Original Article

Antibioticoprofilaxia em cesariana: Fatores de risco associados à infecção de ferida cirúrgica e sepse neonatal

Antibiotic Prophylaxis in Cesarean section: Wound infection and Neonatal Sepsis risk factors

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Submissão: 16/07/16

Aceite: 08/09/16

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RESUMO

Justificativa e Objetivos: A infecção de ferida cirúrgica (IFC) é uma das principais complicações da cesariana e profilaxia pré-operatória antimicrobiana é indicada antes da incisão ou após o pinçamento do cordão umbilical. O objetivo deste estudo é comparar as taxas de IFC e sepse neonatal durante dois diferentes protocolos de profilaxia. **Métodos**: Estudo observacional, prospectivo, de 2012 a 2015, em maternidade de referência para assistência de alto risco obstétrico. Todas as mulheres grávidas submetidas à cesariana e seus recém-nascidos foram incluídos. As informações foram obtidas durante contato telefônico e em prontuário médico. Os critérios de infecção seguiram as recomendações do *National Healthcare Safety Network* e da Agência Nacional de Vigilância Sanitária. A análise foi realizada no *Statistical Package for Social Sciences*. O estudo foi aprovado pelo Comitê de Ética em Pesquisa. **Resultados:** Um total de 3.230 gestantes foi submetido à cesárea. Deste total, 2.351 binômios mãe-recém-nascidos (72,7%) foram seguidos. Ao comparar o evento infecção considerando os dois períodos de momento profilaxia diferente (antes ou depois da clampeamento do cordão), não houve diferença estatística para IFC (X2 = 1,98; p = 0,16) ou sepse neonatal (X2 = 0,94; p = 0,33). Nenhuma variável analisada foi associada com IFC materna. No entanto, menor idade materna (p <0,003), menor idade gestacional (p <0,001), corioamniotite (p = 0,001), emergência hipertensiva materna (p <0,001), centralização do fluxo sanguíneo (p = 0,02) classificação de ASA ≥ 3 (p = 0,02), distocia ou indução de falha (p = 0,003) foram significativamente associados à sepse neonatal. Apenas a idade gestacional permaneceu significativa em análise multivariada (p =

0,004). **Conclusão**: Não houve nenhum impacto negativo sobre o desfecho clínico do recém-nascido para a ocorrência de sepse. No entanto, não foi observada redução da IFC materna e tempo ideal para a administração antibiótico deve ser reavaliado.
DESCRITORES: cesárea; antibioticoprofilaxia; infecção de ferida operatória; recém-nascido.

ABSTRACT

Justification and objectives: Post-surgical site infection (SSI) is one of the major complications of cesarean section and preoperative antimicrobial prophylaxis is indicated before the incision or after umbilical cord clamping. The aim of this study is to compare the SSI rates and neonatal sepsis with two different prophylaxis protocols. **Methods:** Prospective observational study, carried out 2012 to 2015, at a reference maternity hospital for high obstetric risk patients. All pregnant women who underwent cesarean section and their newborns were included. Information was obtained when they were contacted by telephone call and by medical records. Infection criteria followed *National Healthcare Safety Network* and Agência Nacional de Vigilância Sanitária recommendations. Analysis was performed using the *Statistical Package for Social Sciences*. The study was approved by the Research Ethics Committee. **Results:** A total of 3230 pregnant underwent cesarean-sections. Of this total, 2,351 mother-newborn binomials (72.7%) were followed. When comparing infection events, considering the two different prophylaxis moments (before or after cord clamping), there was no statistical difference for SSI (X^2 =1,98; p = 0.16) or neonatal sepsis (X^2 = 0.94; p = 0.33). No analyzed variable was associated with maternal SSI. However, lower maternal age (p <0.003), lower gestational age (p <0.001), chorioamnionitis (p = 0.001), maternal hypertensive emergency (p < 0.001), centralization of blood flow (p = 0.02), ASA classification ≥ 3 (p = 0.02), dystocia or induction failure (p = 0.003) were significantly associated to neonatal sepsis. Only lower gestational age was significant in the multivariate analysis (p = 0.004). **Conclusion**: There was no negative impact on the clinical outcome of the newborn regarding the occurrence of sepsis. However, reduction in maternal SSI proportion was not observed and optimal time for antibiotic administration should be reevaluated.
KEYWORDS: cesarean section; antibiotic prophylaxis; surgical wound infection; newborn infant.

INTRODUCTION

Cesarean sections are currently one of the most frequently performed surgical procedures.[1,2] However, post-surgical site infection (SSI) is one of the major complications of cesarean sections.[2,3] Women undergoing a caesarean section have a 5 to 20-fold greater risk of infection when compared to those with a vaginal delivery.[4] Other factors increases SSI risk, such as extremes of age, increased body mass index (BMI), premature rupture of membranes, hypertensive disorders, diabetes, immunosuppressive disorders, chorioamnionitis, prolonged surgical time and use of staples to close the wounds.[4-6]

There are several Healthcare Associated Infections (HAI) related to cesarean section: endometritis, wound infection, puerperal fever and consequent mortality. Moreover,

another problem is that infections after delivery can become an obstacle to mother-child bonding, due to a higher maternal hospitalization rate.[3,7,8]

Various strategies have been implemented to prevent infections associated with the surgical procedure, including the use of antibiotic prophylaxis , adequate hair removal and improved aseptic practices of the surgical team.[4,5]

Prophylaxis is to achieve antibiotic therapeutic tissue levels to prevent microbial contamination during the whole surgery. The prophylactic antibiotic of choice, for use in C-section, is usually a first-generation cephalosporin.[1,9]

Traditionally, antibiotic prophylaxis is indicated after umbilical cord clamping, due to the possibility of passage of some amount of the drug to the newborn and the masking of sepsis.[5,8,10] However, in recent years, the prophylactic administration of antibiotics before skin incision has been adopted in clinical practice.[1,3,6]

The literature shows that the preoperative administration of antibiotics before the skin incision compared to the use of prophylaxis after cord clamping is associated with a reduction of approximately 40% in postpartum endometritis, 30% reduction in wound infection and 29% in general maternal morbidity.[2,11] In addition, it is recommended that antibiotic prophylaxis be administered ideally 60 minutes before the surgical procedure, aiming at lower infection rates.[2,8,10]

In relation to neonatal outcomes, no changes in neonatal sepsis rates, newborn hospitalization or treatment of suspected neonatal infection have been observed.[9] Antibiotic use is considered as minimal risk to the fetus in relation to antibiotic safety.[7, 9]

Thus, the aim of this study is to compare surgical wound infection rates and neonatal sepsis with the use of two different prophylaxis protocols for SSI in cesarean sections in a reference hospital for high-risk obstetric patients and identify risk factors associated with maternal SSI and neonatal sepsis.

Patients and Methods

This is a prospective observational study, conducted between January 2012 and December 2015, during four full years of active surveillance. The study was carried out at Maternidade Otto Cirne, Hospital das Clínicas, Federal University of Minas Gerais (HC/UFMG), which is a reference hospital for high obstetric risk patients. There are around 240 births per month with five delivery rooms, 17 rooming-in beds, four Kangaroo-Care beds and 20 beds for neonatal Intensive Care Unit and Intermediate Care Therapy.

Inclusion criteria were: pregnant women who were submitted to cesarean section and were contacted by telephone within 45 days after delivery. Those who were not contacted during this period, were considered lost to follow-up.

The mother-newborn binomials were divided into two groups: a) Group 1, consisting of women who received antibiotics after clamping of the umbilical cord, corresponding to Caesarean sections performed from January 2012 to December 2013, and b) Group 2, consisting of women whose administration of antimicrobials was performed before skin incision, corresponding to caesarean sections performed from January 2014 to December 2015.

Data was collected daily from medical records filled out by medical students trained and supervised by professionals of Hospital Infection Control Committee of the HC / UFMG. Phone calls were also made at 15, 30 and 45 days to complete the recommended surveillance period after surgical procedures. At least four calls were made to obtain contact or the patient was considered as lost to follow-up. When women had any doubt about the questions to fulfill SSI criteria, they were asked to seek primary care service or to return to the hospital.

The variable Surgical Site Infection (SSI) was notified in accordance with criteria established by National Healthcare Safety Network (NHSN) according to the topography: Superficial Incisional SSI (SISSI), Deep Incisional SSI (DISSI) and Organ or space SSI (OSSSI).[12] The infection was not considered if the recommended criteria were not confirmed.

Newborn follow up included the presence of sepsis and infection classification. The newborn infection criteria followed the criteria of the National Health Surveillance Agency (ANVISA), which are based on the NHSN criteria.[13,14]

Variables associated with infection were also analyzed such as age, gestational age, type of cesarean delivery (elective or urgency / emergency), comorbidity, premature rupture of fetal membranes (PROM) over 18h, chorioamnionitis, intrapartum fever, urinary tract infection (UTI), number of digital vaginal examinations surgery duration (<57 minutes or ≥ 57 minutes), ASA (American Society of Anesthesiologists) classification, surgical risk index (which considers type of cesarean surgery, surgery duration and ASA classification), centralization of blood flow, dystocia or induction failure, and non-reassuring fetal status. In cases where there was infection, the need for hospitalization was also analyzed.

Database was included in the Statistical Package for Social Sciences version 19.0. Statistical analysis included descriptive analysis with frequency and percentage of

categorical variables in addition to mean and standard deviation, median and range of continuous variables. The comparative analysis of categorical variables was performed by X^2 or Fisher test and comparative analysis of quantitative variables was performed by t-test (when distribution was normal) or Mann-Whitney (when distribution was not normal). Variables with statistical significance were considered when $p < 0.05$, which were included in the multivariate analysis by binary logistic regression.

The study was approved by the Research Ethics Committee of UFMG (ETIC 476/10).

RESULTS

Between the years 2012 and 2015, a total of 3230 pregnant women who underwent cesarean delivery in this service were followed. Of this total, 2351 mother-newborns binomials (72.7%) had post-partum follow-up. Women had a mean age of 29 years (SD = 6.97), ranging from 11 to 47 years.

A total of 1591 (67.6%) deliveries were carried to term, with mean gestational age (GA) of 37.90 weeks (SD: 2.72) weeks, with a minimum of 27 and a maximum of 42 weeks. The cesarean section was considered elective in 1190 (50.6%) cases and urgency or emergency in 1076 (45.8%) cases, while 85 (3.6%) were not specified. The mean length of stay at hospital was 4.29 days (SD: 4.23).

The most frequent comorbidities of pregnant women were *Diabetes mellitus* in 250 (10.6%) and HIV infection in 102 (12.9%), as shown in Table 1.

Table 1 - Comorbidities of pregnant women undergoing cesarean section, maternidade Otto Cirne, Hospital das Clínicas da UFMG, 2012 a 2015.

COMORBIDITY	n	%
Alcoholism	27	1,1
Asthma	52	2,2
Cardiopathy	31	1,3
Diabetes mellitus	250	10,6
Psychiatric disorders / epilepsy	38	1,6
Rheumatic diseases	21	0,9
HIV infection	102	4,3

Obesity	32	1,4
Smoking	98	4,2
Use of illicit substances	11	0,5

Considering diagnosis and risk factors for infection identified in the women at admission and during labor, chorioamnionitis was observed in seven (0.3%); intrapartum fever in four (0.2%), PROM over 18h in 385 (16.4%); UTI in 92 (3.9%); hypertensive emergency in 423 (18%); centralization of blood flow in 44 (1.9%) and dystocia or induction failure in 489 (20.8%). Non-reassuring fetal status was also observed in 330 (14%) cases.

The mean surgical duration was 58.04 minutes (SD: 12.99). Considering ASA classification, patients were classified as ASA I in 392 (16.7%) cases, ASA II in 801 cases and (34.1%) ASA III in 70 cases (3%). The most frequent surgical risk ratio was 1 in 833 cases (35.4%) (Table 2).

Table 2 - Surgical Risk Index of pregnant women undergoing cesarean section, maternidade Otto Cirne, Hospital das Clínicas da UFMG, 2012 a 2015.

Surgical Risk Index	**N**	**%**
0 points	304	12.9
1 point	833	35.4
2 point	449	19.1
3 point	48	2.0

A total of 96 SSI (4.1%) were identified during surveillance. Of those, 67 (2.8%) had SISSI; 21 (0.9%) had DISSI and 8 (0.3) had OSSSI. The diagnosis of infection was identified within a mean 13.98 days (SD = 8.67), ranging from 3 to 50 days.

A total of 22 patients with SSI (0.9%) required hospitalization for treatment, 14 with DISSI and 8 with OSSSI. The mean duration of treatment was 8.49 days (SD = 5.56).

Among the newborns, 73 (3.1%) had neonatal sepsis. Of these, 32 (1.4%) met the clinical criteria and 41 (1.7%) had laboratory evidence of sepsis. Early-onset sepsis was considered in 25 (1.1%) and late-onset sepsis in 45 (1.9%).

When comparing infection events, considering the two moments of prophylaxis (before or after cord clamping), there was no statistical difference between SSI (X^2 =1,98; p = 0.16) and neonatal sepsis (X^2 = 0.94; p = 0.33).

No analyzed variable was associated with maternal SSI (Table 3). However, when maternal diagnosis and risk factors were evaluated for neonatal sepsis, it was observed that lower maternal age (p <0.003), lower gestational age (p <0.001), chorioamnionitis (p = 0.001), maternal hypertensive emergency (p < 0.001), centralization of blood flow (p = 0.02) ASA classification ≥ 3 (p = 0.02), dystocia or induction failure (p = 0.003) were significantly associated with it (Table 4).

Table 3 - Association of maternal diagnosis of risk factors with Surgical Site Infection, maternidade Otto Cirne, Hospital das Clínicas da UFMG, 2012 a 2015.

	Surgical Site Infection		p	Relative Risk
	Yes	No		(95%) CI
Maternal age in years / mean (SD)	27.53 (6.65)	29.06 (6.98)	0.41*	-
Gestational age in weeks / mean (SD)	38.21 (3.02)	37.88 (2.71)	0.57*	-
Cesarean section (n) Elective	44	1,146	0.63**	0.90

Urgency / Emergency	44	1,032		(0.59 to 1.38)
Comorbidities (n) YES NO	 16 80	 339 1,916	 0.66**	 1.24 (0.67 to 1.9)
Premature rupture of fetal membranes (PROM) > 18 h (n) YES NO	9 87	375 1,880	0.07**	0.53 (0.27 to 1.04)
Chorioamnionitis (n) YES NO	 0 88	 7 2,171	 1.0***	 1.04 (1.03 to 1.05)
Intrapartum fever (n) YES NO	 0 96	 4 2,251	 1.0***	 1.04 (1.03 to 1.05)
Urinary Tract Infection (n) YES NO	 3 93	 89 2,166	 1***	 0.79 (0.26 to 2.58)
Surgical duration (n) ≤ 57 minutes > 57 minutes	 35 51	 837 1,300	 0.78**	 1.06 (0.70 to 1.62)
ASA (n) 0 or I III to V	 65 6	 1,556 119	 0.67**	 0.83 (0.35 to 1.95)

Surgical Risk Index (n) 1 or 2 points 3 or 4 points	 42 24	 1,094 473	 0.29** 	 0.77 (0.47 to 1.25)
Hypertensive Emergency (n) YES NO	 17 79	 406 1,849	 0.94** 	 0.98 (0.57 to 1.67)
Centralization of blood flow (n) YES NO	 1 95	 43 2,211	 1*** 	 0.55 (0.08 to 3.87)
Dystocia / induction failure (n) YES NO	 27 69	 462 1,793	 0.07** 	 1.49 (0.96 a 2.40)
Non-reassuring fetal status (n) YES NO	 13 83	 317 1,938	 0.89** 	 0.96 (0.54 a 1.70)

* T test ; **X^2 ***Fisher

Table 4 - Association of maternal diagnosis of risk factors with Neonatal Sepsis, maternidade Otto Cirne, Hospital das Clínicas da UFMG, 2012 a 2015.

	Neonatal Sepsis		p	Relative Risk
	YES	NO		(95%) CI
Maternal age in years /				-

mean (SD)	26.56 (6.79)	29.08 (6.96)	**0.003***	
Gestational age in weeks / mean (SD)	36 (28 to 41)	39 (27 to 42)	**<0,.001****	-
Cesarean section (n) Elective Urgency / Emergency	 37 33	 1153 1043	 0.95***	1, 01 (0.63 a1.63)
Comorbidities (n) YES NO	 7 66	 348 1930	 0.18***	 0,60 (0.28 a 1.29)
Premature rupture of fetal membranes (PROM) > 18 h (n) YES NO	 13 60	 371 1907	 0.73***	 1,11 (0.61 a 2.00)
Chorioamnionitis (n) YES NO	 2 71	 5 2273	 **0.018******	 9,43 (2.86 a 31.11)
Intrapartum fever (n) YES NO	 0 73	 4 2274	 1****	 1.03 (1.03 a 1.04)
Urinary Tract Infection (n) YES NO	 3 70	 89 2189	 1****	 1.05 (0.34 a 3.28)
Surgical duration (n)				

≤ 57 minutes > 57 minutes	22 43	850 1308	0.37***	0,79 (0.47 a 1.33)
ASA (n) 0 or I III to V	52 9	1569 116	**0.02*** **	**0,45** **(0.23 a 0.88)**
Surgical Risk Index (n) 1 or 2 points 3 or 4 points	35 19	1101 478	0.44***	0,81 (0.47 a 1.40)
Hypertensive Emergency (n) YES NO	27 46	396 1882	**<0.001*** **	**2.78** **(1.71 a 4.54)**
Centralization of blood flow YES NO	4 69	40 2238	**0.046**** **	**3,04** **(1.16 a 7.96)**
Dystocia / induction failure (n) YES NO	5 68	484 1794	**0.003*** **	**0.28** **(0.11 a 0.69)**
Non-reassuring fetal status (n) YES NO	5 68	325 1953	0.07***	0.44 (0.17 a 1.10)

* T test ; ** Mann Whitney; ***X^2. ****Fisher

When multivariate logistic regression analysis was performed, the only variable with statistical significance for sepsis was lower gestational age (p = 0.004).

DISCUSSION

Active postpartum surveillance after cesarean section in Maternidade Otto Cirne HC/UFMG was started in 2010 and allowed the follow-up of women submitted to cesarean-section and establishment of SSI rates and associated risk factors.[15,16] Now, the present analysis evaluated the impact due to change in the time of antibiotic prophylaxis administration. In this study, changes in SSI rates were not identified when comparing pre-incisional administration of antimicrobial agents to the antimicrobial administration after clamping of the umbilical cord, showing no difference in the occurrence of events. However, one question should be raised considering the non-reduction in infection rates, when medication administration is performed exactly at the time of the incision, and not at the recommended moment, i.e., 30 to 60 minutes before the surgical incision, according to the literature.[2,5,8,10]

The immediate administration would not be sufficient to ensure adequate serum and tissue levels at the moment of incision, with no real difference from the administration after the umbilical cord clamping. Unfortunately, this was not one of the variables evaluated in our study and it still remains a question to be resolved.

Nupur et al. conducted a similar study in Missouri, between January 2003 and December 2010.[5] During this period, a total of 8668 cesarean-sections were performed and the rate of maternal infection after the procedure was compared with different protocols for surgical prophylaxis. In this study, the implementation of prophylactic antibiotic administration at least 1 hour prior to the surgical incision was responsible for a 48% reduction in the incidence of SSI. Similar results were found in a meta-analysis conducted by Constantine et al, which included 3 randomized studies, showing a 53% reduction in the

rate of post-cesarean endometritis and 50% of the morbidity associated with infectious events.[1] In a retrospective study, Stephanie et al compared the incidence of puerperal infection in groups submitted to different surgical prophylaxis protocols.[2] Between July 2002 and November 2004, patients submitted to cesarean-sections received antimicrobial prophylaxis after cord clamping, while in the period between June 2005 and August 2007, there antimicrobial prophylaxis was administered before the surgical incision. There was a reduction in endometritis incidence rates after procedure modification, from 3.9% to 2.2%, and a decrease in SSI incidence from 3.6% to 2.5%, without observation of neonatal adverse effects resulting from changes in protocol. Kaimal et al, in a similar cohort, observed a reduction in SSI incidence, from 6.5% to 2.5%, as well as a reduction in endometritis from 4.8% to 2.1%, but there was no evaluation of neonatal outcome.[20]

Furthermore, there are studies that assess whether the prophylaxis administration by intravenous or other routes would be comparable. Nabhan et al, in a systematic review that included 10 studies with 1354 women undergoing elective or emergency caesarean section, compared different antibiotic routes of administration and evaluated maternal infection events, such as endometritis, SSI, puerperal fever and urinary tract infection.[17] Nine of these studies, with 1274 women, compared intravenous administration and local irrigation with antimicrobials during surgery, with no difference in endometritis rates between the two groups. However, for other events there was no sufficient evidence of what would be the best prophylaxis route of administration. The quality of this meta-analysis evidence was questioned, mainly due to the quality of the designs of the evaluated studies, being necessary to carry out well-designed studies. It would also be necessary to include evaluation of neonatal sepsis outcome, which has not been evaluated.

In the present study, there was also no change in the rate of presumed or confirmed neonatal sepsis. It is assumed that there was no negative impact of the antibiotic prophylaxis

protocol modification, since the possibility of the passage of some amount of the drug to the fetus and masking of sepsis was not confirmed, thus considering a minimal risk of adverse effects due to the use of antibiotics.[7,9] Zhang et al performed a randomized controlled multicenter study, between January 2012 and June 2013, comparing different times of surgical prophylaxis administration in elective cesarean sesctions.[10] A total of 195 pregnant women were allocated to received prophylactic antibiotic therapy between 60 and 30 minutes before the surgical incision,. There were 199 pregnant women in the control group, who received prophylaxis after clamping of the umbilical cord. There were no differences in the incidence rates of neonatal sepsis prognosis of newborns and admission in the intensive care unit, between the newborns from the different groups. Moreover, as a secondary endpoint of the study, there was no difference between the bacterial flora of the newborn infants included in the study.

The evaluation of risk factors was considered for SSI and sepsis, since the maternity is a tertiary university hospital specialized in high obstetric risk patients. Chaim et al. conducted a cross-sectional study between January 1989 and December 1997, at University Hospital in Israel, where they evaluated clinical variables associated with postpartum infectious events.[6] There was an associations between cesarean-section and preterm delivery and endometritis, Gestational Diabetes and SSI, previous cesarean section and endometritis and SSI. In this study, some of these clinical variables and other variables already established as a risk factor for maternal and neonatal infections were analyzed.[21,22] No analyzed variable was associated with maternal SSI, but there was an association between maternal age, gestational age of the newborn, chorioamnionitis, maternal hypertensive emergency, Centralization of blood flow, ASA classification, dystocia or induction failure and neonatal sepsis. Some of these factors, such as gestational age of the newborn and prolonged labor are already well established as risk factors for neonatal sepsis. It is

noteworthy in the present analysis, however, the absence of association between risk factors previously established in the literature with the diagnosis of neonatal sepsis, including UTI and PROM.[21,22] Other factors such as maternal colonization, presence of meconium in the amniotic fluid, invasive fetal or maternal monitoring and birth weight, were not assessed.

In two previous studies carried out in the same hospital, maternal risk factors association with neonatal sepsis were not evaluated. In a prospective observational study conducted between April 2011 and March 2012, Romanelli et al found an association between the number of digital vaginal examinations and development of post-cesarean SSI.[18] In a prospective cohort study, conducted between April 2012 and March 2013, Chianca et al. found no association between surgical risk index and clinical variables associated with development of post-cesarean SSI.[19]

It is important to emphasize that the multivariate analysis showed that only lower gestational age remained as a significant factor for neonatal sepsis, which is a well-defined variable for sepsis in the literature.[21,22] It is likely that other variables may directly interfere with gestational age. Maternal age may be associated with hypertensive emergency and centralization of blood flow, which may interfere with maternal ASA classification, all of them favoring a preterm delivery.[23,24]

Although no recommendations are considered the gold standard for the follow-up of women after hospital discharge during the puerperal period, the major limitation of this study was the difficulty in making telephone contact, representing 27.3% of patients lost to follow-up. It represents difficulties in information collection to complete standard criteria for SSI and neonatal sepsis through active surveillance.[12,13] This limitation, however, does not apply to reported cases of neonatal sepsis with admission to the ICU, since in these cases, the information was obtained directly from medical records. About the limitations of the

study, it is necessary to consider that it was performed in a single medical center, although sample calculation was based on the prevalence of events.

The moment of antimicrobial administration for SSI prophylaxis showed no negative impact on the clinical outcome of the newborn for the occurrence of sepsis. However, no reduction was observed in maternal SSI and the optimal time for antibiotic administration should be reevaluated, aiming at the benefit of reducing maternal infection. Furthermore, other risk factors should be considered for proper management of maternal SSI and neonatal sepsis prevention.

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