BMC Pregnancy and Childbirth

RESEARCH

Open Access

Cefazolin versus placebo for surgical antibiotic prophylaxis in low-risk cesarean delivery: a feasibility blinded randomized controlled trial

Victoria A. Eley[1,2*], Severine Navarro[3,4], Elizabeth Martin[5,6], Akwasi Amoako[2,7], Gunter Hartel[8,9], Christine Woods[1,2], Yan Lu[3,4], Jeffrey Lipman[2,10,11], Jason Roberts[12,13], Mimi Tang[14,15] and Leonie Callaway[2,7]

Abstract

Background Pre-incisional antibiotics are recommended for all patients having cesarean delivery, despite emerging concerns regarding effects on the infant. In this feasibility blinded randomized controlled trial we aimed to test research processes in low-risk women receiving cefazolin or placebo prior to elective cesarean delivery.

Methods The trial was prospectively registered (ACTRN12619001705178). Eligible women were aged ≥ 18 and < 40 years, ≥ 37 weeks gestation, at low risk of surgical site infection (SSI) and recruited from a single tertiary centre. We reported proportions of women eligible and consenting; adherence to perioperative infection prevention; blinding adequacy of staff using Bang's blinding index; SSI surveillance and diagnosis according to the Centre for Disease Control definitions and patient reported outcome measures using validated questionnaires up to 90 days.

Results We screened 1651 women, with 1245 (75%) ineligible based on body mass index or presence of diabetes. Of 287 eligible women, 30 were randomized (11%) with 15 in each group. Reasons for non-participation included "wanting antibiotics" (68, 27%), "no reason" (62, 25%) and lack of research staff (33, 13%). Compliance with perioperative infection prevention occurred in 5 of 7 steps. Spontaneous placental separation occurred in 25 (83%) and Comfeel dressing in 29 (97%). Blinding was adequate for all staff groups. SSI surveillance occurred in 156 of 210 (74%) timepoints. SSI occurred in two patients who received pre-incisional cefazolin and were successfully treated as outpatients. Patient reported outcome questionnaires were completed at 136 of 180 (76%) timepoints. There was no difference in maternal health-related quality of life between the groups.

Conclusions Feasibility was impacted by the high-risk population and patient desire for antibiotics. Adherence to perioperative infection prevention practices were high but incomplete. These study processes could be effectively applied in a larger population, targeting low risk maternity patients.

Trial registration Prospectively registered 4/12/2019 with the Australian New Zealand Clinical Trials Registry (ACTRN12619001705178).

*Correspondence:
Victoria A. Eley
v.eley@uq.edu.au

Full list of author information is available at the end of the article

Keywords Allergy, Antibiotics, Atopy, Cesarean delivery, Surgical prophylaxis, Surgical site infection, Wound infection

Introduction

Routine administration of antibiotics to patients having cesarean delivery (CD) is recommended to reduce maternal surgical site infection (SSI) [1]. Following a Cochrane review published in 2014 [1], international guidelines have incorporated this recommendation for elective and emergency CD [2–5]. Another Cochrane review published in the same year supported antibiotic administration prior to skin incision rather than after cord clamping [6]. Both Cochrane reviews acknowledged that short-term and long-term effects on the neonate were unknown [1, 6]. Globally the rate of post-cesarean infection varies from 2.5 to 20.5%, with lower rates observed in high resource settings [5].

With over 40% of pregnant women receiving intrapartum antibiotics for a range of supported indications [7, 8], there is emerging concern that neonatal exposure to antibiotics can impact the neonatal microbiome, immune function and long term health [9–11]. While surgical antibiotic prophylaxis comprises a single dose, this results in therapeutic levels in the newborn [12]. There is uncertainty in the literature concerning the relative contribution of mode of delivery and timing of intrapartum antibiotic administration on demonstrated changes in the neonatal microbiome [13, 14]. With routine antibiotic administration now considered standard of care, it is difficult for researchers and clinicians to explore the potential impacts of pre-delivery antibiotics on the neonate at a metabolomic, microbiome and clinical level.

In this feasibility randomized controlled trial (RCT) we aimed to assess the feasibility of randomising women who were at low risk of SSI, to receive cefazolin or placebo prior to skin incision, in a setting where cefazolin administration is standard of care. Feasibility outcomes included recruitment rate, perioperative management adherence, blinding adequacy, SSI surveillance and global health questionnaire completion. Our results may provide foundational information to support a fully-powered RCT.

Materials and methods

This prospective, single centre, double-blind, concealed feasibility randomized controlled trial was undertaken at the Royal Brisbane and Women's Hospital (RBWH), Queensland, Australia. Ethical approval was granted by the Human Research Ethics Committee of the RBWH (HREC/2020/QRBW/58840, 17/2/2020) and the trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619001705178). RBWH is tertiary referral centre with approximately 4500 annual deliveries and a CD rate of 37%.

Feasibility outcomes included recruitment rate, perioperative management adherence, blinding adequacy, SSI surveillance and global health questionnaire completion. The primary clinical outcome measure was the incidence of infant allergic disease assessed using parental questionnaires based on modified Barwon Infant Study questionnaires administered by email at 12 months postdelivery [15]. These data will be reported separately, following completed analyses of collected biological samples (maternal blood, amniotic fluid, infant faeces, maternal breast milk).

Recruitment occurred in the pre-anesthesia clinic and written informed consent was obtained. Women were eligible if they were over 18 years of age, scheduled for elective CD and considered low risk of surgical site infection. Low risk was defined as < 40 years of age, a pre-pregnancy body mass index (BMI) < 25 kg/m^2, > 37 weeks gestation, membranes intact, not contracting, non-smoking, non-diabetic (Type 1, Type 2 or gestational diabetes), hemoglobin ≥ 110 g/L, American Society of Anesthesiologists score of 2 [16]. Women were excluded if they had a known allergy to cephalosporin antibiotics or chlorhexidine, conditions pre-disposing to hemorrhage (anticoagulation, thrombocytopaenia, abnormal placentation) conditions pre-disposing to infection (immunodeficiency, immunosuppression, autoimmune disorders, systemic steroid use), complex cardiac or respiratory disease, planned vertical uterine incision or planned use of a wound drain.

Participant characteristics collected included age, gestation, parity, ethnicity, BMI based on a weight within two weeks of delivery, overseas travel within six months, antenatal corticosteroid use, personal history of atopy, family history of atopy, existence of furred pets at home (inside or outside). Day of surgery data included lowest patient temperature pre-operatively, intraoperatively and post-operatively. Anesthesia details were recorded, included primary and secondary anesthesia technique. Anesthesia care was at the discretion of the anesthetist. Usual institutional care involves the insertion of an intravenous cannula, use of standard monitoring and placement of neuraxial anesthesia. Normotension was maintained using an infusion of phenylephrine or metaraminol. Within 30 min prior to skin incision [17] the intervention was administered by the intravenous route. The time of administration of the intervention was recorded, as was the time of skin incision.

The intervention was either 2 g cefazolin (antibiotic group) [2] or sodium chloride 0.9% (control group). Cefazolin was prepared in 100 mL of sodium chloride 0.9% and the placebo consisted of a 100 ml bag of sodium

chloride 0.9%, both with opaque labelling masking the contents of the bag. When diluted in 100 mL of normal saline, cefazolin is colour-free, odourless and does not cause pain or nausea on infusion. The participant and anesthetic, obstetric team and surgical nursing teams were blinded to allocation status. Block randomization was undertaken by an unblinded research staff member using the REDcap computerized facility, with a 1:1 allocation ratio and randomly chosen blocks of two, four or six. The unblinded staff member prepared the blinded intervention, which was provided to the treating anesthetist by a second, blinded research nurse. All other activities were undertaken by blinded research staff (consent, inpatient data collection and outpatient surveys).

Seven steps of perioperative infection prevention were standardized and recorded. These included: administration of intervention within 30 min of skin incision; skin preparation with alcoholic chlorhexidine solution; lower segment uterine incision only; spontaneous separation of placenta when possible; wound closure using sutures rather than staples, no routine use of a wound drain and use of a standardized wound dressing (Comfeel® Plus Transparent (Coloplast A/S, Humlebaek, Denmark). Vaginal preparation was recorded but not standardized.

Feasibility outcomes

The proportion of eligible women was calculated as a fraction of the total number screened and expressed as a percentage, as was the proportion of eligible women providing consent. Recruitment rate was reported as number of eligible women approached and number randomized, expressed as participants per month. The proportion of women excluded and reasons for exclusion were reported, together with any withdrawals. Reasons for non-participation were collected if freely offered.

Standardisation of perioperative infection prevention was assessed by observation and reported as the compliance with each of seven components of standardisation. Adequacy of blinding was assessed via survey [17], completed on the day of surgery by the most senior anesthetist and obstetrician present and the blinded research nurse providing the intervention. Personnel were required to indicate on a 5-point scale whether they thought the patient had received cefazolin or placebo, their degree of certainty and an overall blinding index was calculated [17].

For a woman who was admitted for three days, complete SSI surveillance included seven time points - daily until discharge and then on Days seven, 14, 21 and 30. Inpatient surveillance involved questioning of the participant, evaluation of the medical record and liaison with the treating team. Wounds were inspected if the participant reported discomfort. Outpatient surveillance consisted of questionnaire administered by telephone or REDcap email link according to participant preference. Women were asked if they had sought medical advice due to wound or other infection, who they consulted, whether they were diagnosed with an infection, samples were sent for microbiology, antibiotics were prescribed and if hospital admission was required. If there were concerns regarding the wound, referral was made for obstetric review. No actual or virtual inspection of the wound was made following discharge. Diagnosis of SSI was categorized according to the 2019 Centre for Disease Control and Prevention Procedure Associated Module [18]. Surveillance completion was reported as a proportion completed at the designated time points and as a percentage of the 210 available reviews (seven reviews for 30 participants).

Evaluation of patient-reported general health outcomes was undertaken using the validated PROMIS-10 Global Health Scale– Short Form 10a (Additional Fig. 1) [19] measured six times, on discharge, Day seven, 14, 21, 30 and 90. This 10-item questionnaire was administered in person on discharge day and subsequently via telephone or REDcap email link. Women responded to statements on five-point scales (and an 11-point scale for report of pain level). It measures health-related quality of life and utility values can be derived from the ten measures. 'Utility' is an economic term referring to satisfaction or happiness, and in health can be quantified for different states of health with a score of 0 being equivalent to death and a score of 1 being a state of full health [20]. PROMIS-10 completion was reported as a proportion of the total (six), at the designated time points and as a percentage of the 180 available for completion (six questionnaires for 30 women).

Sample size and statistical analysis

The aim was to test research processes and collect biological samples for bioanalysis after randomisation of 50 participants. While data pertaining to the primary outcome were collected, this was for feasibility purposes and the study was not powered to detect a significant difference in atopy between groups. We performed an intention-to-treat analysis and as-treated analysis. Descriptive statistics were used to summarize the data, with normally distributed variables presented as mean (SD) and non-normal variables as median (IQR). Bang's blinding index was calculated for research staff, anesthesia staff and obstetric staff. The reference range for this index is (−1 to 1), with a value of −1 indicating complete blinding, 0 indicating random guessing and 1 indicating complete unblinding. The index was presented with 95% confidence intervals (CI) and blinding considered adequate if the 95% CI included zero [18]. These analyses were undertaken using JMP Pro (v 17.2.0, SAS Institute, Cary, NC, USA).

A Health Measures [19] algorithm was used to derive utility values from the PROMIS-10 scores. Independent sample t-tests (for normally distributed samples) and Mann Whitney U tests were conducted to identify significant differences in the ten PROMIS-10 domains of health as well as utility values between the antibiotic and control groups. Univariate analysis was undertaken, including variables known to impact health-related quality of life (parity, gestation, ethnicity, age, birthweight, length of stay, family history of atopy, primary anesthetic technique, surgeon seniority, blood transfusion, feeding method on discharge), or those identified as significantly different between groups, in the descriptive analysis. Potential predictors of utility values were included in a linear regression model, along with the variable antibiotic/control. Significant variables in the univariate analysis were included in multivariable linear regression models. A parsimonious approach was taken, applying stepwise backward elimination and a p-value < 0.05 was considered significant. These analyses were undertaken using SPSS (IBM Version 29.0. Armonk, NY: IBM Corp).

Results

Recruitment occurred over 22 months between August 2021 and June 2023. Due to a low proportion of eligible women, slow recruitment and resource restriction, recruitment ceased after 30 women were randomized. The recruitment flowchart is shown in Fig. 1. Of 1651 patients screened, 287 (17.4%) were eligible. Of the 287 eligible women, 30 (10.5%) consented and were randomized. The recruitment rate was 1.4 per month. The main reasons for ineligibility were pre-pregnancy BMI > 25 kg/m^2 (855, 63%), the presence of diabetes (390, 29%) and factors pre-disposing to hemorrhage (320, 23%). The most common reasons for non-participation of 257 eligible women were: declined (wanted antibiotics, 68, 27%), declined (no reason offered, 63, 25%) and lack of research or laboratory staff (33, 13%). All reasons for ineligibility and non-participation are summarized in Tables 1 and 2. Seventy-one eligible women were incorrectly excluded, on the basis of their breech presentation. Of the 30 consenting participants, all were randomized, 15 to each group. Unblinding occurred in two control group participants who were administered cefazolin; one inadvertent and one intentional (following discovery of localized folliculitis). One woman in the antibiotic group withdrew on Day 19 post-operatively due to having an unwell baby. SSI surveillance and PROMIS questionnaires were partially completed and included in this analysis.

Table 3 shows the participant characteristics, surgical and anesthesia information, by intention to treat. Additional Table 1 presents the as-treated analysis, with 13 receiving normal saline and 17 receiving antibiotics. There was no statistically significant differences between the groups in terms of age, gestation, ethnicity, BMI at delivery, personal or family history of atopy and furred pets at home. No women were administered antenatal corticosteroids. The primary anesthetic technique was neuraxial in all cases, (one woman in the antibiotic group required general anesthesia due to inadequate neuraxial anesthesia). Specialist surgeons were present for most cases. The mean (SD) duration of surgery was 83 (22) minutes and there was no difference between the groups. One patient in the antibiotic group required intraoperative transfusion. The median (range) length of inpatient stay was 2.3 (1.3–8.2) days.

The intervention was administered to 29 women within 30 min of skin incision; in one woman it was administered at skin incision. The mean (SD, range) interval between intervention and skin incision was 12.1 (11.1, 0.0–42.0) minutes. In 30 (100%) there was compliance with 5 of 7 infection prevention steps. All had surgical skin preparation with chlorhexidine, a lower uterine segment incision, delayed cord-clamping, skin closure using sutures and none had a wound drain inserted. A Comfeel dressing was used in 29 (97%), spontaneous separation of the placenta occurred in 25 (83%) and eight (27%) had vaginal preparation performed (Table 3).

Blinding questionnaires were completed by anesthetic, obstetric and research nurse personnel for 28 women, excluding the two women in whom unblinding occurred. The blinding indices (95% CI) for research staff: cefazolin 0.13 (-0.23, 0.50), placebo 0.77 (-0.32, 0.47); for anesthesia staff: cefazolin −0.27 (-0.61, 0.08) placebo −0.15 (-0.44, 0.14); for obstetric staff: cefazolin 0.07 (-0.16, 0.29) placebo 0.00 (-0.21, 0.21), indicating adequate blinding within all groups.

SSI surveillance occurred at 156 of 210 (74%) timepoints. Seven post-operative SSI surveillance reviews were completed for 9 (30%) women, six reviews in eight (27%) and five reviews in seven (23%) women. The minimum SSI surveillance was two time-points in one woman. The woman who withdrew completed four SSI surveillance reviews. Figure 2 shows the completion of SSI surveillance by women in the two groups and the timing of the SSI diagnoses. Two women reported SSI, both in the antibiotic group. Both infections were diagnosed by general practitioners with outpatient oral antibiotic treatment. Endometritis was diagnosed on Day 21 and treated for seven days with amoxycillin and metronidazole. A superficial SSI was diagnosed on Day 20 and treated for six days with oral cefazolin. Microbiology results were unavailable. In four other patients, oral antibiotics were administered for non-SSI indications: mastitis (three) and folliculitis (one).

PROMIS-10 questionnaires were completed at 136 of 180 (76%) timepoints. All six post-operative questionnaires were completed by seven (23%) women, five

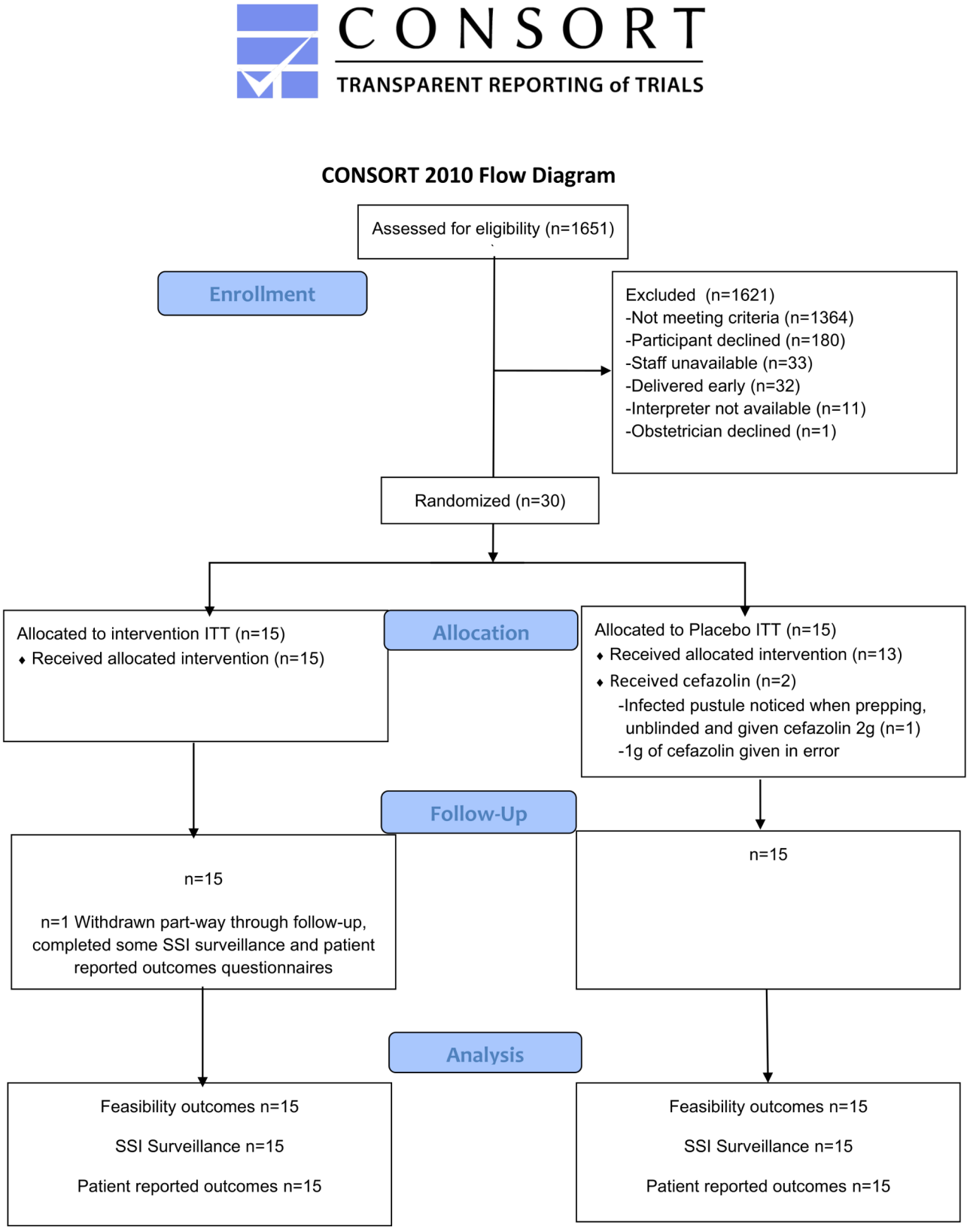

Fig. 1 CONSORT flowchart. ITT = intention to treat; SSI = Surgical site infection

Table 1 Reasons for non-participation, 257 patients meeting inclusion and exclusion criteria and not participating

Reason	Number (%)
Declined, wanted antibiotics	68 (27)
Declined, no reason provided	63 (25)
Research or laboratory staff unavailable	33 (13)
Delivered prior to scheduled date	32 (13)
Declined (other)	15 (6)
Declined, already in another study	12 (5)
Declined, anxious	11 (4)
Interpreter not available	11 (4)
Declined, concerns about baby	9 (4)
Declined, not willing to be followed-up	2 (0)
Obstetrician declined	1 (0)

Table 2 Reasons for ineligibility in 1364 screened women not meeting inclusion and exclusion criteria

Inclusion criteria*	Number (%) not meeting criteria
Pre-pregnancy body mass index < 25 kg/m2	855 (63)
Non-diabetic	390 (29)
Age 18–40 years	80 (6)
Singleton pregnancy	59 (4)
Non-smoking	38 (3)
Hemoglobin > 110 g/L	28 (2)
ASA ≤ 2	20 (1)
Membranes intact	3 (0)
All inclusion criteria satisfied	240 (18)
Exclusion criteria*	
Factors predisposing to hemorrhage	320 (23)**
Factors predisposing to infection	129 (9)
Significant cardiovascular or respiratory disease	51 (4)
Planned vertical uterine incision	5 (0.4)
Unable to consent	3 (0.0)
Allergy to chlorhexidine	1 (0.0)
All exclusion criteria satisfied	906 (66)

*more than one may apply

**71 patients were incorrectly excluded on the basis of breech presentation

questionnaires completed by 10 (33%) and four completed by seven (23%). The minimum completion was two questionnaires, by two (7%) women. The woman who withdrew completed two questionnaires. Questionnaires were not necessarily completed on schedule and mean utility values were calculated for a point in time that ranged several days in reality The ten domains of health measured using the PROMIS-10 and utility were not significantly different between the antibiotic and control groups at any time points in either the univariate of multivariable analysis. Differences in utility value mean are reported in Fig. 3.

Discussion

The recruitment rate was slower than anticipated and impacted by strict inclusion criteria, unavailability of research staff and patient reluctance to participate. Administration of the intervention occurred prior to skin incision in 29 of 30 cases and adherence to other intraoperative procedures was incomplete. Presentation of cefazolin in 100 ml normal saline proved to be adequate in terms of blinding, masking colour, odour of cefazolin and the recognized discomfort on injection. This is essential in a placebo-controlled trial undertaken in awake patients. Participant compliance with SSI surveillance and patient reported outcome questionnaires was high, but incomplete. The two SSI diagnosed in women receiving antibiotics were diagnosed and managed successfully in a primary care setting.

For ethical acceptability, we recruited women at very low risk of SSI. Our definition of low-risk was based on identified risk factors for infection, expert opinion and tended to very conservative [21–26]. As a tertiary referral centre, this substantially reduced the number of eligible patients. Obesity and gestational diabetes, both occurring commonly in Australian maternity care, were also commonly identified as reasons for not meeting inclusion/exclusion criteria. A local multisite survey indicated that women had concerns about the use of antibiotics in the peripartum period [27]. However, it is possible that community attitudes toward infection prevention and treatment (bacterial and viral) were influenced by the COVID pandemic which was ongoing during the first year of recruitment. Obstetric and anesthesia staff were largely comfortable with randomization of these low-risk women.

Standardisation of intraoperative procedures was defined in the protocol based on factors known to influence SSI. Skin preparation, uterine incision, delayed cord-clamping, skin closure and lack of wound drain were consistently applied to all patients. While use of a standardized dressing is relatively easy to address, spontaneous separation of the placenta (where possible) is harder to standardize. While the World Health Organisation recommends vaginal preparation with povidone-iodine for all elective and emergency CD [28], in the RBWH it is generally reserved for emergency CD. Dressing type, spontaneous separation of the placenta and vaginal preparation may all influence SSI and would be important to control between groups in a larger study [29]. For a multicentre study, this would require confirmation of site-specific policies and practices relating to vaginal preparation and methods of placental delivery.

Surveillance for SSI according to CDC criteria is costly in terms of time and human resources. Our study has demonstrated effective surveillance of post-partum women via telephone and REDcap email link, despite the

Table 3 Characteristics, anesthesia and surgical information for 30 women and their 30 neonates. Intention-to-treat analysis. Data are reported as number (%) except when indicated

Characteristics	Control Group *n* = 15	Antibiotic Group *n* = 15
Age (mean, SD)	34.9 (3.3)	34.5 (4.4)
BMI at delivery mean (SD), range	25.0 (3.6)	24.4 (3.0)
Ethnicity		
Caucasian	11 (73)	10 (67)
Asian	4 (27)	3 (20)
Indian	0 (0)	1 (7)
Other	0 (0)	1 (7)
Nulliparous	2 (13)	1 (7)
Gestation (weeks, mean, SD)	39.3 (0.7)	39.1 (0.7)
Recent overseas travel	0 (0)	1 (7)
Personal history of atopy	1 (7)	2 (13)
Family history of atopy	7 (47)	4 (27)
Furred pets at home	7 (47)	6 (40)
Primary anesthesia technique		
Neuraxial	15 (100)	15 (100)
Second anesthesia technique		
Neuraxial	0 (0)	1 (7)
General anesthesia	0 (0)	1 (7)
Surgeon seniority		
Specialist	9 (60.0)	11 (73)
Pre-operative lowest temperature* mean (SD)	36.8 (0.4)	36.7 (0.3)
Intraoperative lowest temperature* mean (SD)	36.4 (0.5)*	36.3 (0.4)**
Recovery lowest temperature* mean (SD)	36.2 (0.2)	36.2 (0.4)
Time between administration of intervention and knife-to-skin, minutes, mean (SD), range	13.4 (11.1) (0.0–42.0)	10.8 (11.3) (1.0, 36.0)
Inpatient length of stay, days median (range)	2.3 (1.3–4.5)	2.4 (1.5–8.2)
Vaginal preparation with betadine	4 (27)	4 (27)
Spontaneous placental separation	12 (80)	13 (87)
Comfeel dressing used	15 (100)	14 (93)
Duration of surgery, minutes, mean (SD)	85.9 (21.5)	80.7 (23.1)
Inpatient length of stay, days (median, range)	2.3 (1.3–4.5)	2.4 (1.5, 8.2)
Apgar score 5 min, mean (SD)	8.9 (0.6)	8.6 (1.4)
Birthweight, grams, mean (SD)	3486 (419.9)	3381 (422.5)
Birth length, cm, mean (SD) (missing = 1, Antibiotic Group)	51.9 (5.7)	50.5 (4.9)
Discharge destination		
Ward	11 (73)	11 (73)
Special care nursery	2 (13)	1 (7)
Intensive care nursery	2 (13)	3 (20)
Feeding method on discharge		
Breast	14 (93)	11 (73)
Formula	0 (0.0)	1 (7)
Mixed	1 (7)	3 (20)

*Degrees Celsius **10 missing values *** 6 missing values

post-partum period being a tumultuous time for women and their families. High completion rates of patient reported outcome measure questionnaires via telephone or email link was also demonstrated, indicating that this is an effective way of evaluating general health in this specific population. Completion of these questionnaires has provided important preliminary economic evaluation data in terms of the differences in utility when comparing antibiotic and control groups.

Once interventions are embedded in international recommendations, it is challenging to re-evaluate their appropriateness with placebo-controlled RCTs. Despite surgical antibiotic prophylaxis being considered standard of care for CD, there was sufficient equipoise to allow ethics approval for this feasibility, blinded, placebo-controlled RCT. In modern maternity practice, this is the first placebo-controlled RCT to evaluate pre-incisional antibiotics with the overarching aim of assessing neonatal outcomes, rather than maternal SSI. Administration

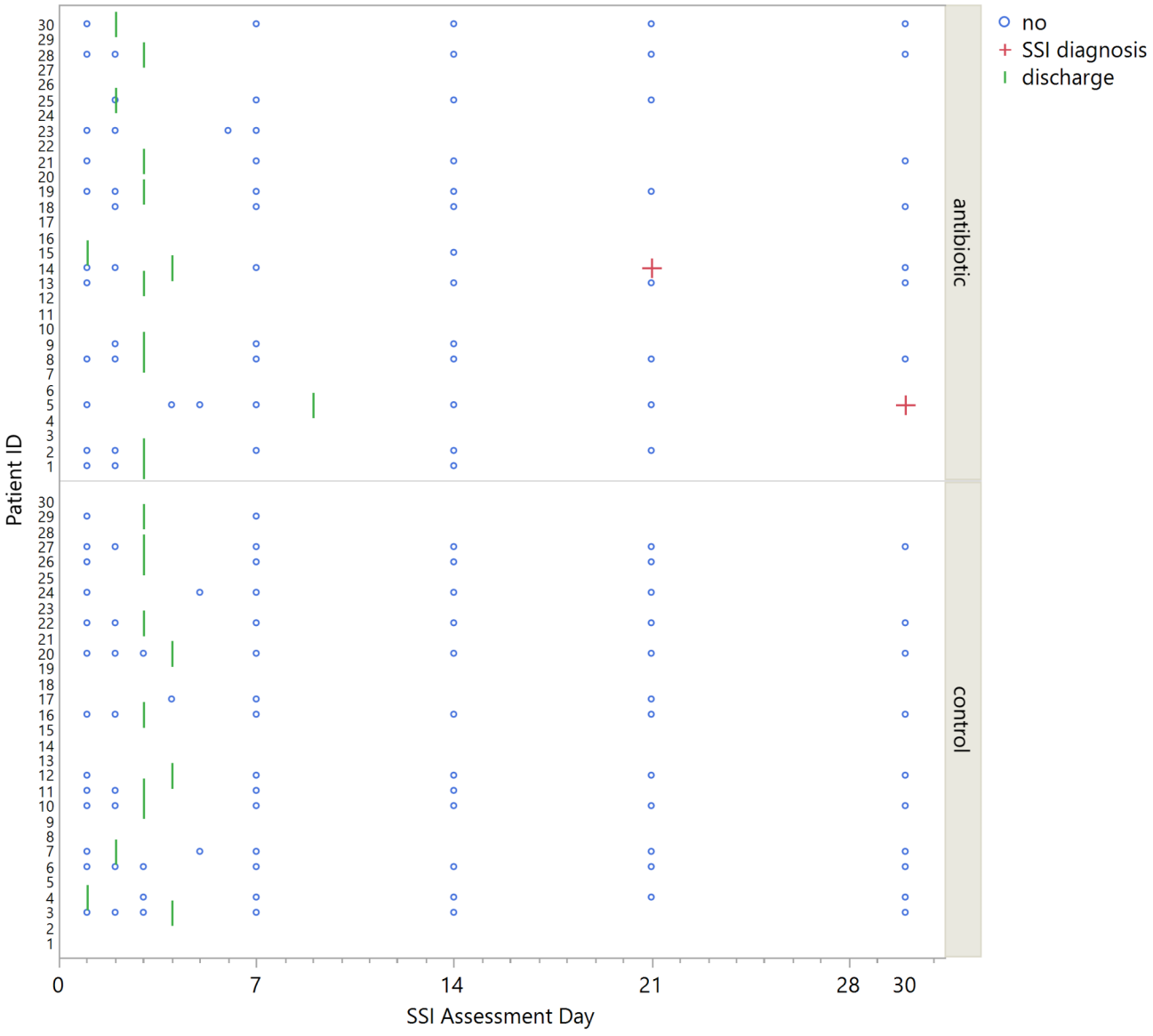

Fig. 2 Surgical site infection (SSI) surveillance and diagnosis

of antibiotics following cord-clamping also reduces SSI [1] and may be more attractive to study participants. However this timing also results in antibiotic excretion in breast milk, resulting in exposure in breastfeeding infants. Although our sample was smaller than anticipated, we have tested our research processes, demonstrated acceptability to patients and clinicians, effective blinding of the intervention and reported high rates of participant compliance with follow-up questionnaires.

As a high resource setting, the baseline rate of infection following CD at this facility would be at the lower end of published ranges [5]. A baseline rate of SSI is to be expected both with and without antibiotic administration; two were detected in the antibiotic group, treated with outpatient oral antibiotics, with no long-term patient harm. While we did not undertake actual or visual wound inspection, we have highlighted that postoperative wound care occurred in a primary care rather than hospital setting and dedicated follow-up is essential for research purposes. The proportion of eligible patients was very low due to our strict inclusion criteria and subsequently the recruitment rate low, impacting feasibility. Inaccurate application of exclusion criteria had a moderate impact on overall eligibility. The pending results of microbiome and metabolome analyses may provide further support for a fully powered study comparing the effect of antibiotics on neonatal outcomes. If so, dissemination to prospective participants could improve the recruitment rate in future studies. Our groups were small and only feasibility outcomes can be concluded from the

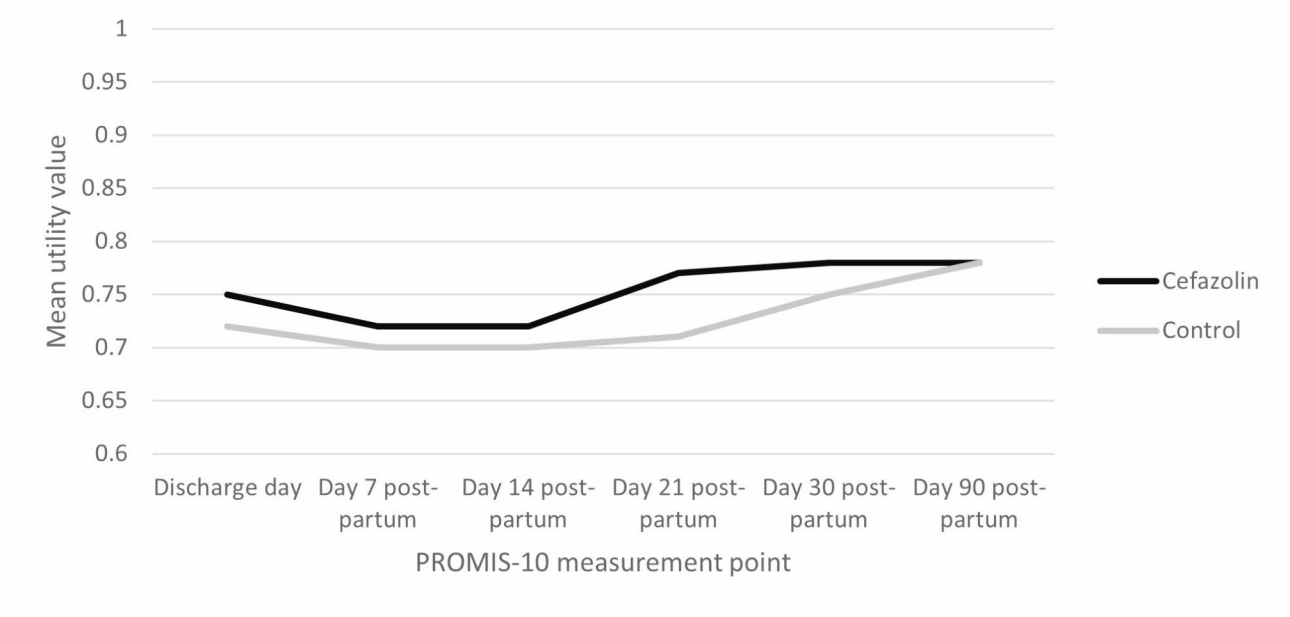

Fig. 3 Mean utility scores for the cefazolin and control groups at each PROMIS-10 measurement point post-partum

data. No inference can be drawn from the SSIs occurring in those receiving antibiotic prophylaxis.

Conclusions

We have demonstrated successful study processes that were hindered by very low recruitment rates. Only with additional project promotion and resourcing, could these processes be effectively applied in a larger population, specifically targeting non-tertiary maternity patients. Reluctance of eligible women to consent to the randomisation may change over time as evidence emerges regarding the effects of peripartum antibiotics on infants. Ongoing re-evaluation of embedded prophylactic healthcare interventions in maternity care is required to avoid unintended effects on maternal and infant outcomes.

Abbreviations

BMI	Body mass index
CD	Cesarean delivery
RBWH	Royal Brisbane and Women's Hospital
RCT	Randomized controlled trial
SSI	Surgical site infection

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-025-07484-5.

Supplementary Material 1: **Additional Table 1:** As-treated analysis.

Supplementary Material 2: **Additional Fig. 1:** PROMIS 10 Questionnaire.

Acknowledgements

The authors would like to thank Ms Margarette Somerville, Dr Heather Reynolds and Ms Jodie Genzel, Department of Anaesthesia and Perioperative Medicine, Royal Brisbane and Women's Hospital, for their assistance with data collection.

Author contributions

VE original conception and design, analysis and interpretation of data, drafting the article, final approval of manuscript; SN contribution to original conception and design, interpretation of data, critical revision of the article, final approval of manuscript; EM contribution to original conception and design, analysis and interpretation of data, critical revision of the article, final approval of manuscript; AA contribution to original conception and design, interpretation of data, critical revision of the article, final approval of manuscript; GH contribution to original conception and design, analysis and interpretation of data, critical revision of the article, final approval of manuscript; CW contribution to original conception and design, interpretation of data, critical revision of the article, final approval of manuscript; YL contribution to original conception and design, interpretation of data, critical revision of the article, final approval of manuscript; JL contribution to original conception and design, interpretation of data, critical revision of the article, final approval of manuscript; JR contribution to original conception and design, interpretation of data, critical revision of the article, final approval of manuscript; MT contribution to original conception and design, interpretation of data, critical revision of the article, final approval of manuscript; LC: original conception and design, interpretation of data, critical revision of the article, final approval of manuscript. All authors agree to be accountable for all aspects of the work.

Funding

Funding was provided by Metro North Collaborative Research Grant CRG-267-2021; Children's Hospital Foundation Preclinical and Clinical Early Career Project Grant CR0062020; 2021 Ferring Pharmaceuticals Research Grant; VE was supported by a Metro North Clinician Research Fellowship CRF-128-2021; The University of Queensland provided co-funding to the Fellowship; SN was supported by Children's Hospital Foundation Grant RCP10317. The funders did not contribute to the design of the study, analysis and interpretation of data or preparation of the manuscript.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval was granted by the Human Research Ethics Committee of the Royal Brisbane and Women's Hospital (HREC/2020/QRBW/58840, 17/2/2020). Written informed consent was obtained from all participants. The project was conducted in compliance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Anaesthesia and Perioperative Medicine, The Royal Brisbane and Women's Hospital, Butterfield St, Herston, Brisbane 4006, Queensland, Australia
[2]Medical School, Faculty of Medicine, The University of Queensland, St Lucia 4067, Brisbane, QLD, Australia
[3]Mucosal Immunology, QIMR Berghofer Medical Research Institute, Herston, Brisbane 4006, Australia
[4]Centre for Childhood Nutrition Research, Queensland University of Technology, Brisbane, Australia
[5]Wesley Research Institute, Auchenflower, Queensland 4066, Australia
[6]Mater Research Institute, The University of Queensland, South Brisbane 4101, Brisbane, QLD, Australia
[7]Women's and Newborns Services, The Royal Brisbane and Women's Hospital, Butterfield St, Herston, QLD 4006, Australia
[8]Statistics Unit, QIMR Berghofer Medical Research Institute, Herston, Brisbane 4006, Australia
[9]School of Public Health, The University of Queensland, Brisbane, QLD, Australia
[10]Jamieson Trauma Institute, The University of Queensland, St Lucia 4067, Brisbane, QLD, Australia
[11]Nimes University Hospital, University of Montpellier, Nimes, France
[12]Centre for Clinical Research, Faculty of Medicine, University of Queensland, The University of Queensland, Brisbane, Australia
[13]Herston Infectious Diseases Institute (HeIDI), Metro North Health, Brisbane 4006, Australia
[14]Allergy Immunology, Murdoch Children's Research Institute, Parkville, VIC 3052, Australia
[15]Department of Paediatrics, The University of Melbourne, Parkville, VIC 3052, Australia

Received: 2 February 2024 / Accepted: 17 March 2025
Published online: 26 March 2025

References

1. Smaill FM, Grivell RM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database of Systematic Reviews 2014(10): [CD007482].
2. Therapeutic Guidelines Ltd. Therapeutic guidelines: eTG complete 2021. Antibiotic: Surgical antibiotic prophylaxis for specific procedures. https://tgldcdp-tg-org-au.ezproxy.library.uq.edu.au/quicklinks?type=Pregnancy%20and%20breastfeeding%26;bf=5a58609.htm (Accessed January 22, 2024).
3. National Institute for Health and Care Excellence. (2019) Surgical site infections: prevention and treatment. (NICE Guideline NG125) https://www.nice.org.uk/guidance/ng125. Accessed January 22, 2024.
4. American College of Obstetricians and Gynecologists. Use of prophylactic antibiotics in labor and delivery. ACOG Pract Bull 199 Obstet Gynecol. 2018;132:e103–19.
5. World Health Organization. WHO recommendation on prophylactic antibiotics for women undergoing caesarean Sect. (2021). https://www.who.int/publications/i/item/9789240028012. Accessed January 22, 2024.
6. Mackeen AD, Packard RE, Ota E, Berghella V, Baxter JK. Timing of intravenous prophylactic antibiotics for preventing postpartum infectious morbidity in women undergoing Cesarean delivery. Cochrane Database Syst Reviews 2014(12) CD009516–CD.
7. National Institute for Health and Care Excellence. (2021). Neonatal infection: antibiotics for prevention and treatment. (NICE Guideline NG195) www.nice.org.uk/guidance/ng195. Accessed January 22, 2024.
8. Broe A, Pottegård A, Lamont RF, Jørgensen JS, Damkier P. Increasing use of antibiotics in pregnancy during the period 2000–2010: prevalence, timing, category, and demographics. BJOG. 2014;121:988–96.
9. Coker MO, Hoen AG, Dade E, Lundgren S, Li Z, Wong AD, Zens MS, Palys TJ, Morrison HG, Sogin ML, et al. Specific class of intrapartum antibiotics relates to maturation of the infant gut microbiota: a prospective cohort study. BJOG. 2020;127:217–27.
10. Wopereis H, Oozeer R, Knipping K, Belzer C, Knol J. The first thousand days–intestinal microbiology of early life: establishing a symbiosis. 2014: 428–438.
11. Kenyon S, Pike K, Jones D, et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. Lancet. 2008;372:1319–27.
12. 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.
13. Stearns JC, Simioni J, Gunn E, McDonald H, Holloway AC, Thabane L, Mousseau A, Schertzer JD, Ratcliffe EM, Rossi L, et al. Intrapartum antibiotics for GBS prophylaxis alter colonization patterns in the early infant gut Microbiome of low risk infants. Sci Rep. 2017;7:16527.
14. Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, Jernberg C, Björkstén B, Engstrand L, Andersson AF. Decreased gut microbiota diversity, delayed bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. Gut. 2014;63:559–66.
15. Vuillermin P, Saffery R, Allen KJ, Carlin JB, Tang ML, Ranganathan S, Burgner D, Dwyer T, Collier F, Jachno K. Cohort profile: the Barwon infant study. Int J Epidemiol. 2015;44:1148–60.
16. American Society of Anesthesiologists. ASA Physical Status Classification System. (2014) https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system Accessed January 22, 2024.
17. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Control Clin Trials. 2004;25:143–56.
18. Centre for Disease Control and Prevention, Procedure-Associated Module CDC. SSI. (2019) https://www.cdc.gov/nhsn/faqs/faq-ssi-proc-codes.html] Accessed January 22, 2024.
19. Code Technology. PROMIS Global-10. (2019) https://www.codetechnology.com/promis-global-10/ Accessed January 22, 2024.
20. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Amtmann D, Bode R, Buysse D, Choi S, et al. The Patient-Reported outcomes measurement information system (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol. 2010;63:1179–94.
21. Carbonnel M, Brot D, Benedetti C, Kennel T, Murtada R, Revaux A, Ayoubi J-M. Risks factors for wound complications after Cesarean section. J Gynecol Obstet Hum Reprod. 2021;50:101987.
22. Acosta CD, Bhattacharya S, Tuffnell D, Kurinczuk JJ, Knight M. Maternal sepsis: a Scottish population-based case-control study. BJOG. 2012;119:474–83.
23. Kvalvik SA, Rasmussen S, Thornhill HF, Baghestan E. Risk factors for surgical site infection following Cesarean delivery: A hospital-based case–control study. Acta Obstet Gynecol Scand. 2021;100:2167–75.
24. Saeed KB, Corcoran P, O'Riordan M, Greene RA. Risk factors for surgical site infection after Cesarean delivery: a case-control study. Am J Infect Control. 2019;47:164–9.
25. Wloch C, Wilson J, Lamagni T, Harrington P, Charlett A, Sheridan E. Risk factors for surgical site infection following caesarean section in England: results from a multicentre cohort study. BJOG. 2012;119:1324–33.
26. Haidar ZA, Nasab SH, Moussa HN, Sibai BM, Blackwell SC. Caesarean delivery surgical site infection: what are expected rates and potentially modifiable risk factors? J Obstet Gynecol Can. 2018;40:684–9.
27. Black M, Kothari A, Chawla G, Pelecanos A, Zahumensky A, McDermott L, O'Connor H, Kalma B, Eley V. Attitudes and awareness of Australian women regarding peripartum antibiotic use: A multicentre survey. Aust N Z J Obstet Gynaecol. 2023;63:171–7.
28. World Health Organization. WHO recommendation on Vaginal preparation with antiseptic agents for women undergoing caesarean Sect. (2021) https://www.who.int/publications/i/item/9789240028067 Accessed January 22, 2024.
29. Martin E, Beckmann M, Barnsbee L, Halton K, Merollini K, Graves N. Best practice perioperative strategies and surgical techniques for preventing

caesarean section surgical site infections: a systematic review of reviews and meta-analyses. BJOG. 2018;125:956–64.

Publisher's note