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Efficacy of adjunctive azithromycin versus single-dose cephalosporins prophylaxis for caesarean scar defect : study protocol for a randomized controlled trial

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Manuscripts

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4 **Efficacy of adjunctive azithromycin versus single-dose cephalosporins**
5 **prophylaxis for caesarean scar defect : study protocol for a randomized controlled**
6 **trial**
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45
46 **ABSTRACT**
47

48 **Introduction** Perioperative infection should be considered predictors of caesarean scar
49 defect (CSD), and multi-dose antibiotics have a protective effect. However, the effects
50 of using adjunctive azithromycin combined cephalosporins to reduce the prevalence of
51 CSD remain unclear. The planned study aims to clarify the protective effect of
52 antibiotics on CSD and to assess the effectiveness of adjunctive azithromycin
53 prophylaxis for CSD.
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58 **Methods and analysis** This study is an open-label, double-blind, parallel control
59 randomized clinical trial in the International Peace Maternity & Child Health Hospital.
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3 Eligible patients will be randomised (1:1) to receive either adjunctive azithromycin or
4 single-dose cephalosporin 30 minutes before the incision. The evaluation criteria are
5 the prevalence and characteristics of CSD as assessed by transvaginal ultrasound (TVU)
6 and saline infusion sonohysterography (SIS) at 42 days, 6 months and 12 months after
7 delivery.
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10
11 **Ethics and dissemination** This protocol received authorization from the Medical
12 Research Ethics Committee of International Peace Maternity and Child Health Hospital
13 on 25 April 2018(approval no. GKLW2017-84). Findings will be distributed through
14 peer-reviewed publications and presentations at international scientific meetings.
15
16

17 **Trial registration number** ChiCTR-INR-17013272
18

19 **Keywords:** caesarean section, caesarean scar defect, azithromycin, RCT, antibiotic
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22 23 24 **ARTICLE SUMMARY**

25 26 **Strengths and limitations of this study:**

- 27
28 1. This is the first interventional randomized controlled trial with the primary aims of
29 assessing the protective effect of antibiotics for CSD and investigating the
30 relationship of CSD occurrence and preoperative infection.
31
32
- 33 2. This study is based on a previous cohort study to improve the study effectiveness
34 and quality of the study objectives¹.
35
36
- 37 3. This is the first time to set the initial CSD assessment timepoint as 6 weeks
38 postpartum and follow patients for 1 year. We can find the optimal timepoint for
39 the early detection of CSD.
40
41
- 42 4. The study is a randomized controlled trial with a relatively large sample size, long
43 follow-up period, and an active control group to control for non-specific effects.
44
45
- 46 5. The trial is based in a single center and only Chinese individuals are included,
47 which might limit the generalizability of the findings.
48

49 50 **INTRODUCTION**

51 The rate of caesarean section (CS) delivery is increasing worldwide, especially in
52 China due to the prevalence of maternally requested caesarean deliveries and the 30-
53 year national one-child policy^{2 3}. According to the data from official figures of the
54 China National Bureau of Statistics, there were approximately 17 million newborns in
55 China in 2017, with caesarean delivery rate of approximately 40%, which means that
56 there are approximately 7 million CS deliveries each year⁴.
57
58

59 Caesarean scar defect (CSD) is associated with abnormal uterine bleeding (75-
60

82%), postmenstrual spotting (29-34%) and caesarean scar ectopic pregnancies (1:1,800-1:2,216) and infertility (32/92^{5 6}). Uterine dehiscence, uterine rupture, caesarean scar pregnancy and morbidly adherent placenta are also associated with CSD⁷⁻¹⁰. There are thousands of fatalities or cases of near-death caused by uterine rupture or haemorrhage originated to CSD annually^{1 11}.

In a random population of women with a history of CS, the prevalence of CSD ranged from 24% to 70% and 56% to 84% when assessed by TVU with and without contrast enhancement, respectively. saline infusion sonohysterography (SIS) is better than traditional TVU for characterizing CSD and has a higher sensitivity¹²⁻¹⁴. Moreover, sonohysterography can more precisely evaluate the size and shape of the defect and thus severity^{2 15-17}. We will record data to compare the difference in these two methods.

Our previously published data first introduced the CSD prevalence in Shanghai of 43.4% (95% confidence interval (CI)=39.1-47.7%, N=514), which is a cause for concern¹. Our cohort study also revealed that infection might be an important risk factor for CSD and that multi-dose antibiotic administration has a significant protective effect compared with single-dose antibiotics (CSD prevalence 31.1%, 95% CI=23.8-38.3% versus 49.0%, 95% CI=43.8-54.3%; aOR=10.4, 95% CI=0.3-0.7)¹⁸⁻²⁰. Furthermore, the single-dose cefuroxime subgroup (n=190) was found to have a significantly lower CSD prevalence than the single-dose cefradine subgroup (n=162) (38.9%, 95% CI=34.7-48.6% vs 56.8%, 95% CI=51.3-66.7%; aOR=0.5, 95% CI=0.3-0.8, P = 0.006). These results strongly indicate that antibiotics may be a protective factor for CSD^{21 22}.

According to the results of pathogen monitoring for nosocomial infections, ureaplasma urealyticum, *escherichia coli*, *enterococcus* and *streptococcus* are the most common infectious agents^{23 24}. Second-generation cephalosporins have a stronger antibacterial effect on *escherichia coli* and *enterobacteriaceae* than first-generation cephalosporins, while azithromycin has stronger antibacterial and bacteriostatic effects on atypical pathogens, such as *mycoplasma chlamydia* and anaerobic bacteria²⁵⁻²⁷. Current recommendations for antibiotic prophylaxis in cesarean delivery include standard use of a narrow-spectrum antibiotic administered before skin incision, most commonly a first-generation cephalosporin. Recent reports on adjunctive azithromycin prophylaxis for caesarean delivery have shown a significant protective effect for maternal endometritis (3.8% vs 6.1%, P=0.02), wound infection (2.4% vs 6.6%, P<0.001), and serious maternal adverse events (1.5% vs 2.9%, P=0.03), while there was no significant between group difference in secondary neonatal composite outcomes²⁸. In a word, the addition of azithromycin to cesarean delivery prophylaxis is less costly and leads to better maternal outcomes in the index and subsequent deliveries^{29 30}.

At present domestic and overseas studies have not been reported. Studies have confirmed that the prophylactic use of cephalosporins combined with azithromycin before surgery can reduce the prevalence of CSD. Therefore, we designed a prospective, randomized, double-blind, parallel-group study to compare the prophylactic use of cephalosporins combined with azithromycin to a single dose to reduce the prevalence of postpartum uterine diverticulum. Our study has a strong theoretical basis and foundation. This topic can provide evidence for the effective use of antibiotics in clinical practice and the reduction in the rate of CSD.

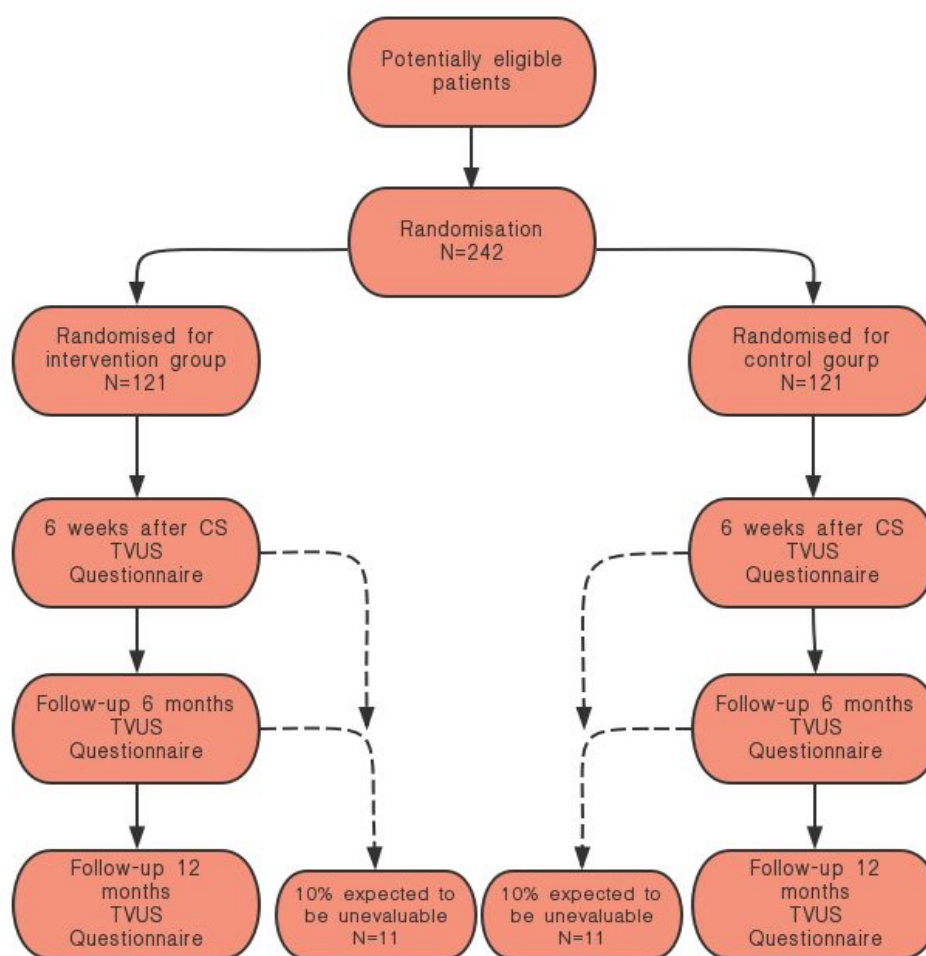


Figure 1 Flowchart of the study. CS, cesarean section; TVUS, transvaginal ultrasound

Objective and hypothesis

The objective of this trial is to clarify the protective effect of antibiotics on CSD and to assess the effectiveness of adjunctive azithromycin prophylaxis for CSD. Our hypothesis is that prophylactic use of cephalosporins combined with azithromycin is superior to a single dose and can reduce the prevalence of CSD.

METHODS AND ANALYSIS

Trial design

The study design is an open-label, double-blind, parallel control design, randomized clinical trial. Pregnant women with singleton pregnancies in cephalic presentation who have ruptured membranes or signs of labour will be informed about the study and the need to undergo CS by the medical team. The subjects will be randomly divided into two groups. The trial group (group A) will be administered the regular single-dose cefuroxime sodium (1.5 g/50 ml 0.9% NaCl) plus azithromycin (0.5 g/250 ml 0.9% NaCl). The control group (group B) will be administered the regular single-dose cefuroxime sodium (1.5 g/50 ml 0.9% NaCl) plus an additional placebo (250 ml 0.9% NaCl) as an intravenous drip 30 min before surgery. The incidence and clinical symptoms of uterine incision malunion or incision diverticulum at 6 weeks, 6 months, and 12 months after delivery will be observed with TVU and SIS. We will include 220 women in total. The primary outcome measure will be the prevalence and characteristic of the CSD as assessed by means of TVU and SIS at 6 weeks after delivery. The secondary outcome measures will be infection indexes and labour results, as shown in Figure 1.

Participants

Patients are included in this study if they meet all the following criteria:

1. Ethnic Han Chinese with a maternal age of 18 years or older;
2. Singleton pregnancy with a gestational age ≥ 37 weeks;
3. Fibrinogen ≥ 2 g/L, platelet count $\geq 100 \times 10^9$, and haemoglobin ≥ 90 g/L before surgery;
4. Nonelective caesarean delivery during labour or after membrane rupture.
5. Labour will be defined as regular contractions with cervical dilation of 3 cm or with documented cervical changes of at least 1 cm of dilation or at least 50% effacement. Women with membrane rupture for at least 4 hours will be eligible, regardless of whether labour has started.

Patients are excluded from study participation if one of the following criteria is met:

1. Patients who decline to participate in the trial;
2. Patients who are known to be allergic to cefuroxime sodium or azithromycin (including an allergy to any kind of macrolides or cephalosporins);
3. Patients who are administered azithromycin within 7 days before randomization;
4. Patients who are positive for Group B Streptococcus haemolyticus (GBS) on screening at approximately 36 weeks;
5. Patients with diagnosed non-reproductive tract infections (appendicitis, upper respiratory infections, urinary tract infections) who need additional antibiotic

- treatment;
6. Patients with severe maternal diseases (pregnant women with severe liver and renal dysfunction, pneumonoedema, cardiac structural abnormalities or taking antiarrhythmic drugs, systematic lupus erythaematosus, or inadequately controlled diabetes);
 7. Stillbirths;
 8. Patients with a preoperative diagnosis of uterine abnormalities (such as uterine

Table 1 Schedule of enrolment, interventions and assesement in the trial										
Data collection	Days									
	BL	0	1	2	3	4	42	6 months	12 months	
Age	×									
BMI	×									
Gestational age	×									

- malformation, adenomyosis, or myoma of uterus); and
9. Patients who have undergone a previous CS.

Randomization

Randomization will be performed by accessing a computer-generated randomization sequence in a 1:1 ratio. Demographical, medical and obstetrical information will be collected at baseline. Antibiotic prophylaxis will be administered within 30 min before incision.

Withdrawal of individual subjects

Subjects will be able leave the study at any time for any reason if they wish to do so without any consequences. The investigator will be able to decide to withdraw a subject from the study for urgent medical reasons. After randomization, if a woman wishes to change her assigned protocol, she will be considered a crossover subject. All subjects will remain in the study for analysis based on the intention-to-treat principle.

Participant timeline

The schedule for enrolment, interventions and assessments are summarised in Table 1.

Day 0 is the day the caesarean section is performed, and D1 is the day antibiotic treatment, which is randomly assigned, is started.

All included patients will undergo randomization and treatment. We will conduct preoperative and postoperative routine blood tests and detection of C-reactive protein (CRP) levels, procalcitonin (PCT) levels, and blood coagulation function. We will also culture vaginal secretions before the surgery and at 42 days postpartum.

Screen	×									
Informed consent	×									
Randomization	×									
TVU							×	×	×	
SIS							×	×	×	
Antibiotics		×								
Blood infection index	×		×							
Blood coagulation function	×		×							
Secretion culture	×	×					×			
Temperature	×	×	×	×	×	×				
The skin infection of incision		×	×	×	×	×				
Endometritis		×	×	×	×	×				
Puerperal fever		×	×	×	×	×				
Other postoperative complications		×								

BL, base line; BMI, body mass index; TVU, transvaginal ultrasound; SIS, saline infusion sonohysterography

Clinical evaluation of the efficacy and safety of anti-infection prophylaxis will be performed during hospitalization, including evaluation of the incidence of puerperal fever, skin infections at the incision site, endometritis and other postoperative complications.

The clinical symptoms will be recorded as well as the prevalence and characteristic of CSD at 6 weeks, 6 months, 12 months after caesarean delivery.

Primary outcome measure

The prevalence and characteristic of CSD will be assessed by TVU and SIS 42 days after delivery.

Secondary outcome measure

1. The changes in infection indexes, such as routine blood routine examinations including C-reactive protein and procalcitonin before and after surgery;
2. Vaginal secretion culture results before surgery and intraoperative uterine cavity culture results;
3. Body temperature 6 hours before and 72 hours after CS;
4. Postoperative morbidity, endometritis and incisional infection after surgery and severe infection in 42 days after delivery;
5. Type and dosage of the all antibiotics administered postoperatively according to standard processes;
6. Appearance of the niche and its location, the thickness of the anterior wall muscle layer at the scar of the lower part of the uterus as detected by TVS and SIS at approximately 6 weeks (which is the primary outcome measure in our RCT), 6

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3 months and 12 months after delivery; and Postpartum questionnaire at
4 approximately 6 weeks, 6 months and 12 months.
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8 **STATISTICAL CONSIDERATIONS**

9 **Sample size calculation**

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12 Based on findings of previous studies, we concluded that the occurrence of CSD
13 decreases from 47.9% to 29% after administration of multi-dose antibiotics during
14 emergency caesarean delivery. We will predict the occurrence of CSD after using two
15 prophylactic antibiotics with PASS sample prediction software version 11.0. We will
16 need to include 220 women in total (two groups of 110 women), with an alpha error of
17 .05. Assuming a 10% drop-out rate, we will need to randomize a total of 242
18 participants (121 participants per group).
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23 **Statistical analysis**

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26 For analysis, the adopted EDC system will be used to collect data uniformly and record
27 all relevant personal information for data collection points. The method of automatic
28 computer verification will be adopted, including data that clearly do not conform to the
29 conventional standards and missing values. Researchers will be required to check the
30 original data, and all changes in the data will be managed with traces. Query tables will
31 be checked if necessary.
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36 The t-test, analysis of variance, chi-square tests and other differential tests will be
37 carried out on the data with SPSS software.
38

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40 Descriptive statistics will be used to analyse demographic data and laboratory indicators,
41 such as the basic information from preoperative period, postoperative hospitalization
42 period, and period 6 weeks postoperatively. Preoperative and postoperative indicators
43 will be used for baseline data, and the normality of the distribution of continuous
44 variables from the baseline data will be tested. Normally distributed data will be
45 reported as the mean and standard deviation, and the two groups will be assessed by the
46 independent samples t-test; if the data are nonnormally distributed, a non-parametric
47 analysis will be performed, and the data will be reported as the median and interquartile
48 range. We will use the chi-square test or Fisher's exact test to analyse categorical
49 variables.
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53

54 We will apply the chi-square test to assess the primary outcome to compare the
55 occurrence rate of the CSD in two groups.
56

57 We will apply the T test, analysis of variance and chi-square test to evaluate the
58 secondary outcome according to the characteristics of the endpoint.
59
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Patient and public involvement

Patients or the public will not be not involved in the study design. They also will not be involved in the recruitment process or conduction of the study. The results will be disseminated to patients via an open access publication and our local trials teams.

DISCUSSION

Since the mechanism of wound healing of uterine caesarean incisions is not fully known and the natural development of CSD over time is still unclear, uterine scars and CSDs may change over time. One prospective observational study showed that the incidence of CSD occurred from 6 weeks to 6 months and even longer²⁹. Another prospective study showed some women with or without CSD may change to the opposite status from 6 weeks to 6 months³⁰. Another cross-sectional study showed that the CSD prevalence varied based on time (3-12 months, 1-5 years, and 5-10 years) after CS. We will set the initial CSD assessment timepoint as 6 weeks postpartum and follow patients for 1 year, aiming to find the optimal timepoint for the early detection of CSD. The data from our previous cohort were based on the measurement of CSD with TVU and may have resulted in an underestimation. Our sample size calculation was also based on those data. Since we believe that the difference between the two groups will be more significant when CSD is measured with SIS, the sample size could be large enough to observe a difference.

ETHICS AND DISSEMINATION

The study has been approved by the Medical Research Ethics Committee of International Peace Maternity and Child Health Hospital (GKLW2017-84). Findings will be distributed through peer-reviewed publications and presentations at international scientific meetings.

All women eligible for participation in the study will be invited for additional counselling by a research doctor to ensure that they are fully informed regarding the nature of the study by means of both oral and written information. Women who agree to participate will be asked to sign written informed consent, of which they will receive a copy.

The protocol of the trial is registered in Chinese Clinical Trials Register(ChiCTR) as ChiCTR-INR-17013272.

Author's contributions:

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3 Yanqing Cai, Hongjie Pan and Ben WJ Mol are responsible for the overall logistical
4 aspects of the trial and drafted the paper. Ding Huang, Ben WJ Mol, Weiwei Chen and
5 Jian Zhang designed the trial and were responsible for the development of the protocol..
6 The senior doctors Ding Huang and Yiru Shi are the main operators for the RCT. Min
7 Zeng and Liye Shi, senior ultrasound doctors, are responsible for the ultrasonographic
8 measurements of the uterus diverticulum. Jinyu, Ying Shen, Sha Chen, Qian Zhu
9 contribute to the protocol including literature retrieval, specimen collection, data
10 analysis, and follow-up visits. Ding Huang is responsible for the project and contributes
11 to the organization and operation of the trial.
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16 **Competing interests:** None declared

17 **Patient consent:** Obtained

18 **Ethics approval:** The study has been approved by the Medical Research Ethics
19 Committee of International Peace Maternity and Child Health Hospital (approval no.
20 GKLW2017-84).
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25 **Provenance and peer review:** Not commissioned; externally peer reviewed.

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27 Development Center Clinical Science and Technology Innovation Project (item number
28 SHDC12017X05).
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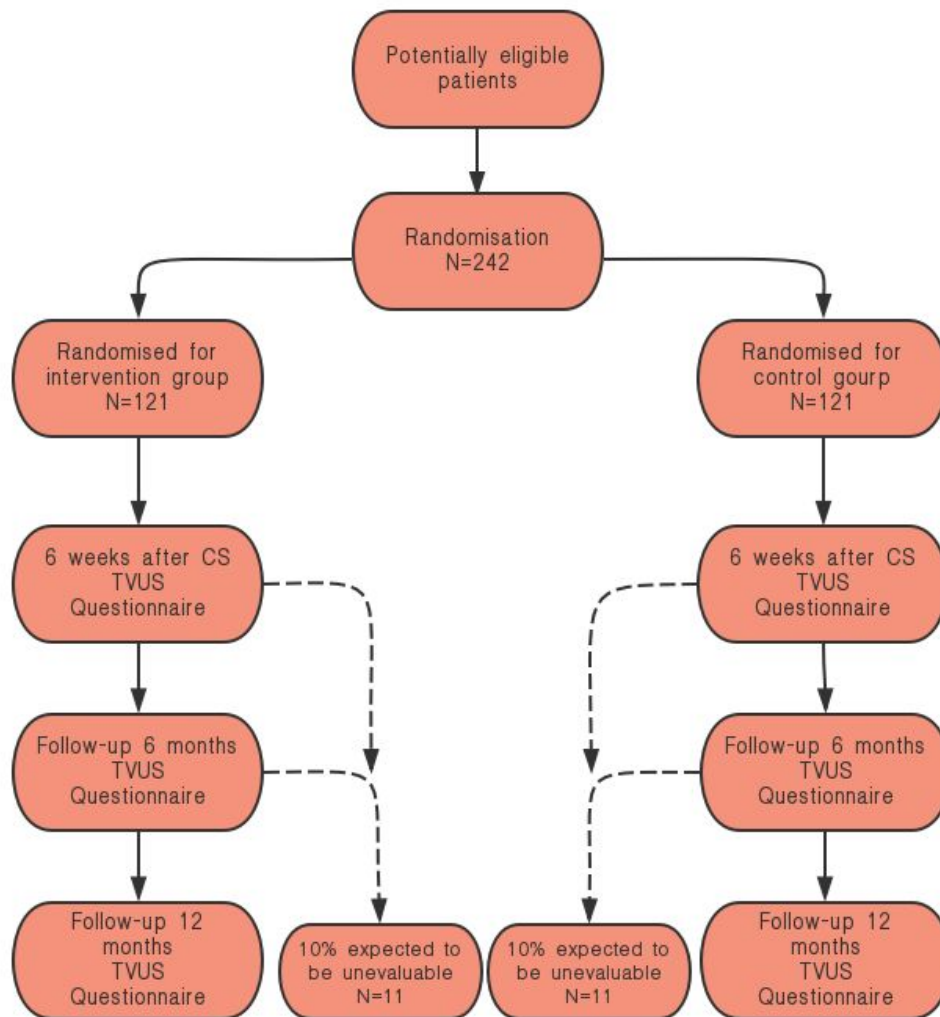


Fig 1 Flowchart of the study. CS, Cesarean-section; TVUS, transvaginal ultrasonography

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Efficacy of adjunctive azithromycin versus single-dose cephalosporin prophylaxis for caesarean scar defect: study protocol for a randomised controlled trial

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4 **Efficacy of adjunctive azithromycin versus single-dose cephalosporin prophylaxis**
5 **for caesarean scar defect: study protocol for a randomised controlled trial**
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44 **ABSTRACT**

45
46 **Introduction** Perioperative infections may be considered predictors of caesarean scar
47 defect (CSD), and multi-dose antibiotics have a protective effect against CSD. However,
48 the ability of adjunctive azithromycin combined with cephalosporin to reduce the
49 prevalence of CSD remains unclear. The planned study aims to clarify the protective
50 effect of antibiotics against CSD and to assess the effectiveness of adjunctive
51 azithromycin prophylaxis for CSD.
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56 **Methods and analysis** This study is a double-blind, parallel-control randomised
57 clinical trial that will be carried out at the International Peace Maternity & Child Health
58 Hospital. A total of 220 eligible patients will be randomised (1:1) to receive either
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3 adjunctive azithromycin or single-dose cephalosporin 30 min before the incision. The
4 evaluation criteria are the prevalence and characteristics of CSD as assessed by
5 transvaginal ultrasound (TVU) and saline infusion sonohysterography (SIS) at 42 days,
6 6 months and 12 months after delivery. The primary outcome will be the prevalence of
7 CSD, and the characteristics of CSD will be assessed by TVU and SIS 42 days after
8 delivery; all other outcomes are secondary.
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12 **Ethics and dissemination** This protocol received authorisation from the Medical
13 Research Ethics Committee of International Peace Maternity and Child Health Hospital
14 on 25 April 2018 (approval no. GKLW2017-84). The findings will be reported in peer-
15 reviewed publications and presentations at international scientific meetings.
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18 **Trial registration number** ChiCTR-INR-17013272
19

20 **Keywords:** caesarean section, caesarean scar defect, azithromycin, randomised control
21 trial, antibiotic
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28 **ARTICLE SUMMARY**

29 **Strengths and limitations of this study:**

- 30 1. This is the first interventional randomised controlled trial with the primary aims of
31 assessing the protective effects of antibiotics against CSD and investigating the
32 relationship between CSD occurrence and preoperative infection.
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- 34 2. This study is based on our previous cohort study, and we want to study the effects
35 of infection and antibiotics on CSD directly.
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- 37 3. The study is a double-blinded randomised controlled trial with a relatively large
38 sample size and a long follow-up period. In this set, we can find the optimal
39 timepoint for the early detection of CSD.
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- 41 4. The trial is based in a single centre, which might limit the generalisability of the
42 findings.
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- 44 5. This study is not a randomised controlled trial of different surgical techniques for
45 uterine incision closure, which may be as or more important than antibiotics.
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54 **INTRODUCTION**

55 The rate of caesarean section (CS) delivery is increasing worldwide, especially in
56 China due to the prevalence of maternally requested caesarean deliveries and the 30-
57 year national one-child policy¹. According to the data from official figures of the China
58 National Bureau of Statistics, there were approximately 17 million new-borns in China
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3 in 2017, with a caesarean delivery rate of approximately 40%, which means that there
4 are approximately 7 million CS deliveries each year².
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7 There is no universal definition of CSD. Most studies refer to the thinning of the
8 myometrium or a triangular defect in the myometrium that is contiguous with the
9 endometrial cavity. The remaining myometrial thickness (RMT) is defined as the
10 distance from the delineation of the endometrium to the serosal surface at the level of
11 the caesarean scar, and total myometrial thickness is measured at the myometrium
12 adjacent to the scar (AMT)^{3 4}. Some authors have suggested the existence of a niche,
13 described as an indentation of the myometrium that is at least 2 mm. Large niches are
14 uncommon, with a reported incidence that varies from 11-45% depending on the
15 definition used. Some authors have suggested that a large CSD penetrates to one
16 involving a depth of at least 50-80% of the anterior myometrium or a RMT that is less
17 than 2.2 mm when evaluated by TVU and less than 2.5mm when evaluated by SIS⁵.
18 Small niches may indeed be quite common but would be clinically unimportant.
19 Large niches are most likely to give rise to long-term sequelae; hence, the focus of
20 research and discussion should be on the causes of large niches and on prevention
21 strategies^{6 7}. In our study, we will also focus on the differences in the prevalence rates
22 and outcomes of CSD and large CSD. Measured parameters such as the height,
23 length, width, RMT, AMT and niche volume of CSD will be collected to present the
24 characteristics of CSD.
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33 In a random population of women with a history of CS, the prevalence of CSD
34 ranges from 24% to 70% and 56% to 84% when assessed by TVU with and without
35 contrast enhancement, respectively⁷. Saline infusion sonohysterography (SIS) is better
36 than traditional TVU for characterising CSD and has a higher sensitivity^{8 9}. Moreover,
37 sonohysterography can more precisely evaluate the size and shape of the defect and
38 thus the severity². In this study, we will apply and compare the differences between
39 TVU and SIS.
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43 Caesarean scar defect (CSD) is associated with abnormal uterine bleeding (75-
44 82%), postmenstrual spotting (29-34%) caesarean scar ectopic pregnancies (1:1,800-
45 1:2,216) and infertility (32/92)^{10 11}. Uterine dehiscence, uterine rupture, caesarean scar
46 pregnancy and morbidly adherent placenta are also associated with CSD¹²⁻¹⁴. Annually,
47 there are thousands of fatalities and near-death cases caused by uterine rupture or
48 haemorrhage from the CSD¹⁵.
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52 Our previously published data first revealed a CSD prevalence of 43.4% (95%
53 confidence interval (CI)=39.1-47.7%, N=514) in Shanghai, which is a cause for
54 concern¹⁶. Our cohort study also showed that infection might be an important risk factor
55 for CSD and that multi-dose antibiotic administration has a significant protective effect
56 compared with single-dose antibiotic administration (CSD prevalence 31.1%, 95%
57 CI=23.8-38.3% versus 49.0%, 95% CI=43.8-54.3%; aOR=0.4, 95% CI=0.3-0.7).
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4 Furthermore, the single-dose cefuroxime subgroup (n=190) was found to have a
5 significantly lower CSD prevalence than the single-dose cefradine subgroup (n=162)
6 (38.9%, 95% CI=34.7-48.6% vs 56.8%, 95% CI=51.3-66.7%; aOR=0.5, 95% CI=0.3-
7 0.8, P=0.006). These results strongly indicate that antibiotics may be a protective factor
8 for CSD¹⁷⁻¹⁹.
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11 According to the results of a study involving pathogen monitoring for nosocomial
12 infections, *Ureaplasma urealyticum*, *Escherichia coli*, Enterococcus and Streptococcus
13 are the most common infectious agents^{20 21}. Second-generation cephalosporins have a
14 stronger antibacterial effect against *E. coli* and *Enterobacteriaceae* than first-generation
15 cephalosporin, while azithromycin has stronger antibacterial and bacteriostatic effects
16 against atypical pathogens, such as *Mycoplasma chlamydia* and anaerobic bacteria^{22 23}.
17 Current recommendations for antibiotic prophylaxis in caesarean delivery include the
18 standard administration of a broad-spectrum antibiotic, most commonly a first-
19 generation cephalosporin, before the skin incision²⁴. Recent reports on adjunctive
20 azithromycin prophylaxis for caesarean delivery showed a significant protective effect
21 against maternal endometritis (3.8% vs 6.1%, P=0.02), wound infection (2.4% vs 6.6%,
22 P<0.001), and serious maternal adverse events (1.5% vs 2.9%, P=0.03) but no
23 significant between-group differences in secondary neonatal composite outcomes²⁵. In
24 other words, the addition of azithromycin to caesarean delivery prophylaxis is less
25 costly and leads to better maternal outcomes in index and subsequent deliveries²⁶⁻²⁹.
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33 Therefore, we designed a prospective, randomised, double-blind, parallel-group
34 study to determine whether the prophylactic use of cephalosporin plus azithromycin
35 combination is superior to that of a single dose of cephalosporin in reducing the
36 prevalence of CSD. Our study has a strong theoretical basis and foundation, and this
37 trial may provide evidence of the effective use of antibiotics in clinical practice and
38 data indicating a reduction in the rate of CSD.
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44 **Objective and hypothesis**

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46 The objective of this trial is to clarify the protective effects of antibiotics against CSD
47 and to assess the effectiveness of adjunctive azithromycin prophylaxis for CSD. Our
48 hypothesis is that the prophylactic use of cephalosporins combined with azithromycin
49 is superior to a single dose of cephalosporin and can reduce the prevalence of CSD.
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54 **METHODS AND ANALYSIS**

55 **Study design and setting**

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57 The study design is that of a double-blind, parallel-control randomised clinical trial.
58 Pregnant women with singleton pregnancies in cephalic presentation who have ruptured
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3 membranes or signs of labour will be informed about the study and the need to undergo
4 CS by the medical team. The subjects will be randomly divided into two groups. The
5 trial group (group A) will be administered the regular single-dose cefuroxime sodium
6 (1.5 g/50 ml 0.9% NaCl) plus azithromycin (0.5 g/250 ml 0.9% NaCl). The control
7 group (group B) will be administered the regular single-dose cefuroxime sodium (1.5
8 g/50 ml 0.9% NaCl) plus an additional placebo (250 ml 0.9% NaCl) as an intravenous
9 drip 30 min before surgery. The prevalence and clinical symptoms of CSD at 6 weeks,
10 6 months, and 12 months after delivery will be observed with TVU and SIS. We will
11 include 220 women in total. The primary outcome measure will be the prevalence of
12 CSD, and the characteristic of CSD will be assessed by TVU and SIS 42 days after
13 delivery. The secondary outcome measures will be infection indexes and labour results,
14 as shown in Figure 1.
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23 Participants

24 Patients will be included in this study if they meet all the following criteria:

- 25 1. Han Chinese ethnicity with a maternal age of 18 years or older,
- 26 2. Singleton pregnancy with a gestational age ≥ 37 weeks,
- 27 3. Fibrinogen ≥ 2 g/L, platelet count $\geq 100 \times 10^9$, and haemoglobin ≥ 90 g/L before
28 surgery,
- 29 4. Non-elective caesarean delivery during labour or after membrane rupture,
- 30 5. Labour defined as regular contractions with cervical dilation of 3 cm or with
31 documented cervical changes of at least 1 cm of dilation or at least 50% effacement
32 (women with membrane rupture for at least 4 hours will be eligible, regardless of
33 whether labour has started).

34 Patients will be excluded from participating in the study if one of the following criteria
35 is met:

- 36 1. The patient declines to participate in the trial,
- 37 2. The patient is known to be allergic to cefuroxime sodium or azithromycin
38 (including an allergy to any kind of macrolide or cephalosporin),
- 39 3. The patient was administered azithromycin within 7 days before randomisation,
- 40 4. The patient is positive for Group B Streptococcus haemolyticus (GBS) on
41 screening at approximately 36 weeks,
- 42 5. The patient has a diagnosis of a non-reproductive tract infection (appendicitis,
43 upper respiratory infection, urinary tract infection) and needs additional antibiotic
44 treatment,
- 45 6. The patient has a severe maternal disease (severe liver or renal dysfunction;
46 pulmonary oedema; cardiac structural abnormality or a condition requiring
47 antiarrhythmic drug use; systematic lupus erythaematosus; or inadequately
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3 controlled diabetes),
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5 7. The patient has a stillbirth,
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7 8. The patient has a preoperative diagnosis of uterine abnormalities (such as uterine
8 malformation, adenomyosis, or myoma of the uterus), or
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10 9. The patient has undergone a previous CS.

11 12 13 **Randomisation**

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15 Demographic, medical and obstetrical information will be collected at baseline. The
16 patient will then be randomised between the trial group (group A) and the control group
17 (group B) according to her serial number (number 1 to 250, depending on the time of
18 trial entry). The randomisation codes will be generated by the block of the statistical
19 software at a 1:1 ratio (SPSS, version 22.0, IBM, Armonk, NY, USA). We will generate
20 a list of 250 randomisation codes (A or B). Each code will correspond to one serial
21 number, and each code will be placed in a black envelope with the serial number printed
22 on the outside. Anyone who will have contact with the patient or other researchers will
23 be blinded to the list. Antibiotic prophylaxis will be administered within 30 min before
24 incision. The medicine will be dissolved in the hospital dispensary, where the patient's
25 envelope will be opened by an independent pharmacist, and the containers will be
26 identical so that no one else can identify the set. The opened envelope will be locked in
27 a non-transparent box until the trial is finished. These settings will ensure that both the
28 participants and investigators or surgeons are blinded to the treatment.
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37 38 **Intervention**

39 All participants will undergo a standard CS with a lower segment uterine incision and
40 double-layer suturing of the uterine wound. The first layer will be the decidua and total
41 myometrium, and the second layer will be the serosa and the upper 1/2 layer of
42 myometrium. All sutures will be continuously unlocked sutures with absorbable suture
43 material. We have three experienced surgeons with the same technical standards who
44 will be responsible for the trial. Each of them will perform approximately 70 CSs
45 randomly in the trial. All the participants will be cared for in the wards, and additional
46 antibiotics will be given if there is a confirmed infection before the patient checks out.
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53 54 **Withdrawal of participants**

55 The participants will be able to leave the study at any time for any reason if they wish
56 to do so, without any consequences. The investigator will be able to decide to withdraw
57 a subject from the study for urgent medical reasons. After randomisation, if a woman
58 wishes to change her assigned protocol, she will be considered a crossover subject. All
59
60

subjects will remain in the study for analysis based on the intention-to-treat principle.

Participant timeline

The schedules for enrolment, interventions and assessments are summarised in Table 1.

Table 1 Patient's characteristics and data collection

Data collection	Days									
	BL	0	1	2	3	4	42	6months	12months	
Age	×									
BMI	×									
Gestational age	×									
Screen	×									
Informed consent	×									
Randomization	×									
TVU							×	×		×
SIS							×	×		×
Antibiotics	×	×								
Blood infection index	×		×							
Blood coagulation function	×		×							
Secretion culture	×	×					×			
Temperature	×	×	×	×	×	×				
The skin infection of incision		×	×	×	×	×				
Endometritis		×	×	×	×	×				
Puerperal fever		×	×	×	×	×				
Other postoperative complications		×								
Questionnaire							×	×		×

BL, baseline; BMI, body mass index; TVU, transvaginal ultrasound; SIS, saline infusion sonohysterography.

The CS will be performed on day 0, and antibiotic treatment, which will be randomly assigned, will be started on day 1.

All included patients will undergo randomisation and treatment. We will conduct preoperative and postoperative routine blood tests and detect C-reactive protein (CRP) levels, procalcitonin (PCT) levels, and blood coagulation function. We will also culture vaginal secretions before surgery and at 42 days postpartum.

Clinical evaluations of the efficacy and safety of anti-infection prophylaxis will be performed during hospitalisation and will include evaluations of the incidence of

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3 puerperal fever, skin infections at the incision site, endometritis and other postoperative
4 complications.
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7 Clinical symptoms as well as the prevalence and characteristics of CSD at 6 weeks, 6
8 months, and 12 months after caesarean delivery will be documented.
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10 11 12 **Primary outcome measure**

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14 The prevalence of CSD, and the characteristic of CSD will be assessed by TVU and SIS
15 42 days after delivery.
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18 19 20 **Secondary outcome measure**

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22 1. The changes in infection indexes, such as routine blood examinations including
23 CRP and PCT before and after surgery;
- 24
25 2. Pre-surgical vaginal secretion culture results and intraoperative uterine cavity
26 culture results;
- 27
28 3. Body temperature 6 hours before and 72 hours after CS;
- 29
30 4. Postoperative morbidity, endometritis and incisional infection after surgery and
31 severe infection 42 days after delivery;
- 32
33 5. Type and dosage of all antibiotics administered postoperatively according to
34 standard processes;
- 35
36 6. Responses to postpartum questionnaires at approximately 6 weeks, 6 months and
37 12 months;
- 38
39 7. Follow-up data from TVU and SIS evaluations performed at 6 months and 12
40 months after delivery; and
- 41
42 8. The size and position of the uterus and the height, length, width, RMT, AMT
43 and niche volume of the defects.
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45 **STATISTICAL CONSIDERATIONS**

46 47 **Sample size calculation**

48
49 Based on the findings of previous studies, we concluded that the occurrence of CSD
50 decreases from 47.9% to 29% after the administration of multi-dose antibiotics during
51 emergency caesarean delivery. We will predict the occurrence of CSD after using two
52 prophylactic antibiotics with PASS sample prediction software version 11.0. We will
53 need to include 220 women in total (two groups of 110 women), with an alpha error of
54 0.05. Assuming a 10% drop-out rate, we will need to randomise a total of 242
55 participants (121 participants per group).
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Statistical analysis

For analysis, the adopted EDC system will be used to collect data uniformly and record all relevant personal information for data collection points. The method of automatic computer verification, which will include data that clearly do not conform to the conventional standards and among which values are missing, will be adopted. Researchers will be required to check the original data, and all changes in the data will be managed with traces. Query tables will be checked if necessary.

For the analysis of the data, t-tests, analysis of variance, chi-square tests and other differential tests will be carried out with SPSS software.

Descriptive statistics will be used to analyse demographic data and laboratory indicators, such as basic information from the preoperative period, from the postoperative hospitalisation period, and at 6 weeks post-surgery. Preoperative and postoperative indicators will be used for baseline data, and the normality of the distribution of continuous variables from the baseline data will be tested. Normally distributed data will be reported as the mean and standard deviation, and the two groups will be assessed by the independent samples t-test; if the data are nonnormally distributed, a non-parametric analysis will be performed, and the data will be reported as the median and interquartile range. We will use the chi-square test or Fisher's exact test to analyse categorical variables.

We will apply the chi-square test to assess the primary outcome to compare the occurrence rate of the CSD in two groups.

We will apply the t-test, analysis of variance and chi-square test to evaluate the secondary outcome according to the characteristics of the endpoint.

Patient and public involvement

Neither the patients nor the public will be involved in the study design. They will also not be involved in the recruitment process or conduction of the study. The results will be disseminated to patients via an open access publication and our local trials teams.

DISCUSSION

Since the mechanism of wound healing in uterine caesarean incisions is not fully known and since the natural development of CSD over time is still unclear, uterine scars and CSD may change over time. One prospective observational study showed that CSD occurred from 6 weeks to 6 months or longer after surgery³⁰. Another prospective study reported that the statuses of some women with or without CSD showed a reversal between 6 weeks and 6 months after surgery (90.7% at 6 weeks and 93.1% at 6 months

(OR 0.96 (0.61-1.49), P=0.91))³¹. This trial is based on our previous cohort study in which CSD was observed at 6 weeks postpartum. We will set the initial CSD assessment timepoint as 6 weeks postpartum and follow patients for 1 year, aiming to find the optimal timepoint for the early detection of CSD. Our sample size calculation is also based on previously published data, which were based on the measurement of CSD with TVU and may have resulted in an underestimation¹⁶. Since we believe that the difference between the two groups will be more significant when CSD is measured with SIS, the sample size could be large enough to observe a difference. We believe that surgical techniques of uterine incision and closure may be important in the occurrence of CSD, and there are many trials that are on-going or that already have results^{32 33}. We will focus on the effects of infection and antibiotics against CSD based on the strong indication of our previous study.

ETHICS AND DISSEMINATION

The study was approved by the Medical Research Ethics Committee of International Peace Maternity and Child Health Hospital (GKLW2017-84). The findings will be reported in peer-reviewed publications and presentations at international scientific meetings.

All women who are eligible for participation in the study will be invited for additional counselling by a research doctor to ensure that they are fully informed regarding the nature of the study by means of both oral and written information. Women who agree to participate will be asked to sign written informed consent forms, of which they will receive a copy.

The protocol of the trial is registered in the Chinese Clinical Trials Register (ChiCTR) as ChiCTR-INR-17013272.

Author's contributions:

Yanqing Cai, Hongjie Pan and Ben WJ Mol are responsible for the overall logistical aspects of the trial and the drafting of this paper. Ding Huang, Ben WJ Mol, Weiwei Chen and Jian Zhang designed the trial and were responsible for the development of the protocol. The senior doctors Ding Huang and Yiru Shi are the main operators of the RCT. Min Zeng and Liye Shi, senior ultrasound doctors, are responsible for the ultrasonographic measurements of the uterus diverticulum. Jinyu is responsible for the design of the randomisation codes and production of the black envelopes. Ying Shen, Sha Chen, Qian Zhu is contributing to the protocol by carrying out literature retrieval, specimen collection, data analysis, and follow-up visits. Ding Huang is responsible for the project and is contributing to the organisation and operation of the trial.

Competing interests: None declared

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3 **Patient consent:** Obtained
4

5 **Ethics approval:** The study was approved by the Medical Research Ethics Committee
6 of International Peace Maternity and Child Health Hospital (approval no. GKLW2017-
7 84).
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10 **Provenance and peer review:** Not commissioned; externally peer reviewed.
11

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20 personnel.
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Figure Legend:

Fig 1 Flowchart of the study.

CS, Cesarean-section; TVUS, transvaginal ultrasonography

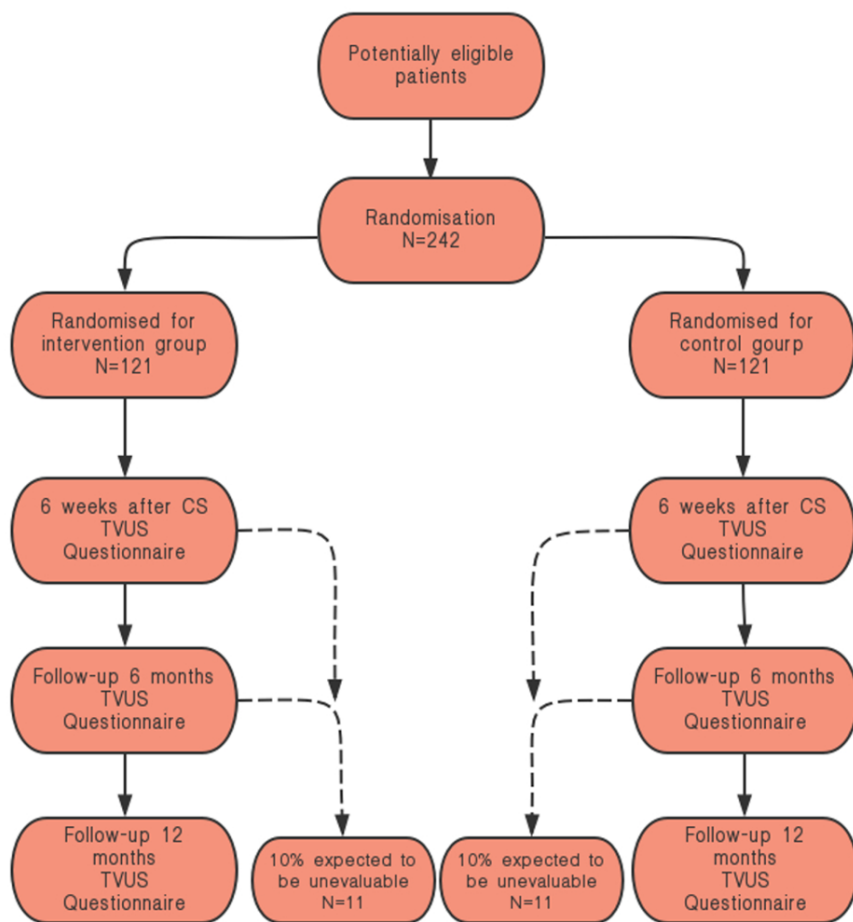


Fig 1 Flowchart of the study.
CS, Cesarean-section; TVUS, transvaginal ultrasonography

90x90mm (300 x 300 DPI)

BMJ Open

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Secondary Subject Heading:	Surgery, Infectious diseases
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4 **Efficacy of adjunctive azithromycin versus single-dose cephalosporin prophylaxis**
5 **for caesarean scar defect: study protocol for a randomised controlled trial**
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44 **ABSTRACT**
45

46 **Introduction** Perioperative infections may be considered predictors of caesarean scar
47 defect (CSD), and multi-dose antibiotics have a protective effect against CSD. However,
48 the ability of adjunctive azithromycin combined with cephalosporin to reduce the
49 prevalence of CSD remains unclear. The planned study aims to clarify the protective
50 effect of antibiotics against CSD and to assess the effectiveness of adjunctive
51 azithromycin prophylaxis for CSD.
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56 **Methods and analysis** This study is a double-blind, parallel-control randomised
57 clinical trial that will be carried out at the International Peace Maternity & Child Health
58 Hospital. A total of 220 eligible patients will be randomised (1:1) to receive either
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3 adjunctive azithromycin or single-dose cephalosporin 30 min before the incision. The
4 evaluation criteria are the prevalence and characteristics of CSD as assessed by
5 transvaginal ultrasound (TVU) and saline infusion sonohysterography (SIS) at 42 days,
6 6 months and 12 months after delivery. The primary outcome will be the prevalence of
7 CSD, and the characteristics of CSD will be assessed by TVU and SIS 42 days after
8 delivery; all other outcomes are secondary.
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12 **Ethics and dissemination** This protocol received authorisation from the Medical
13 Research Ethics Committee of International Peace Maternity and Child Health Hospital
14 on 25 April 2018 (approval no. GKLW2017-84). The findings will be reported in peer-
15 reviewed publications and presentations at international scientific meetings.
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19 **Trial registration number** ChiCTR-INR-17013272
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21 **Keywords:** caesarean section, caesarean scar defect, azithromycin, randomised control
22 trial, antibiotic
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26 27 28 **ARTICLE SUMMARY**

29 **Strengths and limitations of this study:**

- 30
31 1. This is the first interventional randomised controlled trial with the primary aims of
32 assessing the protective effects of antibiotics against CSD and investigating the
33 relationship between CSD occurrence and preoperative infection.
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- 35
36 2. This study is based on our previous cohort study, and we want to study the effects
37 of infection and antibiotics on CSD directly.
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- 39
40 3. The study is a double-blinded randomised controlled trial with a relatively large
41 sample size and a long follow-up period. In this set, we can find the optimal
42 timepoint for the early detection of CSD.
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45 4. The trial is based in a single centre, which might limit the generalisability of the
46 findings.
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49 5. This study is not a randomised controlled trial of different surgical techniques for
50 uterine incision closure, which may be as or more important than antibiotics.
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54 **INTRODUCTION**

55
56 The rate of caesarean section (CS) delivery is increasing worldwide, especially in
57 China due to the prevalence of maternally requested caesarean deliveries and the 30-
58 year national one-child policy¹. According to the data from official figures of the China
59 National Bureau of Statistics, there were approximately 17 million new-borns in China
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3 in 2017, with a caesarean delivery rate of approximately 40%, which means that there
4 are approximately 7 million CS deliveries each year.
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6
7 There is no universally accepted definition or criterion for caesarean scar defect
8 (CSD). In most studies, CSD is defined as “the thinning of the myometrium or a
9 triangular defect in the myometrium that is contiguous with the endometrial cavity”².
10 It was stated in the research by Di Spiezio Sardo et al³ that remaining myometrial
11 thickness (RMT) is defined as “the distance from the delineation of the endometrium
12 to the serosal surface at the level of the Caesarean scar, and total myometrial
13 thickness was measured at the myometrium adjacent to the scar”, which refers to
14 adjacent myometrium thickness (AMT). Some researchers have also indicated that a
15 niche should be described as the indentation of myometrium with a depth of at least 2
16 mm^{4,5}. Additionally, according to Osser et al⁶, a large CSD was defined as “thickness
17 of the remaining myometrium over the defect ≤ 2.2 mm by TVU and ≤ 2.5 mm by
18 SIS, ratio between the thickness of the remaining myometrium over the defect and
19 the myometrial thickness adjacent to the defect $\leq 23\%$ by TVU and $\leq 29\%$ by SIS for
20 women who had undergone only one Cesarean section”. Small CSDs may be
21 definitely common and not considered significant. Nevertheless, large CSDs may lead
22 to some long-term potential sequelae⁷. In our study, we will focus on the differences
23 in the prevalence rates and outcomes of CSDs and large CSDs. Data on measured
24 parameters such as the height, length, width, RMT, AMT and niche volume of the
25 CSD will be collected to present the characteristics of CSD.
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28
29 In a random population of women with a history of CS, the prevalence of CSD
30 ranges from 56% to 84% and 24% to 70% when assessed by TVU with and without
31 contrast enhancement, respectively⁸. Saline infusion sonohysterography (SIS) is better
32 than traditional TVU for characterising CSD and has a higher sensitivity⁹. Moreover,
33 sonohysterography can more precisely evaluate the size and shape of the defect and
34 thus the severity¹⁰. In this study, we will apply and compare the differences between
35 TVU and SIS.
36

37
38 Caesarean scar defect (CSD) is associated with abnormal uterine bleeding (75-
39 82%), postmenstrual spotting (29-34%) caesarean scar ectopic pregnancies (1:1,800-
40 1:2,216) and infertility (32/92)^{4,11,12}. Uterine dehiscence, uterine rupture, caesarean scar
41 pregnancy and morbidly adherent placenta are also associated with CSD¹³⁻¹⁵. Annually,
42 there are thousands of fatalities and near-death cases caused by uterine rupture or
43 haemorrhage from the CSD¹⁶.
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47 Our previously published data first revealed a CSD prevalence of 43.4% (95%
48 confidence interval (CI)=39.1-47.7%, N=514) in Shanghai, which is a cause for
49 concern¹⁷. Our cohort study also showed that infection might be an important risk factor
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for CSD and that multi-dose antibiotic administration has a significant protective effect compared with single-dose antibiotic administration (CSD prevalence 31.1%, 95% CI=23.8-38.3% versus 49.0%, 95% CI=43.8-54.3%; aOR=0.4, 95% CI=0.3-0.7)¹⁸⁻²⁰. Furthermore, the single-dose cefuroxime subgroup (n=190) was found to have a significantly lower CSD prevalence than the single-dose cefradine subgroup (n=162) (38.9%, 95% CI=34.7-48.6% vs 56.8%, 95% CI=51.3-66.7%; aOR=0.5, 95% CI=0.3-0.8, P=0.006). These results strongly indicate that antibiotics may be a protective factor for CSD.

According to the results of a study involving pathogen monitoring for nosocomial infections, *Ureaplasma urealyticum*, *Escherichia coli*, Enterococcus and Streptococcus are the most common infectious agents^{21 22}. Second-generation cephalosporins have a stronger antibacterial effect against *E. coli* and *Enterobacteriaceae* than first-generation cephalosporin, while azithromycin has stronger antibacterial and bacteriostatic effects against atypical pathogens, such as *Mycoplasma chlamydia* and anaerobic bacteria^{23 24}. Current recommendations for antibiotic prophylaxis in caesarean delivery include the standard administration of a broad-spectrum antibiotic, most commonly a first-generation cephalosporin, before the skin incision²⁵. Recent reports on adjunctive azithromycin prophylaxis for caesarean delivery showed a significant protective effect against maternal endometritis (3.8% vs 6.1%, P=0.02), wound infection (2.4% vs 6.6%, P<0.001), and serious maternal adverse events (1.5% vs 2.9%, P=0.03) but no significant between-group differences in secondary neonatal composite outcomes²⁶. In other words, the addition of azithromycin to caesarean delivery prophylaxis is less costly and leads to better maternal outcomes in index and subsequent deliveries²⁷⁻³⁰.

Therefore, we designed a prospective, randomised, double-blind, parallel-group study to determine whether the prophylactic use of cephalosporin plus azithromycin combination is superior to that of a single dose of cephalosporin in reducing the prevalence of CSD. Our study has a strong theoretical basis and foundation, and this trial may provide evidence of the effective use of antibiotics in clinical practice and data indicating a reduction in the rate of CSD.

Objective and hypothesis

The objective of this trial is to clarify the protective effects of antibiotics against CSD and to assess the effectiveness of adjunctive azithromycin prophylaxis for CSD. Our hypothesis is that the prophylactic use of cephalosporins combined with azithromycin is superior to a single dose of cephalosporin and can reduce the prevalence of CSD.

METHODS AND ANALYSIS

Study design and setting

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3 The study design is that of a double-blind, parallel-control randomised clinical trial.
4 Pregnant women with singleton pregnancies in cephalic presentation who have ruptured
5 membranes or signs of labour will be informed about the study and the need to undergo
6 CS by the medical team. The subjects will be randomly divided into two groups. The
7 trial group (group A) will be administered the regular single-dose cefuroxime sodium
8 (1.5 g/50 ml 0.9% NaCl) plus azithromycin (0.5 g/250 ml 0.9% NaCl). The control
9 group (group B) will be administered the regular single-dose cefuroxime sodium (1.5
10 g/50 ml 0.9% NaCl) plus an additional placebo (250 ml 0.9% NaCl) as an intravenous
11 drip 30 min before surgery. The prevalence and clinical symptoms of CSD at 6 weeks,
12 6 months, and 12 months after delivery will be observed with TVU and SIS. We will
13 include 220 women in total. The primary outcome measure will be the prevalence of
14 CSD, and the characteristic of CSD will be assessed by TVU and SIS 42 days after
15 delivery. The secondary outcome measures will be infection indexes and labour results,
16 as shown in Figure 1.
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26 Participants

27 Patients will be included in this study if they meet all the following criteria:

- 28 1. Han Chinese ethnicity with a maternal age of 18 years or older,
- 29 2. Singleton pregnancy with a gestational age ≥ 37 weeks,
- 30 3. Fibrinogen ≥ 2 g/L, platelet count $\geq 100 \times 10^9$, and haemoglobin ≥ 90 g/L before
31 surgery,
- 32 4. Non-elective caesarean delivery during labour or after membrane rupture,
- 33 5. Labour defined as regular contractions with cervical dilation of 3 cm or with
34 documented cervical changes of at least 1 cm of dilation or at least 50% effacement
35 (women with membrane rupture for at least 4 hours will be eligible, regardless of
36 whether labour has started).

37 Patients will be excluded from participating in the study if one of the following criteria
38 is met:

- 39 1. The patient declines to participate in the trial,
- 40 2. The patient is known to be allergic to cefuroxime sodium or azithromycin
41 (including an allergy to any kind of macrolide or cephalosporin),
- 42 3. The patient was administered azithromycin within 7 days before randomisation,
- 43 4. The patient is positive for Group B Streptococcus haemolyticus (GBS) on
44 screening at approximately 36 weeks,
- 45 5. The patient has a diagnosis of a non-reproductive tract infection (appendicitis,
46 upper respiratory infection, urinary tract infection) and needs additional antibiotic
47 treatment,

6. The patient has a severe maternal disease (severe liver or renal dysfunction; pulmonary oedema; cardiac structural abnormality or a condition requiring antiarrhythmic drug use; systematic lupus erythaematosus; or inadequately controlled diabetes),
7. The patient has a stillbirth,
8. The patient has a preoperative diagnosis of uterine abnormalities (such as uterine malformation, adenomyosis, or myoma of the uterus), or
9. The patient has undergone a previous CS.

Randomisation

Demographic, medical and obstetrical information will be collected at baseline. The patient will then be randomised between the trial group (group A) and the control group (group B) according to her serial number (number 1 to 250, depending on the time of trial entry). The randomisation codes will be generated by the block of the statistical software at a 1:1 ratio (SPSS, version 22.0, IBM, Armonk, NY, USA). We will generate a list of 250 randomisation codes (A or B). Each code will correspond to one serial number, and each code will be placed in a black envelope with the serial number printed on the outside. Anyone who will have contact with the patient or other researchers will be blinded to the list. Antibiotic prophylaxis will be administered within 30 min before incision. The medicine will be dissolved in the hospital dispensary, where the patient's envelope will be opened by an independent pharmacist, and the containers will be identical so that no one else can identify the set. The opened envelope will be locked in a non-transparent box until the trial is finished. These settings will ensure that both the participants and investigators or surgeons are blinded to the treatment.

Intervention

All participants will undergo a standard CS with a lower segment uterine incision and double-layer suturing of the uterine wound. The first layer will be the decidua and total myometrium, and the second layer will be the serosa and the upper 1/2 layer of myometrium. All sutures will be continuously unlocked sutures with absorbable suture material. We have three experienced surgeons with the same technical standards who will be responsible for the trial. Each of them will perform approximately 70 CSs randomly in the trial. All the participants will be cared for in the wards, and additional antibiotics will be given if there is a confirmed infection before the patient checks out.

Withdrawal of participants

The participants will be able to leave the study at any time for any reason if they wish

to do so, without any consequences. The investigator will be able to decide to withdraw a subject from the study for urgent medical reasons. After randomisation, if a woman wishes to change her assigned protocol, she will be considered a crossover subject. All subjects will remain in the study for analysis based on the intention-to-treat principle.

Participant timeline

The schedules for enrolment, interventions and assessments are summarised in Table 1.

Table 1 Patient's characteristics and data collection

Data collection	Days									
	BL	0	1	2	3	4	42	6months	12months	
Age	×									
BMI	×									
Gestational age	×									
Screen	×									
Informed consent	×									
Randomization	×									
TVU							×	×		×
SIS							×	×		×
Antibiotics	×	×								
Blood infection index	×		×							
Blood coagulation function	×		×							
Secretion culture	×	×					×			
Temperature	×	×	×	×	×	×				
The skin infection of incision		×	×	×	×	×				
Endometritis		×	×	×	×	×				
Puerperal fever		×	×	×	×	×				
Other postoperative complications		×								
Questionnaire							×	×		×

BL, baseline; BMI, body mass index; TVU, transvaginal ultrasound; SIS, saline infusion sonohysterography.

The CS will be performed on day 0, and antibiotic treatment, which will be randomly assigned, will be started on day 1.

All included patients will undergo randomisation and treatment. We will conduct preoperative and postoperative routine blood tests and detect C-reactive protein (CRP) levels, procalcitonin (PCT) levels, and blood coagulation function. We will also culture vaginal secretions before surgery and at 42 days postpartum.

Clinical evaluations of the efficacy and safety of anti-infection prophylaxis will be performed during hospitalisation and will include evaluations of the incidence of puerperal fever, skin infections at the incision site, endometritis and other postoperative complications.

Clinical symptoms as well as the prevalence and characteristics of CSD at 6 weeks, 6 months, and 12 months after caesarean delivery will be documented.

Primary outcome measure

The prevalence of CSD, and the characteristic of CSD will be assessed by TVU and SIS 42 days after delivery.

Secondary outcome measure

1. The changes in infection indexes, such as routine blood examinations including CRP and PCT before and after surgery;
2. Pre-surgical vaginal secretion culture results and intraoperative uterine cavity culture results;
3. Body temperature 6 hours before and 72 hours after CS;
4. Postoperative morbidity, endometritis and incisional infection after surgery and severe infection 42 days after delivery;
5. Type and dosage of all antibiotics administered postoperatively according to standard processes;
6. Responses to postpartum questionnaires at approximately 6 weeks, 6 months and 12 months;
7. Follow-up data from TVU and SIS evaluations performed at 6 months and 12 months after delivery; and
8. The size and position of the uterus and the height, length, width, RMT, AMT and niche volume of the defects.

STATISTICAL CONSIDERATIONS

Sample size calculation

Based on the findings of previous studies, we concluded that the occurrence of CSD decreases from 47.9% to 29% after the administration of multi-dose antibiotics during emergency caesarean delivery. We will predict the occurrence of CSD after using two prophylactic antibiotics with PASS sample prediction software version 11.0. We will need to include 220 women in total (two groups of 110 women), with an alpha error of 0.05. Assuming a 10% drop-out rate, we will need to randomise a total of 242

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3 participants (121 participants per group).
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6 7 **Statistical analysis**

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9 For analysis, the adopted EDC system will be used to collect data uniformly and record
10 all relevant personal information for data collection points. The method of automatic
11 computer verification, which will include data that clearly do not conform to the
12 conventional standards and among which values are missing, will be adopted.
13 Researchers will be required to check the original data, and all changes in the data will
14 be managed with traces. Query tables will be checked if necessary.
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18 For the analysis of the data, t-tests, analysis of variance, chi-square tests and other
19 differential tests will be carried out with SPSS software.
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22 Descriptive statistics will be used to analyse demographic data and laboratory indicators,
23 such as basic information from the preoperative period, from the postoperative
24 hospitalisation period, and at 6 weeks post-surgery. Preoperative and postoperative
25 indicators will be used for baseline data, and the normality of the distribution of
26 continuous variables from the baseline data will be tested. Normally distributed data
27 will be reported as the mean and standard deviation, and the two groups will be assessed
28 by the independent samples t-test; if the data are nonnormally distributed, a non-
29 parametric analysis will be performed, and the data will be reported as the median and
30 interquartile range. We will use the chi-square test or Fisher's exact test to analyse
31 categorical variables.
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35 We will apply the chi-square test to assess the primary outcome to compare the
36 occurrence rate of the CSD in two groups.
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40 We will apply the t-test, analysis of variance and chi-square test to evaluate the
41 secondary outcome according to the characteristics of the endpoint.
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45 **Patient and public involvement**

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47 Neither the patients nor the public will be involved in the study design. They will also
48 not be involved in the recruitment process or conduct of the study. The results will be
49 disseminated to patients via an open access publication and our local trials teams.
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53 **DISCUSSION**

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55 Since the mechanism of wound healing in uterine caesarean incisions is not fully known
56 and since the natural development of CSD over time is still unclear, uterine scars and
57 CSD may change over time. One prospective observational study showed that CSD
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occurred from 6 weeks to 6 months or longer after surgery³⁰. Another prospective study reported that the statuses of some women with or without CSD showed a reversal between 6 weeks and 6 months after surgery (90.7% at 6 weeks and 93.1% at 6 months (OR 0.96 (0.61-1.49), P=0.91))³¹. This trial is based on our previous cohort study in which CSD was observed at 6 weeks postpartum. We will set the initial CSD assessment timepoint as 6 weeks postpartum and follow patients for 1 year, aiming to find the optimal timepoint for the early detection of CSD. Our sample size calculation is also based on previously published data, which were based on the measurement of CSD with TVU and may have resulted in an underestimation¹⁶. Since we believe that the difference between the two groups will be more significant when CSD is measured with SIS, the sample size could be large enough to observe a difference. We believe that surgical techniques of uterine incision and closure may be important in the occurrence of CSD, and there are many trials that are on-going or that already have results^{32,33}. We will focus on the effects of infection and antibiotics against CSD based on the strong indication of our previous study.

ETHICS AND DISSEMINATION

The study was approved by the Medical Research Ethics Committee of International Peace Maternity and Child Health Hospital (GKLW2017-84). The findings will be reported in peer-reviewed publications and presentations at international scientific meetings.

All women who are eligible for participation in the study will be invited for additional counselling by a research doctor to ensure that they are fully informed regarding the nature of the study by means of both oral and written information. Women who agree to participate will be asked to sign written informed consent forms, of which they will receive a copy.

The protocol of the trial is registered in the Chinese Clinical Trials Register (ChiCTR) as ChiCTR-INR-17013272.

Author's contributions:

Yanqing Cai, Hongjie Pan and Ben WJ Mol are responsible for the overall logistical aspects of the trial and the drafting of this paper. Ding Huang, Ben WJ Mol, Weiwei Chen and Jian Zhang designed the trial and were responsible for the development of the protocol. The senior doctors Ding Huang and Yiru Shi are the main operators of the RCT. Min Zeng and Liye Shi, senior ultrasound doctors, are responsible for the ultrasonographic measurements of the uterus diverticulum. Jinyu is responsible for the design of the randomisation codes and production of the black envelopes. Ying Shen, Sha Chen, Qian Zhu is contributing to the protocol by carrying out literature retrieval, specimen collection, data analysis, and follow-up visits. Ding Huang is responsible for

1
2
3 the project and is contributing to the organisation and operation of the trial.
4

5 **Competing interests:** None
6

7 **Patient consent:** Obtained
8

9 **Ethics approval:** The study was approved by the Medical Research Ethics Committee
10 of International Peace Maternity and Child Health Hospital (approval no. GKLW2017-
11 84).
12

13 **Provenance and peer review:** Not commissioned; externally peer reviewed.
14

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17 SHDC12017X05). And it was supported by the medical engineering cross youth funds
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19

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21 medicine for free and for his confidentiality regarding all the participants and
22 personnel.
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33 Figure Legend:
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36 Fig 1 Flowchart of the study.
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40 CS, Cesarean-section; TVUS, transvaginal ultrasonography
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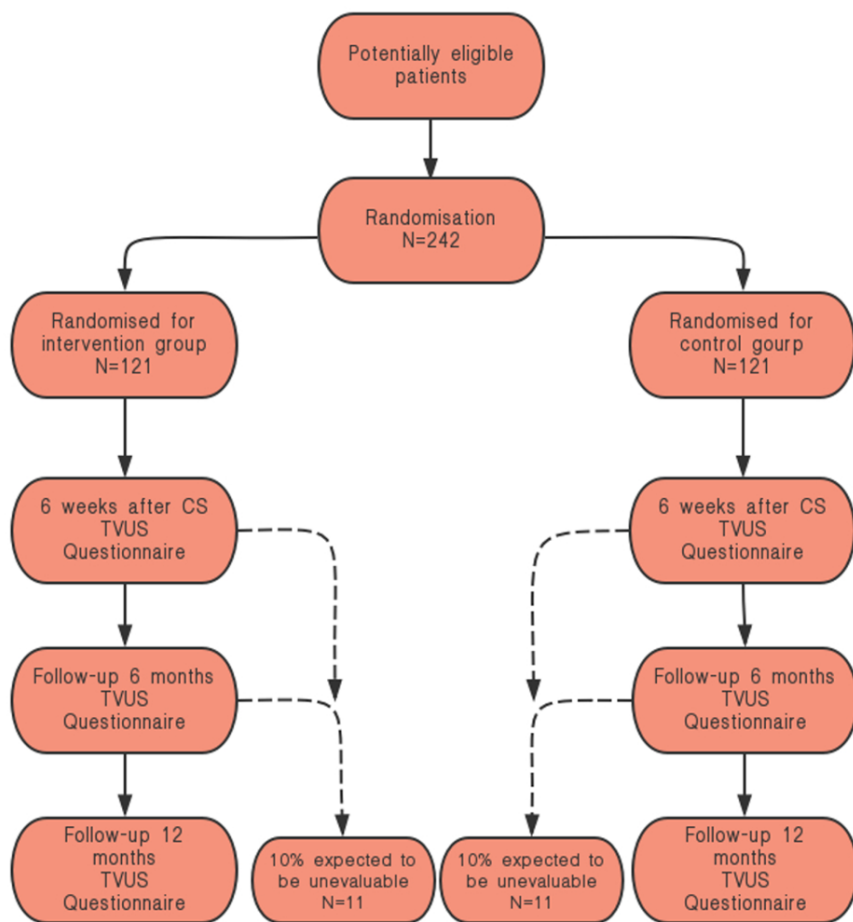


Fig 1 Flowchart of the study.
CS, Cesarean-section; TVUS, transvaginal ultrasonography

90x90mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Page1,line1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (Page2,line13)
	2b	All items from the World Health Organization Trial Registration Data Set (Page2,line13)
Protocol version	3	Date and version identifier (N/A)
Funding	4	Sources and types of financial, material, and other support (Page11,line9)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (Page1,line4)
	5b	Name and contact information for the trial sponsor (Page11,line9)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (N/A)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (N/A)

Introduction

1			
2	Background and	6a	Description of research question and justification for undertaking the
3	rationale		trial, including summary of relevant studies (published and
4			unpublished) examining benefits and harms for each intervention
5			(Page2,line31)
6			
7		6b	Explanation for choice of comparators
8			(Page3,line5)
9			
10	Objectives	7	Specific objectives or hypotheses
11			(Page4,line30)
12			
13	Trial design	7	Description of trial design including type of trial (eg, parallel group,
14			crossover, factorial, single group), allocation ratio, and framework (eg,
15			superiority, equivalence, noninferiority, exploratory)
16			(Page4,line36)
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19			
20	Methods: Participants, interventions, and outcomes		
21			
22	Study setting	9	Description of study settings (eg, community clinic, academic hospital)
23			and list of countries where data will be collected. Reference to where
24			list of study sites can be obtained
25			(Page5,line5)
26			
27	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility
28			criteria for study centres and individuals who will perform the
29			interventions (eg, surgeons, psychotherapists)
30			(Page5,line14)
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33	Interventions	11a	Interventions for each group with sufficient detail to allow replication,
34			including how and when they will be administered
35			(Page6,line25)
36			
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38		11b	Criteria for discontinuing or modifying allocated interventions for a
39			given trial participant (eg, drug dose change in response to harms,
40			participant request, or improving/worsening disease)
41			(N/A)
42			
43		11c	Strategies to improve adherence to intervention protocols, and any
44			procedures for monitoring adherence (eg, drug tablet return,
45			laboratory tests)
46			(N/A)
47			
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49		11d	Relevant concomitant care and interventions that are permitted or
50			prohibited during the trial
51			(Page7,line1)
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2	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
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9			(Page8,line8)
10			
11	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
12			
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15			(Page7,line8)
16			
17	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
18			
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21			(Page8,line28)
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23	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
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25			(N/A)
26			

Methods: Assignment of interventions (for controlled trials)

Allocation:

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31	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
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38			(Page6,line14)
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40	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
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45			(Page6,line15)
46			
47	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
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50			(Page6,line13)
51			
52	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
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56			(Page6,line23)
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- 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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Methods: Data collection, management, and analysis

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- Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
(Page9,line8)
- 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
(N/A)
- Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
(Page9,line13)
- Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
(Page9,line22)
- 20b Methods for any additional analyses (eg, subgroup and adjusted analyses)
(N/A)
- 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
(Page9,line5)

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Methods: Monitoring

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- Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
(N/A)

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2		21b	Description of any interim analyses and stopping guidelines, including
3			who will have access to these interim results and make the final
4			decision to terminate the trial
5			(N/A)
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7	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
8			spontaneously reported adverse events and other unintended effects
9			of trial interventions or trial conduct
10			(N/A)
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12			
13	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
14			whether the process will be independent from investigators and the
15			sponsor
16			(N/A)
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18			
19	Ethics and dissemination		
20			
21	Research ethics	24	Plans for seeking research ethics committee/institutional review board
22	approval		(REC/IRB) approval
23			(Page10,line17)
24			
25	Protocol	25	Plans for communicating important protocol modifications (eg,
26	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
27			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
28			regulators)
29			(N/A)
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32	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
33			participants or authorised surrogates, and how (see Item 32)
34			(Page10,line21)
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37		26b	Additional consent provisions for collection and use of participant data
38			and biological specimens in ancillary studies, if applicable
39			(N/A)
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41	Confidentiality	27	How personal information about potential and enrolled participants will
42			be collected, shared, and maintained in order to protect confidentiality
43			before, during, and after the trial
44			(N/A)
45			
46			
47	Declaration of	28	Financial and other competing interests for principal investigators for
48	interests		the overall trial and each study site
49			(Page11,line3)
50			
51	Access to data	29	Statement of who will have access to the final trial dataset, and
52			disclosure of contractual agreements that limit such access for
53			investigators
54			(N/A)
55			
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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			(N/A)
5			
6	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
7	policy		participants, healthcare professionals, the public, and other relevant
8			groups (eg, via publication, reporting in results databases, or other
9			data sharing arrangements), including any publication restrictions
10			(N/A)
11			
12		31b	Authorship eligibility guidelines and any intended use of professional
13			writers
14			(N/A)
15			
16		31c	Plans, if any, for granting public access to the full protocol, participant-
17			level dataset, and statistical code
18			(N/A)
19			
20			
21			
22			
23	Appendices		
24	Informed consent	32	Model consent form and other related documentation given to
25	materials		participants and authorised surrogates
26			(N/A)
27			
28			
29	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
30	specimens		specimens for genetic or molecular analysis in the current trial and for
31			future use in ancillary studies, if applicable
32			(N/A)
33			

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.