0.5 was added to each cell before computing the OR and its corresponding 95% CI. In order to test whether the groups differed in the continuous outcomes, a Student *t* test or the nonparametric Mann-Whitney U test (if the sample means had not satisfied the normality assumption) was conducted. Using the variables that were significant in the univariate analysis, a multivariate logistic regression was estimated. From the results of this model, we adjusted the OR, and its corresponding 95% CI was obtained.

To analyze the relationship between the administering time of the antibiotic prophylaxis and the primary outcome, we conducted 2 separate analyses adjusted to 2 different divisions of the time interval. In the first analysis, we divided the timeline into the following 4 disjoint time intervals: 0-15 minutes, 16-30 minutes, 31-45 minutes, and 46-60 minutes. In the second analysis, the timeline was considered as a continuous variable. For both parts, we estimated univariate and multivariate logistic regression models, respectively. For the last analysis, the inclusion criteria of variables in the regression model were based on the variables’ potential role as primary outcome risk factors. Due to the large number of candidate explanatory variables, variable selection was performed by the forward selection method. The inclusion criterion was a significant increase in the area under the receiver operating characteristic curve (AUC).20 The AUC statistic provides an indication of the classifier’s efficacy. Once the increase in the AUC was insignificant, we stopped the process and took the model from the previous step as the final one. For each of the regression coefficients, we computed the 2-tailed *P* values, where *P* < 0.05 was considered statistically significant. Statistical analyses were performed using the SAS software package version 9.4 (SAS Institute, Cary, NC) and R statistical software version 3.6.1.21

**Results**

A total of 3202 cesarean deliveries took place during the study period. Of those, 213 (6.7%) had missing data regarding the exact timing of antibiotic prophylaxis administration or had received prophylaxis outside the range of 0 to 60 minutes before incision and therefore were not included in the analysis. Overall, 2989 women were eligible and included in the final analysis: 2791 in group 1 and 198 in group 2.

Maternal demographics and obstetric characteristics are presented in Table 1. Intrapartum comparisons between the groups are presented in Table 2. The mean time from antibiotic prophylaxis to skin incision was 14.37±7.92 minutes in group 1 and 43.41±37.40 minutes in group 2 (*P* < .001; Table 3). The primary composite outcome occurred in 125 women (4.48%) who received antibiotic prophylaxis within 30 minutes before surgical incision and in 8 (4.04%) who received antibiotic prophylaxis 30 to 60 minutes before surgical incision (OR, 1.114; 95% CI, 0.537–2.310; *P* = .7726; Table 3). The incidence of SSI only was 1.08% and 0.51% among groups 1 and 2, respectively (OR, 2.130; 95% CI, 0.289–15.704; *P* = .7189). There was no difference between the groups when any of the SSIs were tested separately (Table 3). The differences in the rates of the primary outcome and SSI between the groups did not differ significantly even after excluding women who underwent cesarean hysterectomy or women who received antibiotics up to 1 week before surgery for other medical reasons including prelabor rupture of membranes or pyelonephritis (data are not shown).

A regression model was used to adjust for antepartum and intrapartum variables that differed significantly between the groups. The results showed that the rates of the primary composite outcome and SSI were still comparable between the groups (adjusted OR, 0.98; 95% CI, 0.46–2.07; *P* = .949; adjusted OR, 0.61; 95% CI, 0.08–4.64; *P* = .635, respectively).

In a further analysis, we increased the timing categories to 4 (0-15, 16-30, 31-45, and 46-60 minutes) before skin incision. The rates of the primary outcome did not differ.

A separate subanalysis was performed regarding intrapartum CDs and CDs in women with a BMI >30 kg/m2 or >35 kg/m2. Again, the rates of the primary outcome and SSI did not differ between the groups (Table 4).

Finally, a univariate logistic regression model was performed to assess differences in the relative frequency of infections as a function of time from antibiotic administration to skin incision. The results showed that for every increase of 1 minute between antibiotic administration and skin incision, the incidence of the primary outcome decreased by a factor of 1.02 (OR, 0.98; 95% CI, 0.96–0.99; *P* = .018). The AUC was 0.55 (95% CI, 0.50–0.61). We then strived to find the best logistic classifier, namely, the most influential factors that can predict the risk of infection. To this end, we used multivariable logistic regression. The results showed that for every 1 minute increase between antibiotic administration and skin incision, the incidence of the primary outcome decreased by a factor of 1.02 (adjusted OR, 0.98; 95% CI, 0.96–0.99; *P* = .021); however, there was a significant increase in the AUC to 0.62 (95% CI, 0.57–0.67). This model was adjusted to the type of incision closure. Performing the same analysis among women with intrapartum CD or with BMI >30 kg/m2 did not show a significant trend.

**Discussion**

The overall infectious morbidity found in the current study is comparable to other reports where antibiotic prophylaxis was given before skin incision.22 Additionally, the results show that the difference in post cesarean infectious morbidity was not affected whether antibiotic prophylaxis was given within 30 minutes or from 30 to 60 minutes before skin incision. The SSI rate alone was also not affected. The results did not differ when the analysis was performed on medical data for obese women only or when the analysis was restricted to intrapartum CDs only. Although a significant trend (decrease) in the incidence of infectious morbidity was found as time between antibiotic prophylaxis administration (within the range of 60 minutes) and skin incision was increased, the AUC was relatively low.

The effect of antibiotic prophylaxis before skin incision in reducing infectious morbidity, compared to after cord clamping, is well established.12,13,17–19 The American College of Obstetricians and Gynecologists recommends antimicrobial prophylaxis for all CDs and that prophylaxis should be administered within 60 minutes before skin incision.8 Nevertheless, this recommendation does not describe a definitive point in time at which antibiotic prophylaxis should be provided within this window in order to obtain adequate tissue levels for prophylaxis.

The objective of preoperative antibiotic prophylaxis is to reduce postoperative infection, presumably by delivering adequate antibiotic to the surgical site in order to suppress bacterial growth.23 Elkomy et al showed that if the time of antibiotic prophylaxis administration is close to 1 hour before incision, the minimum inhibitory concentration (MIC) in maternal blood is reduced at surgery compared to administration less than 30 minutes before incision.15 Hence, it is necessary to shorten the dosing interval or increase the dose in pregnancy to compensate for accelerated elimination and preserve a free drug plasma concentration similar to that in nonpregnant adults.15,22

A randomized trial evaluating the administration of cefazolin at the time of skin incision (at-incision group) compared with administration after umbilical cord clamping (cord-clamping group) in laboring CDs reported a significant decrease in the incidence of endometritis but not in wound infection among the at-incision group.24 The lack of protective effect on wound infection may be related to timing of antibiotic administration, implying that administration at incision may still not differ significantly from administration at cord clamping.

Data are lacking regarding a definitive point in time at which antibiotic prophylaxis should be provided within 1 hour before skin incision in cases of CDs in order to attain adequate tissue levels for prophylaxis. Data regarding other surgical procedures is conflicting. A prospective observational cohort study analyzed the incidence of SSI by the timing of antimicrobial prophylaxis in a series of 3836 surgical procedures other than CDs. When antibiotic prophylaxis was used 30 to 59 minutes before incision, less SSI was observed compared to administration at less than 30 minutes. The authors concluded that antibiotic prophylaxis timing should ensure that serum and tissue drug levels at the beginning of the operation exceed the MIC for organisms likely to be present in the surgical environment. Administering surgical antimicrobial prophylaxis close to the incision time may not suffice to guarantee appropriate tissue levels at the surgical site.14

In contrast, 29 hospitals prospectively obtained information from 4472 randomly selected surgical procedures other than CDs. The SSI risk increased incrementally as the interval of time between antibiotic infusion and the incision increased, with a trend toward lower risk occurring when antibiotic prophylaxis was given within 30 minutes prior to incision. The lower infection rate seen in the group receiving prophylaxis closest to incision does allay concerns that antibiotics can be administered too close to incision.25 Compared to other surgical procedures, the incidence of SSI in CDs did not differ whether antibiotic prophylaxis was given within 30 minutes or from 30 to 60 minutes of the incision, according to the results of the current study.

One limitation of this study is the use of a retrospective database. However, inaccuracies were minimized by the use of multiple sources and by manual validation of individual medical files. Additionally, the fact that the study was conducted at a single hospital may limit its generalizability. The major strength of this study was the inclusion of a large sample size. Additionally, the use of standardized guidelines and surgical techniques is probably a distinctive advantage related to a single-center study.

In conclusion, implementing a refined optimal time window for the prophylactic administration of antibiotics in clinical practice and adhering to an optimal time window are probably hard. Nevertheless, the aim should be to apply prophylaxis at the optimal time, despite practical and logistic difficulties. According to the results of the current study, rate of infectious morbidity was comparable when antibiotic prophylaxis was given within 30 minutes or between 30 and 60 minutes before incision. Compared to other nonobstetric surgical procedures where the optimal window was within 30 minutes, the results of the current study may ease the adherence and lead to a higher compliance rate.

 **References**

1. Smaill FM, Grivell RM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev 2014;(10):CD007482.

2. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Birth: final data for 2014. Natl Vital Stat Rep 2015;64:1–64.

3. Zuarez-Easton S, Shalev E, Salim R. Trend in major neonatal and maternal morbidities accompanying the rise in the cesarean delivery rate. Sci Rep 2015;5:12565.

4. Mugford M, Kingston J, Chalmers I. Reducing the incidence of infection after caesarean section: implications of prophylaxis with antibiotics for hospital resources. BMJ 1989;299:1003–6.

5. Perencevich EN, Sands KE, Cosgrove SE, Guadagnoli E, Meara E, Platt R. Health and economic impact of surgical site infections diagnosed after hospital discharge. Emerg Infect Dis 2003;9:196–203.

6. Dinsmoor MJ, Gilbert S, Landon MB, Rouse DJ, Spong CY, Varner MW, et al. Perioperative antibiotic prophylaxis for nonlaboring cesarean delivery. Obstet Gynecol 2009;114:752–6.

7. Chelmow D, Ruehli MS, Huang E. Prophylactic use of antibiotics for nonlaboring patients undergoing cesarean delivery with intact membranes: a meta-analysis. Am J Obstet Gynecol 2001;184:656–61.

8. ACOG Practice Bulletin No. 199 summary: use of prophylactic antibiotics in labor and delivery. Obstet Gynecol 2018;132:798–800.

9. Classen D, Evans R, Pestotnik S, Horn S, Menlove R, Burke J. The timing of prophylactic administration of antibiotics and the risk of surgical wound infection. N Engl J Med 1992;326:281–6.

10. Constantine MM, Rahman M, Ghulmiyah L, Byers BD, Longo M, Wen T, et al. Timing of perioperative antibiotics for cesarean delivery: a metaanalysis. Am J Obstet Gynecol 2008;199:301.e1–6.

11. Baaqeel H, Baaqeel R. Timing of administration of prophylactic antibiotics for caesarean section: a systematic review and meta-analysis. BJOG 2013;120:661–9.

12. Bollig C, Nothacker M, Lehane C, Motschall E, Lang B, Meerpohl JJ, et al. Prophylactic antibiotics before cord clamping in cesarean delivery: a systematic review. Acta Obstet Gynecol Scand 2018;97:521–35.

13. Olsen MA, Butler AM, Willers DM, Devkota P, Gross GA, Fraser VJ. Risk factors for surgical site infection after low transverse cesarean section. Infect Control Hosp Epidemiol 2008;29:477–84.

14. Weber WP, Marti WR, Zwahlen M, Misteli H, Rosenthal R, Reck S, et al. The timing of surgical antimicrobial prophylaxis. Ann Surg 2008;247:918–26.

15. Elkomy MH, Sultan P, Drover DR, Epshtein E, Galinkin JL, Carvalho B. Pharmacokinetics of prophylactic cefazolin in parturients undergoing cesarean delivery.

Antimicrob Agents Chemother 2014;58:3504–13.

16. Heikkila A, Erkkola R. Review of beta-lactam antibiotics in pregnancy:

the need for adjustment of dosage schedules. Clin Pharmacokinet 1994;27:49–62.

17. Moulton LJ, Munoz JL, Lachiewicz M, Liu X, Goje O. Surgical site infection after cesarean delivery: incidence and risk factors at a US academic institution. J Matern Fetal Neonatal Med 2018;31:1873–80.

18. CDC. Surgical site infection (SSI) event. 2016. Available at: [www.cdc.gov/nhsn/PDFs/pscmanual/9pscssicurrent.pdf](http://www.cdc.gov/nhsn/PDFs/pscmanual/9pscssicurrent.pdf). Accessed Month XX, 20XX.

19. Salim R, Braverman M, Teitler N, Berkovic I, Suliman A, Shalev E. Risk factors for infection following cesarean delivery: an interventional study. J Matern Fetal Neonatal Med 2012;25:2708–12.

20. Pencina MJ, D’Agostino RB, Massaro JM. Understanding increments in model performance metrics. Lifetime Data Anal 2013;19:202–18.

21. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2018. Available at: <https://www.R-project.org>. Accessed Month XX, 20XX.

22. Sullivan SA, Smith T, Chang E, Hulsey T, Vandorsten JP, Soper D. Administration of cefazolin prior to skin incision is superior to cefazolin at cord clamping in preventing postcesarean infectious morbidity: a randomized, controlled trial. Am J Obstet Gynecol 2007;196:455.e1–5.

23. Young OM, Shaik IH, Twedt R, Binstock A, Althouse AD, Venkataramanan R, et al. Pharmacokinetics of cefazolin prophylaxis in obese gravidae at time of cesarean delivery. Am J Obstet Gynecol 2015;213:541.e1–7.

24. Thigpen BD, Hood WA, Chauhan S, Bufkin L, Bofill J, Magann E, et al. Timing of prophylactic antibiotic administration in the uninfected laboring gravida: a randomized clinical trial. Am J Obstet Gynecol 2005;192:1864–8.

25. Steinberg JP, Braun BI, Hellinger WC, Kusek L, Bozikis MR, Bush AJ, et al. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. Ann Surg 2009;250:10–6.