A randomised trial comparing preoperative administration of single-dose kefazolin to kefazolin plus metronidazole as prophylactic antibiotics at caesarean section

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Background. Caesarean section is a life-saving procedure which is associated with high rates of maternal and neonatal complications. It has been estimated that globally, 29.7 million births occur by caesarean section annually. The risk of postpartum infection is estimated to be five to ten times higher compared with normal vaginal delivery. Pregnancy-related sepsis was listed as a top-six cause of maternal mortality in the South African Saving Mothers report between 2017 and 2019. Multiple trials have been conducted in an attempt to optimise administration of prophylactic antibiotics in an effort to reduce postpartum infection and maternal sepsis, and current practice guidelines suggest that there is sufficient evidence that extended-spectrum antibiotics, in combination with kefazolin, result in reduction of postpartum infections.
Objectives. To investigate the effect of perioperative administration of kefazolin alone compared with kefazolin plus metronidazole on postpartum infection in women undergoing caesarean section at Kalafong Provincial Tertiary Hospital, Pretoria, South Africa.
Method. All patients undergoing emergency or elective caesarean section were randomised and then sequentially numbered in opaque sealed envelopes, which were placed in the caesarean section operating theatre. The intervention group received kefazolin and a sealed envelope with metronidazole. The control group received kefazolin and a sealed envelope with normal saline.
Results. A total of 57/1 010 patients (5.64%) had surgical site infections, of which 27 (5.33%) were in the control group, and 30 (5.96%) were in the intervention group (p=0.66). Two patients in each arm (0.40% in the intervention arm and 0.39% in the control arm) underwent laparotomy procedures, while three women (0.60%) in the intervention arm and four women (0.79%) in the control arm underwent hysterectomy procedures. There were no statistically significant differences in all the measured secondary outcomes between the two groups.
Conclusion. The overall sepsis rate in this study was 5.64%. Postpartum infection is multifactorial and there are multiple factors that can be addressed in strengthening the sepsis care bundle. We do not recommend the addition of metronidazole to kefazolin as prophylaxis at caesarean section.

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Caesarean section is a life-saving procedure that is associated with high rates of maternal and neonatal complications. It has been estimated that globally, 29.7 million births occur by caesarean section annually.[1]

Caesarean section is the most important risk factor contributing to the development of postpartum infection.[2] The risk of postpartum infection is estimated to be 5 - 10 times higher compared with normal vaginal delivery.[2] In South Africa (SA), the number of deaths related to sepsis decreased every year between 2017 and 2019 and increased again until 2021.[3] Following caesarean section, the pathogenesis of infection is multifactorial.[4] However, two common mechanisms are known: firstly, wound contamination by skin flora, and secondly, the spread of contaminants from the genital tract and intra-uterine cavity.[4,5] Postpartum infection is manifested in the form of endometritis, wound infections, intra-abdominal abscesses and urinary tract infections (UTIs).[4]

Postpartum infection can lead to maternal sepsis which, in both high-income and low-income environments, can lead to mortality, serious morbidity and consumption of healthcare resources.[6] Pregnancy-related sepsis was the third most common direct cause of maternal mortality in SA in 2021.[3] Strategies to prevent maternal sepsis include measures to reduce postpartum infection.

Prophylactic antibiotics involve administering antibiotics to patients who show no signs of infection at the time of administration. They are commonly employed to minimise the likelihood of postpartum infections. The primary aim of antibiotic prophylaxis is to prevent postpartum infections, rather than addressing or curing pre-existing diseases.[7]

Multiple trials have been conducted in an attempt to optimise administration of prophylactic antibiotics in an effort to reduce postpartum infection and maternal sepsis, and current practice guidelines suggest that there is sufficient evidence that prophylactic antibiotics significantly reduce the risk of infection in both elective and emergency caesarean sections. Several studies have shown that wound infection rates can be as high as 30%, with 60% of patients developing endometritis when prophylactic antibiotics were not administered.[8] A Cochrane review[9] showed a significant reduction in postpartum infections for both elective and emergency caesarean sections with the use of prophylactic antibiotics. They found that extended-spectrum antibiotics, particularly azithromycin in combination with kefazolin, resulted in a reduction of postpartum infections.[7]

In prophylactic antibiotic use, the aim is to reach adequate serum antibiotic levels prior to maximal levels of exposure to a pathogen.[7] According to the American College of Obstetricians and Gynaecologists

(ACOG), antibiotic administration should be prior to skin incision for caesarean section, as this has shown a reduction in postpartum infections as opposed to after clamping of the umbilical cord.[7]

Current clinical practice guidelines recommend antibiotics that are effective against gram-positive, gram-negative and anaerobic bacteria.[7] ACOG suggests the administration of 1 g kefazolin an hour before incision, 2 g kefazolin in obese patients, and 3 g in women ≥120 kg.[7]

There are currently insufficient data to suggest that kefazolin plus metronidazole is superior to kefazolin alone in the reduction of postpartum infection. One trial conducted at the University of Tennessee randomised 160 women into prophylaxis with 2 g kefazolin or 1 g kefazolin and 500 mg metronidazole. There was a significant reduction in postpartum infections in the kefazolin and metronidazole group compared with kefazolin alone.[10] Although this trial showed significant differences in the two groups, the sample size is inadequate to draw conclusions for an entire population.

Metronidazole was selected as the treatment option because postpartum infections are well-documented to involve multiple types of microorganisms.[11] It is known that kefazolin primarily targets gram-positive and gram-negative bacteria, excluding anaerobes. Moreover, metronidazole proves to be a cost-effective medication with minimal side-effects.[12]

Data on sepsis rates following caesarean section in SA are scarce, and according to published literature they range between 2.91% and 12.5%.[13-15]

Postpartum sepsis is a serious complication and effective measures to reduce it should be investigated. This study aims to investigate the impact of kefazolin plus metronidazole compared with kefazolin alone on postpartum infection rates in women undergoing caesarean section at Kalafong Provincial Tertiary Hospital.

Methods

This study was a prospective randomised controlled trial (RCT) investigating possible interventions to reduce post-caesarean section infections. The research was conducted among pregnant patients undergoing emergency or elective caesarean sections at the maternity unit of the Kalafong Provincial Tertiary Hospital. Kalafong Provincial Tertiary Hospital provides primary obstetric care to the residents of Atteridgeville, and secondary and tertiary care to referred patients from the Southwest District. This socioeconomic group with a low- to medium-income level resides in Pretoria West, located in Gauteng Province.

All patients undergoing emergency or elective caesarean section, aged ≥18 years, who were willing and able to provide informed consent to take part in the study, were eligible for recruitment. Women who were already receiving antibiotic therapy, patients with suspected or known existing maternal infection, patients with known allergy to kefazolin and/or metronidazole, and patients regarded as not suitable for recruitment to the study by the treating doctor were excluded.

A total of 1 596 patients who met the inclusion criteria were randomised into either the treatment group (kefazolin plus metronidazole) or the control (kefazolin only) group.

Permutated block randomisation consisted of 12 patients per block using prefilled arm allocation, mixed, and then sequentially numbered opaque sealed envelopes. The envelopes were placed in the caesarean section operating theatre, and were opened in the numbered sequential order, after which patients were allocated to the arm as per the content of the opened envelope.

All patients underwent the same preoperative and postoperative care as per the institutional protocol. The anaesthetist in consultation with the obstetrician prescribed postoperative analgesia.

Medication for both the treatment and control groups was pre-packed and sealed in opaque envelopes.

Both arms received, according to body weight, 1 g, 2 g or 3 g intravenous (IVI) kefazolin packaged in 1 g powdered vials. In addition, the intervention group received 500 mg IVI metronidazole packaged in a 100 mL bag of fluid with the label covered, while the control group received 100 mL of normal saline packaged in a 100 mL bag of fluid with the label covered. Medication was administered 30 - 60 minutes prior to caesarean section. Kefazolin was administered as a slow IVI injection of 1 g, 2 g or 3 g kefazolin diluted in 20 mL of normal saline, followed by either saline or metronidazole administration as an infusion.

Trained and experienced professional nurses, blinded to the arm the patient was randomised to, were assigned to postoperatively inspect the caesarean section wounds and remove the sutures on day 7 post caesarean section. Wounds were inspected for signs of infection such as redness, swelling, cellulitis, discharge or pus draining from the wound, wound dehiscence, warmth to touch and localised tenderness.

Estimating the incidence of surgical site infection following standard of care during caesarean section as 10%, and an expected 50% reduction in incidence of postpartum infections in the intervention group to 0.05 (5%), a sample size of 474 patients per group would have 90% power to detect the anticipated reduction in surgical site infection (SSI) when testing one-sided at the 0.05 level of significance. The aim was to recruit 500 patients per arm for this study.

The primary outcome for this study was the development of postpartum infection within 7 days post caesarean section, defined as wound infection requiring treatment. The secondary outcomes were endometritis requiring antibiotic treatment or surgery, UTI on day 3 post caesarean section and medication-related side-effects, namely nausea, vomiting, diarrhoea, urticaria or anaphylaxis. UTI was defined as $\geq 10^5$ colony-forming units/ml of a uropathogen cultured from the urine. Ethics approval was obtained from the Faculty of Health Sciences Research Ethics Committee (ref. no. 560/2020). The trial was registered with ClinicalTrials.gov (NTC04792710).

Statistical analysis

Data were analysed on an intention-to-treat basis. Demographic data were summarised by group, reporting mean, standard deviation, median and range for continuous data, while for discrete data frequencies and proportions were reported. In either case 95% confidence intervals were reported. A one-sided χ^2 test was employed to compare study groups with respect to the incidence of postpartum infection. Multivariable logistic regression was used to control for confounders.

Results

Recruitment was from 9 March 2021 to 31 January 2022. During this period, 2 276 patients underwent caesarean sections, of whom 2 088 patients were eligible for inclusion. A total of 680 patients were excluded for various reasons. A total of 1 010 patients were part of this particular RCT, of which 507 patients were randomised to the control arm, and 503 patients to the intervention arm, as depicted in Fig. 1.

The mean age of the study population was 30.17 (range 18 - 47) years. There were no statistically significant patient characteristic differences between the intervention and control groups. Obstetric-related data, as well as the proportions of patients who were HIV-infected and who had type 2 diabetes, were also comparable. The data are shown in Table 1.

A total of 57 patients (5.64%) had surgical site infections, of which 27 (5.33%) were in the control group, and 30 (5.96%) were in the intervention group (p=0.66). Two patients in each arm (0.40% in the

intervention and 0.39% in the control arm) underwent laparotomy procedures, while three women (0.60%) in the intervention arm and four women (0.79%) in the control arm underwent hysterectomy procedures. There were no statistically significant differences in all the measured secondary outcomes between the two groups, as shown in Table 2.

There were 718 emergency caesarean sections, in which 41 women (5.7%) developed SSI, compared with 16 women (5.5%) who developed SSI of the 289 women who underwent elective caesarean section procedures (p=0.96).

Results for UTIs were available for 207 women in the control group and 187 women in the intervention group. Fifty-seven women (27.54%) in the control group and 49 women (26.2%) in the intervention group had UTIs (p=0.76) (Table 2).

Side-effects were comparable in the two groups. The most prevalent side-effect was nausea, which occurred in 13 patients (2.57%) in the control group and 8 patients (1.59%) in the intervention group. The rest of the side-effects are shown in Table 3.

Comparing different subgroups did not show significant differences between the intervention and control arms. These subgroups included elective and emergency caesarean section, HIV infection and diabetes mellitus. The multivariate analysis is shown in Table 4.

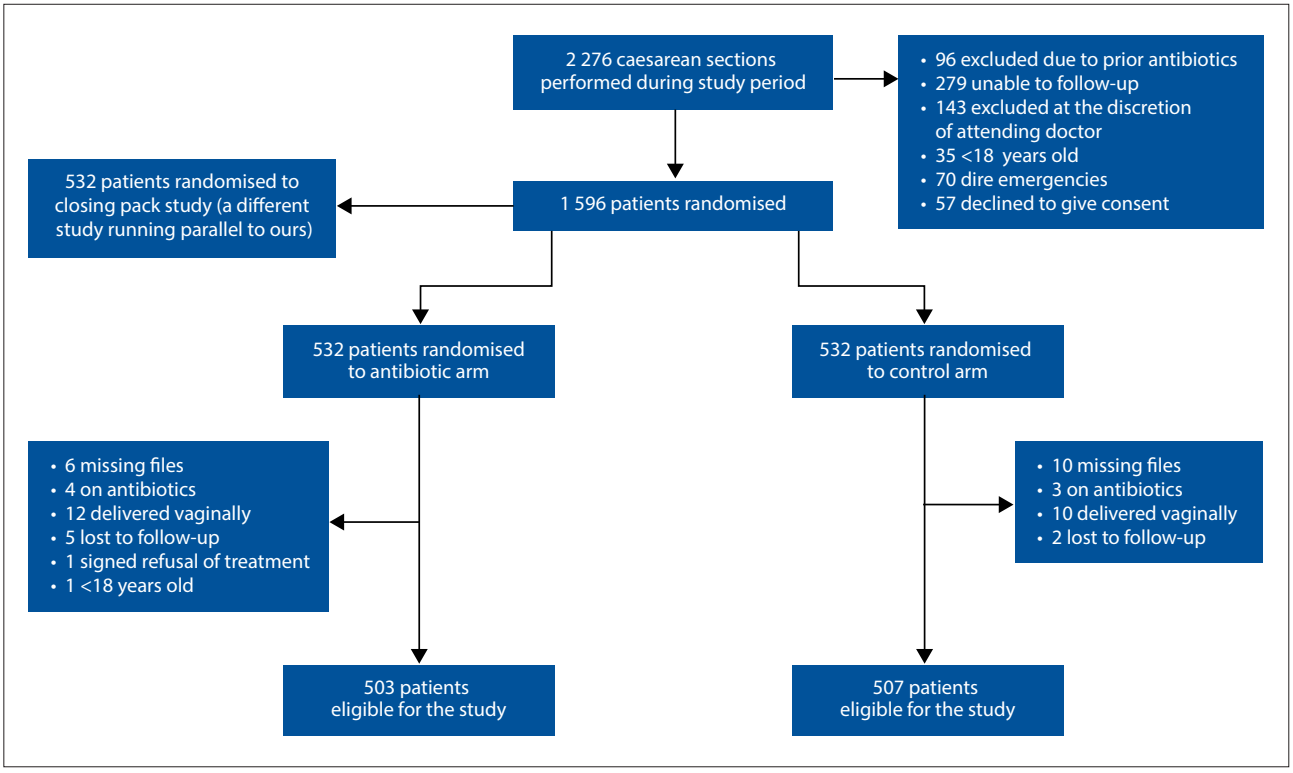

Fig. 1. Trial profile.

Table 1. Patient characteristics

Patient characteristic	Control (n=507)	Intervention (n=503)	p-value
Age (years)	30.3	29.9	0.27
Height (cm)	159	159	0.78
Weight (kg)	78.4	77.6	0.28
Parity	1.3	1.3	0.81
Gravidity	2.6	2.6	0.91
Smoking, n (%)	4 (0.79)	5 (0.99)	0.72
Comorbidity			
HIV-positive, n (%)	95 (18.7)	100 (19.92)	0.64
Diabetes mellitus, n (%)	17 (3.35)	15 (2.98)	0.73
Obstetric information			
Prolonged labour	45 (8.88)	30 (5.96)	0.07
Elective procedures, n (%)	149 (29.5)*	140 (27.9)†	0.57
Emergency procedures, n (%)	356 (70.5)	362 (72.11)	0.57
Pre operation haemoglobin value	12.3	12.4	0.47
Post operation haemoglobin value	11.1	11.02	0.31
Blood loss (mL)	539.9	557.3	0.69

* Control group: 2 patients not allocated to type of caesarean section.
†Intervention group: 1 patient not allocated to type of caesarean section.

Table 2. Secondary outcomes

Outcome, *n* (%)	Control (*n*=507), *n* (%)	Intervention (*n*=503), *n* (%)	*p*-value
Antibiotics administered	24 (4.73)	25 (4.97)	0.86
Wound dressings applied	23 (4.54)	25 (4.97)	0.74
Re-admission for treatment	10 (1.97)	9 (1.79)	0.83
Debridement of septic wounds	1 (0.2)	1 (0.2)	0.99
Laparotomy for sepsis	2 (0.39)	2 (0.40)	0.99
Hysterectomy for sepsis	4 (0.79)	3 (0.60)	0.71
Urinary tract infection	57/207 (27.54)	49/187 (26.2)	0.76
Side-effects of antibiotics	17 (3.3)	13 (2.5)	0.44

Table 3. Side-effects reported

Side-effect	Control group, *n* (%)	Intervention group, *n* (%)	Total, *n* (%)	*p*-value
Nil	488 (96.63)	490 (97.42)	978 (97.02)	0.46
Diarrhoea	0	1 (0.20)	1 (0.10)	0.31
Nausea	13 (2.57)	8 (1.59)	21 (2.08)	0.27
Vomiting	3 (0.59)	0	3 (0.30)	0.08

Table 4. Multivariate analysis

	Control group		Intervention group	
Variable	OR	95% CI	OR	95% CI
Emergency compared with elective caesarean section	0.70	0.31 - 1.56	1.58	0.63 - 3.97
HIV infection compared with HIV-negative	1.25	0.49 - 3.20	0.60	0.20 - 1.77
Diabetes mellitus compared with no diabetes mellitus	1.11	0.14 - 8.76	1.13	0.14 - 8.92

OR = odds ratio; CI = confidence interval.

Discussion

The overall sepsis rate in this study was 5.64%. This is in keeping with the reported incidence in the literature that ranges between 2.91% and 12.5%.[13-15] The power calculation for this trial was based on an expected incidence of surgical site infection of ~10% in the control arm. The SSI rate in this study was lower than expected. This study might therefore be underpowered if lower sepsis rates were used. However, we think the findings are still valid, because of the similarity between the two groups and the absence of any trends favouring the intervention group.

Emergency caesarean section cases carry a 2.5× increased risk of maternal complications. One study labelled emergency caesarean section as a significant risk factor in the development of postpartum infection.[16] The SSI rate in women undergoing elective caesarean sections (5.53%) in this study was similar to that of women undergoing emergency caesarean section (5.57%). Two studies from Nepal reported 6.58% and 33.5% wound infection in women undergoing emergency caesarean section compared with 3.44% and 7.0%, respectively, in elective procedures.[17,18] A study from India reported wound infection rates of 12.78% in women undergoing elective compared with 26.62% undergoing emergency caesarean section.[19]

This study confirmed the well-known increased risk for HIV-infected women to develop wound sepsis. In the intervention group, however, there was a decrease in the odds ratio (OR) in HIV-infected women. Although this was not statistically significant, most likely because of small patient numbers, HIV-infected women might benefit from adding metronidazole to kefazolin.

The incidence of UTIs was higher in both groups compared with what has been reported in the literature, with incidences ranging between 8.42% and 16.4% for patients undergoing caesarean section.[17,19] The UTI rate in this study was 26.9%, although only 39% of women had urine microscopy, culture and sensitivity as per the intention of the protocol.

Diabetes leads to dysfunction of the immune system. Diabetic patients are therefore also categorised as immunocompromised patients, and therefore more susceptible to infection than the general population.[20] No significant differences were found between the two groups.

More women in the control group required re-admission, but it was comparable with the intervention group. In both these categories there was a higher number of patients requiring intervention in the control group. Laparotomy procedures were performed in two patients in both groups, and there were no significant differences between the groups. Four patients underwent hysterectomy in the control group, constituting 0.39% of patients in the study, compared with three in the intervention group, constituting 0.29% of patients recruited in this study (p=0.71).

With the introduction of a second drug in the intervention group, side-effects were monitored to investigate whether the addition of metronidazole would result in increased side-effects. Although there was a greater number of patients in the intervention group without side-effects (97.42% compared with 96.63%) in the control group, it was not significant. The most common side-effect was nausea in both groups (Table 3).

Conclusion

This trial showed no statistically significant differences between patients receiving kefazolin only or kefazolin and metronidazole as prophylaxis in the prevention of postpartum infection at caesarean section. The current sepsis rate is low, indicating that current interventions are sufficient in the prevention of surgical site infection post caesarean section. The addition of a second antibiotic is currently not recommended for all patients but can be considered for HIV-infected women. UTIs post caesarean sections were high, and more meticulous monitoring of urine at antenatal visits is recommended.

Declaration. This work was submitted for RL's Masters in Medicine degree in Obstetrics and Gynaecology at the University of Pretoria.

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Author contributions. RL: principal investigator; LSn: supervisor; Lse: co-supervisor; GJ: fellow researcher data collection; PB: biostatistician

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Conflicts of interest. None.

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