OBSTETRICS

Povidone-iodine 1% is the most effective vaginal antiseptic for preventing post-cesarean endometritis: a systematic review and network meta-analysis

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BACKGROUND: Direct comparison metaanalyses have reported benefits with presurgical vaginal preparation before cesarean delivery for the reduction of endometritis. These reports did not perform a multitreatment comparison of the various antiseptic solutions assessed in previous studies.

OBJECTIVE: The purpose of this study was to review the literature systematically and quantitate and summarize indirectly the comparative efficacy of antiseptic formulations and their concentrations that are used for the preparation of the vagina before cesarean delivery in the prevention of endometritis and other infectious complications.

STUDY DESIGN: We used MEDLINE, EMBASE (from their inception to November 2018) and Cochrane databases, biographies, and conference proceedings. We used randomized clinical trials of patients who underwent surgical preparation of the vagina with antiseptic formulations before cesarean delivery with the aim of reducing the risk of infectious morbidity. Our systematic review was registered and followed the Preferred Reporting Items for Systematic Review and Meta-analysis Extension for network meta-analysis guidelines. Network meta-analysis was performed with computerized software and used user-written programs to assess consistency, inconsistency, ranking probabilities, and graphing results. Direct and indirect pairwise comparisons of the various formulations and their concentrations were performed with the use of multivariate random-effects models and metaregression. A frequentist inference method was employed for the fitted model to estimate the ranking probabilities. Subgroup analyses for patients in labor, not in labor, and with ruptured membranes were conducted.

RESULTS: For the prevention of endometritis, we identified 23 studies that comprised 7097 women who were allocated to the following treatments: povidone-iodine (1%, 5%, 10%), chlorhexidine (0.2%, 0.4%), metronidazole gel, cetrimide, or normal saline solution/no treatment. Direct and indirect pairwise comparisons indicated that, when compared with saline solution or no treatment, all antiseptic formulations decreased rates of endometritis (5.2% vs 9.1%; odds ratio, 0.48; 95% confidence interval, 0.35—0.65; 22 studies/6994 women). Individually, povidone-iodine (odds ratio, 0.43; 95% confidence interval, 0.28—0.64; 16 studies/5968 women), cetrimide (odds ratio, 0.34; 95% confidence interval, 0.13—0.90; 1 study/200 women), and metronidazole (odds ratio, 0.38; 95% confidence interval, 0.16—0.90; 1 study/224 women) significantly reduced the risk of endometritis. Rankings of vaginal preparations indicated that povidone-iodine 1% had the highest probability (72.7%) of being the most effective treatment for the prevention of endometritis. For the secondary outcomes of postoperative wound infection and fever, a significant reduction was found only with povidone-iodine (odds ratio, 0.61; 95% confidence interval, 0.48—0.78; 16 studies/5968 women; and odds ratio, 0.58; 95% confidence interval, 0.40—0.83; 12 studies/4667 women). Subgroup analyses also found that povidone-iodine significantly reduced risk of endometritis for women in labor (odds ratio, 0.42; 95% confidence interval, 0.20—0.88; 5 studies/1211 women), with ruptured membranes(odds ratio, 0.21; 95% confidence interval, 0.10—0.44; 4 studies/476 women), and undergoing planned cesarean delivery (odds ratio, 0.39; 95% confidence interval, 0.27—0.57; 8 studies/1825 women).

CONCLUSION: Among patients who underwent cesarean delivery, presurgical vaginal irrigation with povidone-iodine had the highest probability of reducing the risk of endometritis, postoperative wound infections, and fever.

Key words: antiseptic, cesarean delivery, endometritis, network meta-analysis, vaginal preparation

Despite evolving guidance aimed at decreasing the cesarean delivery rate in the United States,[1–3] a high rate of cesarean birth persists (32% for the year 2017).[4] Cesarean delivery is the most important risk factor for postpartum infectious morbidity (endometritis and wound infections) that ranges from 7—20%, depending on the practice setting and the patient population.[5] Systemic antibiotic prophylaxis, which reduces the incidence of post—cesarean delivery infectious morbidity by approximately 75%, has become routine.[6–8] The morbidity and mortality rates associated with postpartum infections create a burden for mothers, their infants, and the healthcare system.

Our challenge as obstetricians is to minimize the occurrence of this common cause of post—cesarean delivery morbidity. Although systemic antibiotic prophylaxis is the most important factor in reducing post—cesarean delivery infectious morbidity, additional evidence-based interventions and techniques have been proposed and implemented, which includes wound closure techniques and skin preparation.[9–13] Because endometritis appears to result from ascending vaginal bacteria, there has been a growing interest in the assessment of the use of solutions for surgical preparation of the vagina before cesarean delivery.[14,15]

Several randomized clinical trials (RCTs) and systematic reviews with meta-analysis have assessed the efficacy

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AJOG at a Glance

Why was this study conducted?

Preoperative vaginal cleansing before cesarean delivery can be achieved with various agents. We sought to compare these agents for the prevention of postpartum infectious complications.

Key findings

Povidone-iodine effectively reduced the rates of postpartum endometritis, wound infection, and fever. A subgroup analysis found benefit for women who undergo planned cesarean delivery, women in labor, and women with ruptured membranes.

What does this add to what is known?

Povidone-iodine appears to be the agent of choice for preoperative vaginal cleansing before cesarean delivery. This benefit extends to patients who undergo elective cesarean delivery.

of vaginally administered antiseptic solutions, which includes povidone-iodine in varying concentrations, chlorhexidine, metronidazole gel, and cetrimide, before performing cesarean delivery. A recently published direct comparison meta-analysis concluded that vaginal cleansing immediately before cesarean delivery reduced the risk of postoperative endometritis and recommended the use of povidone-iodine 10%.[14] Similar conclusions were reached by Cochrane reviews.[16,17] The American College of Obstetricians and Gynecologists Committee Opinion states that solutions of chlorhexidine gluconate with low concentrations of alcohol are both safe and effective as vaginal surgical preparations and may be used as an alternative to iodine-based preparations such as povidone-iodine.[15]

Although the systematic reviews and the included RCTs referred to earlier have suggested a benefit for the adjunctive use of these antiseptic agents for the prevention of post−cesarean delivery endometritis, none of the studies were designed as a multitreatment comparison to assign superiority to 1 specific vaginal antiseptic over another. These systematic reviews have generated aggregated estimates based on the difference in rates of infectious complications from the use of antiseptic solutions vs placebo or no treatment, with the use of direct comparison pairwise meta-analysis. However, conventional pairwise meta-analysis cannot compare ≥3 treatment regimens simultaneously. In contrast, multitreatment comparisons (network meta-analysis) for each outcome measure can compare the efficacy of the different treatments indirectly. Accordingly, we conducted a systematic review with network meta-analysis, synthesizing both direct and indirect evidence from clinical trials, to estimate the relative effects of antiseptic vaginal solutions before cesarean delivery in the reduction of postpartum infectious morbidity (endometritis, wound infection, and postoperative fever).

Materials and Methods

This systematic review and network meta-analysis was preceded by a written protocol registered in PROSPERO (CRD42018094968) and conducted and reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis[18] statement extension for the reporting of systematic reviews that incorporate network meta-analysis of healthcare interventions.[19]

Criteria for inclusion and exclusion of studies

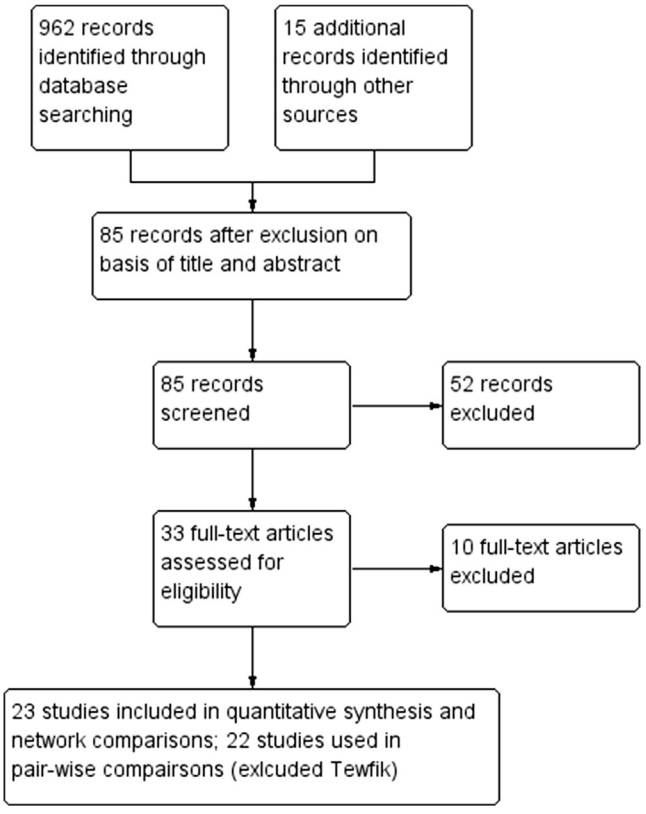
We included RCTs with the following characteristics: (1) studies that compared vaginal antiseptic solutions administered before cesarean delivery with the aim of reducing post−cesarean delivery infectious morbidity, (2) studies that compared vaginal antiseptic solutions with each other or against placebo or no treatment, (3) studies in which prophylactic systemic antibiotics were administered before or during the cesarean delivery, (4) published or unpublished full texts articles, published abstracts presented at scientific meetings, or doctoral dissertations, and (5) articles written in any language. A single quasi-randomized controlled trial (method of allocation by alternation) was also included.[20] We assumed that participants who fulfilled the inclusion criteria were equally eligible to be assigned randomly to any of the interventions of interest (to meet the assumption of transitivity). This study was exempt from Institutional Review Board approval.

The prespecified primary outcome was endometritis, most often defined as maternal temperature >38°C (100.4°F) with uterine tenderness and/or foul-smelling vaginal discharge. Secondary outcomes were wound infection and postoperative fever. Wound infection was defined most often as swelling, erythema, discharge, seroma, hematoma, or disruption of the incision line. Fever was defined as temperature greater than 38.4°C (101.2°F) at least 24 hours after delivery.

Electronic literature search

We comprehensively searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov from their inception to November 14, 2018. The search strategy included related text words and medical subject headings regarding vaginal solution, cesarean delivery, endometritis, wound infection, chlorhexidine, povidone-iodine, metronidazole, cetrimide, and pregnancy (Appendix 1). We reviewed references of included studies for additional related articles and searched for abstracts from national or international meetings. A list of the unique PubMed identification numbers of all relevant articles was compiled, and a search for related articles was performed. This technique has been shown to be highly effective in the identification of relevant studies.[21]

FIGURE 1
Flow diagram



Flow diagram of study identified in the systematic review.

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Screening, data extraction, and risk of bias assessment

Titles and abstracts were screened independently by 2 investigators (J.T.R. and L.S.R.). Trials that did not meet the eligibility criteria were excluded. After omitting the duplicated and unrelated studies, we reviewed the full texts of the remaining studies and ascertained whether they met our eligibility criteria. Any discrepancies were solved by a third reviewer (A.K.). If multiple publications were derived from the same data set, the study with the most complete data and the longest follow-up was included.

Two investigators (J.T.R. and L.S.R.) independently extracted the information from the original studies using a standardized data abstraction list that included study characteristics, patient characteristics, and intervention details for each treatment group and outcome measure. Authors were contacted for clarification as needed, and data were recalculated into a form that was appropriate for analysis when needed. Any disagreements regarding data extraction were resolved by discussion with a third author.

Two investigators (J.T.R. and L.S.R.) appraised the risk of bias for individual studies according to the Cochrane Handbook.[22] The criteria for assessment involved randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases. Each of the domains was determined as "low risk," "unclear risk," or "high risk." Studies with a high risk of bias in $\geq$1 key items were regarded to be at a high risk of bias. For example, for the domain of random sequence generation, low risk of bias would include studies in which randomization was performed by random number generation. A high risk of bias for this domain would include subjects randomly assigned based on day of the week (even or odd). If insufficient detail was provided in the article/manuscript, the domain was labelled "unclear risk." Studies with a low risk of bias in all key items were regarded to be at a low risk of bias. Otherwise, they were regarded to be at an unclear risk of bias. Disagreements were resolved via a discussion with a third author.

Methods for evidence synthesis

We began with a narrative overview of the clinical and methodologic characteristics of the included trials, thereby helping to explore the assumptions of homogeneity and consistency for direct and indirect comparisons. We generated descriptive statistics for all relevant trials and study population characteristics to provide a transparent representation of the patients in this analysis.

Whenever possible, statistical analyses were based on an intent-to-treat method and included all randomly allocated women. For each outcome, we reviewed the network geometry of all comparisons to confirm that the network was connected. Standard pairwise and network metaanalyses were conducted to calculate odds ratios and log odds ratios for the dichotomous outcomes, endometritis, wound infection, and postoperative fever. Direct estimates for traditional pairwise metaanalyses were calculated with the use of a DerSimonian-Laird random effects model.[23] Direct pairwise comparison results were reported as odds ratios (ORs), corresponding 95% confidence intervals (CIs), and 95% predictive intervals, which describe the approximate predictive distribution of future trials.[24] Heterogeneity was tested with the I^2 index and the Cochrane's Q statistic. I^2 values of $\geq$50% or a probability value of $<$.10 for Cochrane's Q chi-squared test indicate that a substantial level of statistical heterogeneity was present.[25] Publication and related biases were assessed by examining funnel plots and statistically using the Egger test.[26]

TABLE 1
Characteristics of included studies

Study	Year	Country	No. of participants (study vs control)	Intervention	Control	Labor, planned, both	Primary Outcome
Ahmed et al[43]	2012	Egypt	218 (109 vs 109)	Chlorhexidine acetate 0.20%	No vaginal cleansing	Planned	Endometritis, febrile morbidity, wound infection
Aref[44]	2018	Saudi Arabia	226 (113 vs 113)	Povidone iodine 10%	No vaginal cleansing	Planned	Composite of endometritis, febrile morbidity, and wound infection
Asghania et al[20]	2011	Iran	568 (284 vs 284)	Povidone iodine 10%	No vaginal cleansing	Both	Endometritis, febrile morbidity, wound infection
Barat et al[45]	2016	Iran	400 (200 vs 200)	Povidone iodine 10%	No vaginal cleansing	Planned	Postoperative fever, wound infection, endometritis
Charoenviboonphan[46]	2011	Thailand	599 (299 vs 300)	Povidone iodine 1%	No vaginal painting	Both	Composite of postoperative fever, endometritis, wound infection, hospital length of stay
Guzman et al[47]	2002	United States	160 (80 vs 80)	Povidone iodine	Saline solution preparation	Planned	Endometritis, wound infection
Haas et al[48]	2010	United States	300 (155 vs 145)	Povidone iodine 1%	No vaginal wash	Both	Composite of postoperative fever, endometritis, sepsis, readmission, wound infection, or complication
Hassan Khedr and Fadel[49]	2016	Egypt	150 (50 vs 100)	Povidone iodine 10%	Saline solution preparation	Planned	Endometritis
Hayat et al[50]	2014	Egypt	200 (100 vs 100)	Povidone iodine	No vaginal cleansing	Planned	Endometritis, wound infection
Kiani et al[51]	2018	Pakistan	434 (217 vs 217)	Povidone iodine 10%	Vulvar and abdominal scrubbing	Labor	Endometritis, fever, wound infection
Memon et al[52]	2011	Pakistan	200 (100 vs 100)	Povidone iodine 10%	No vaginal cleansing	Both	Endometritis, fever, wound infection
Mohamed et al[53]	2015	Egypt	200 (100 vs 100)	Cetrimide	No vaginal cleansing	Planned	Endometritis, fever, wound infection
Mwangi et al[54]	2013	Kenya	402 (206 vs 196)	Povidone	No vaginal cleansing	Both	Endometritis
Nandi et al[55]	2015	India	274 (136 vs 138)	Povidone iodine 5%	No vaginal cleansing	Both	Endometritis, wound infection
Olmez et al[56]	2013	Turkey	667 (332 vs 335)	Povidone iodine 5%	No vaginal preparation	Both	Wound infection, endometritis
Pitt et al[57]	2001	United States	224 (112 vs 112)	Metronidazole 5g 0.75% gel	Placebo vaginal gel	Both	Endometritis, fever, wound infection
Reid et al[58]	2001	United States	430 (217 vs 213)	Povidone iodine 10%	No vaginal cleansing	Both	Endometritis, fever, wound infection
Rouse et al[59]	1997	United States	120 (62 vs 58)	0.2% Chlorhexidine	Sterile water	Both	Chorioamnionitis and endometritis
Rouse et al[60]	2003	United States	208 (110 vs 98)	0.2% Chlorhexidine	Sterile saline solution	Both	Chorioamnionitis and endometritis
Starr et al[61]	2005	United States	308 (142 vs 166)	Povidone iodine 5%	No vaginal cleansing	Both	Endometritis, fever, wound infection
Sweeten et al[62]	1997	United Stated	64 (32 vs 32)	Chlorhexidine	Sterile water	Labor	Intraamniotic infection

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TABLE 1
Characteristics of included studies *(continued)*

Study	Year	Country	No. of participants (study vs control)	Intervention	Control	Labor, planned, both	Primary Outcome
Tewfik et al[32]	2015	Egypt	93 (46 vs 47)	Povidone iodine 10%	Chlorhexidine gluconate	Planned	Endometritis, fever
Yildirim et al[63]	2012	Turkey	669 (334 vs 335)	Povidone iodine 10%	No vaginal cleansing	Both	Endometritis

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Network metaanalyses that consisted of direct and indirect comparisons of vaginal preparations and their concentrations were performed in a frequentist framework by expressing the consistency and inconsistency models as multivariate random-effects metaanalyses or metaregression.[27,28] This method evaluates jointly the comparative effectiveness of multiple available treatments for a condition of interest, even when most, if not all, have not been compared directly in primary studies.[28–30] The assumption of consistency and inconsistency was assessed with an augmented format in which all treatments were compared with a reference treatment, generally patients who did not receive vaginal preparation. The assumption of consistency implies that estimates of treatment effects from direct and indirect evidence are in agreement, subject to the usual variation characteristic of the random-effects models for meta-analysis. Inconsistency is noted when there is discrepancy between direct and indirect comparisons. The design-by-treatment interaction described by Higgins et al[31] was used for investigating inconsistency. A probability value of $>.05$ indicated that the direct and indirect comparisons were in agreement within the network.

The comparative efficacy of the vaginal preparations that were included in this analysis was assessed with the use of placebo or no treatment, as the reference group. A single trial compared povidone vs chlorhexidine.[32] The probability that each vaginal preparation was the best among those analyzed was determined by evaluation of the rank probabilities and surface under the cumulative ranking curve (SUCRA) for the efficacy results of the network meta-analysis.[33] A higher SUCRA value indicates better results for the respective intervention.[34]

Results from the network meta-analyses were presented as a summary of relative effect sizes for each possible pair of treatments and reported as log odds ratios with 95% confidence intervals. A league table was constructed to tabulate all comparisons estimated from the network.

Sensitivity and subgroup analyses performed

After each pairwise direct comparison, we investigated the influence of each individual study on the overall summary estimate by reestimating the meta-analysis after sequentially omitting each study. An individual study was suspected of having excessive influence if the point estimate of its "omitted" analysis lies outside the confidence interval of the "combined" analysis. Subgroup analyses and metaregression were conducted to explore the impact of potentially important effect modifiers on findings from network meta-analysis. These separate analyses included covariates in metaregression models that considered the presence or absence of premature rupture of membranes and the presence or absence of labor before the cesarean delivery. In addition, subgroup analyses of the treatment networks were conducted to compare the concentration of the antiseptic used for vaginal preparation in the prevention of endometritis and other infectious complications.

Software considerations

We used the user-written commands from the package "metan" for Stata SE software (version 15.0; StataCorp, College Station, TX) to perform the pairwise direct comparison metaanalyses. Similarly, for network meta-analysis, we used several network "meta-" user-written commands to perform multivariate random-effects meta-analysis and multivariate random-effects metaregression.

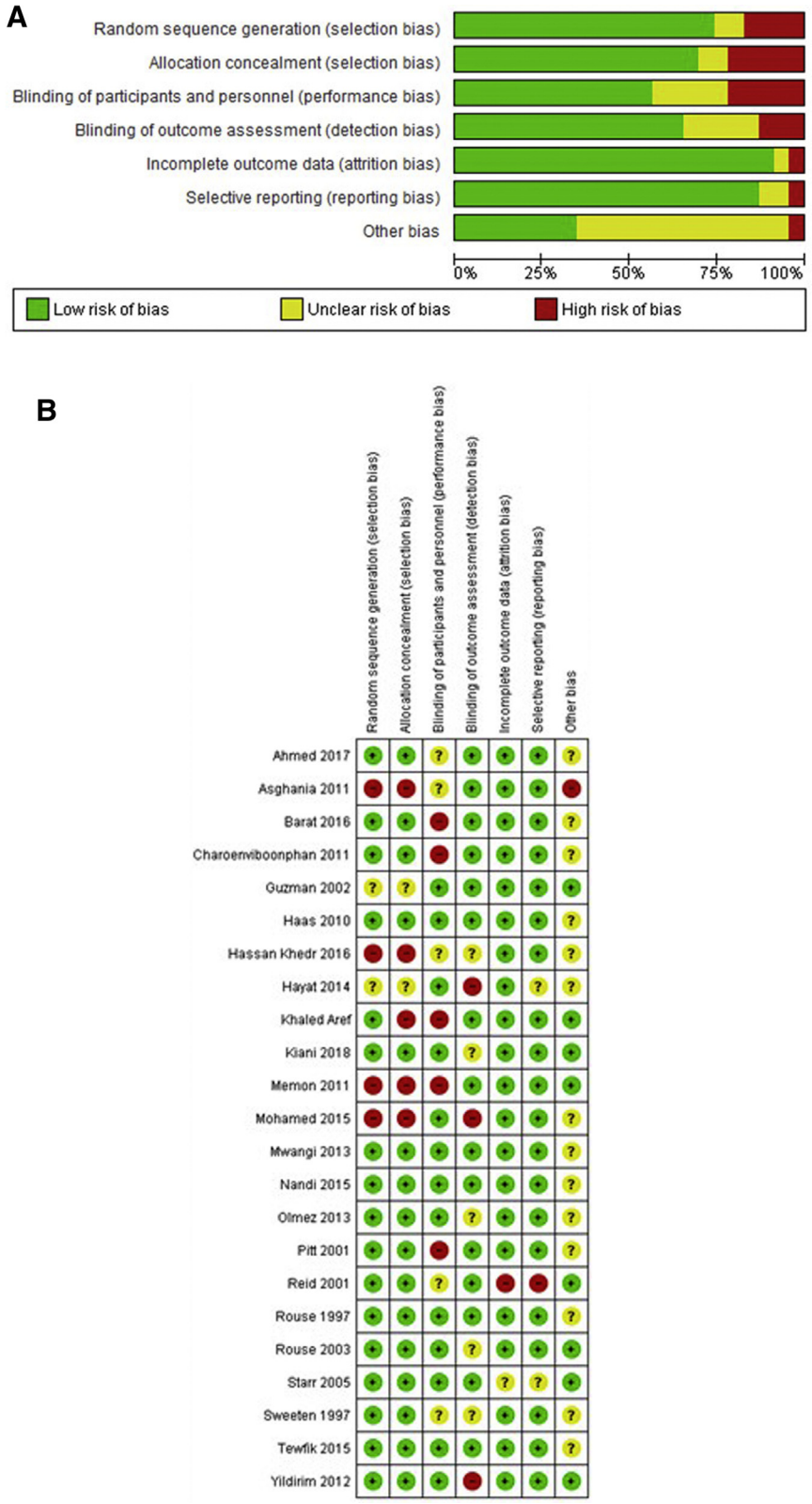
Results

Results of the search

After a review of the titles and abstracts, 33 full-text articles were assessed for eligibility. After review, 23 studies were selected for inclusion in this systematic review and meta-analysis (Figure 1). Women were assigned randomly to vaginal cleansing with an antiseptic or with saline solution/no vaginal cleansing. The formulations for vaginal cleansing included povidone-iodine (1%, 5%, 10%), chlorhexidine (0.2% and 0.4%), metronidazole gel (0.75%), cetrimide solution (a mixture of different quaternary ammonium salts that included cetrimonium bromide), or placebo (sterile water or sterile saline solution)/no treatment. Characteristics of included studies are detailed in Table 1.

A majority of the studies used povidone-iodine as the treatment compared with placebo cleansing or no treatment (16 RCTs, 5968 patients). Four RCTs (602 patients) randomly assigned women to chlorhexidine vs placebo cleansing or no treatment. There was 1 RCT that assessed metronidazole (224 women), and 1 RCT that used cetrimide (200 women). Another study of 93

FIGURE 2
Assessment of risk of bias



A, Risk of items presented as percentages across all included studies. **B,** Summary of risk for each trial.

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women directly compared chlorhexidine with povidone-iodine.[32]

Of the 23 studies, 22 studies with 6994 women were included in the pair-wise meta-analysis of various agents that were used for vaginal cleansing vs placebo/no treatment. One study was excluded from the pair-wise meta-analysis but was included in the network meta-analysis because this study compared povidone-iodine with chlorhexidine.[32] Twenty-three studies were included in the network meta-analysis.

Included studies were published from 1997–2018 and were conducted in various countries with differing levels of economic resources. Trials varied with respect to inclusion criteria: some trials included only women who had undergone planned cesarean delivery (8/23), and other trials included laboring women (16/23). Systemic antibiotics were administered preoperatively or intraoperatively in each study. Vaginal cleansing commonly was accomplished with a sponge or gauze stick in the vagina. Overall, the risk of bias was low. For random sequence generation, 4 of 23 studies were rated as high risk of bias according to Cochrane Handbook criteria (Figure 2). There was evidence of publication bias, as shown by funnel plots and Eggers test (P=.002; Appendix 2, A-C).

Grouped results: vaginal preparation vs no vaginal preparation

When the treatments were grouped together into vaginal preparation vs no vaginal preparation, vaginal antiseptics significantly reduced endometritis (5.2% vs 9.1%; OR, 0.48, 95% CI, 0.35–0.65; 22 studies, 6994 women), wound infection (3.9% vs 6.1%; OR, 0.63, 95% CI, 0.50–0.79; 21 studies, 6920 women), and fever (7.8% vs 13.0%; OR, 0.56, 95% CI, 0.42–0.76; 15 studies, 5291 women; Table 2). These results did not included 1 study that directly compared chlorhexidine with povidone-iodine.[32]

Reduction of endometritis

With respect to the prevention of endometritis, we identified 16 studies that used povidone-iodine for vaginal preparation of varying concentrations. As

TABLE 2
Outcomes of pairwise comparisons

Variable	Endometritis			Wound infection			Fever		
	Studies/ women, n	Odds ratio[a]	95% Confidence interval	Studies/ women, n	Odds ratio[a]	95% Confidence interval	Studies/ women, n	Odds ratio[a]	95% Confidence interval
All agents	22/6994	0.48[b]	0.35–0.65	21/6920	0.63	0.50–0.79	15/5291	0.56[b]	0.42–0.76
Povidone	16/5968	0.43	0.28–0.64	16/5968	0.61	0.48–0.78	12/4667	0.58[b]	0.40–0.83
Chlorhexidine	4/602	0.71[b]	0.38–1.33	3/528	0.44	0.15–1.23	1/200	0.47	0.08–2.63
Metronidazole	1/224	0.38	0.16–0.90	1/224	1.70	0.40–7.28	1/224	0.67	0.33–1.38
Cetrimide	1/200	0.34	0.13–0.90	1/200	0.53	0.17–1.65	1/200	0.37	0.17–0.83

[a] Calculated with the use of the random effects model; [b] I^2 heterogeneity >50%.

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shown in Table 2 and Figure 3, povidone-iodine significantly reduced the risk of endometritis when compared with placebo (OR, 0.43; 95% CI, 0.28–0.64; 16 studies, 5968 women). Chlorhexidine vaginal preparation did not significantly reduce the risk of endometritis (OR, 0.71; 95% CI, 0.38–1.33; 4 studies, 602 women). Single trials that used metronidazole gel and cetrimide each found a significant reduction in endometritis (OR, 0.38;

FIGURE 3
Forest plot for the risk of endometritis

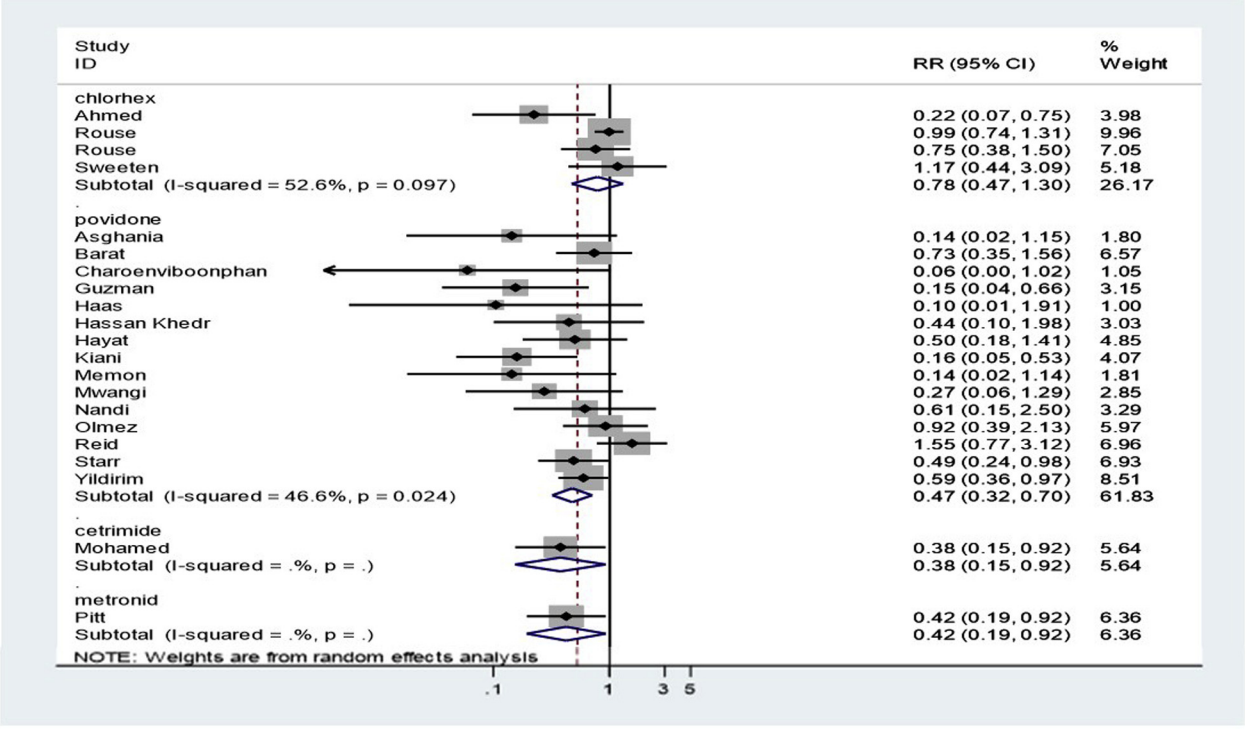

Figure shows the pooled effect estimate (odds ratio) for the various treatments vs placebo/no treatment for the prevention of endometritis. The *boxes* indicate the point estimate of effect with the area of the box proportional to each study's assigned weight. The *horizontal lines* represent the 95% confidence intervals. The *diamond* and *broken vertical line* represent the overall summary estimate. The *solid vertical line* represents null effect.

CI, confidence interval; *ID*, identification; *RR*, relative risk.

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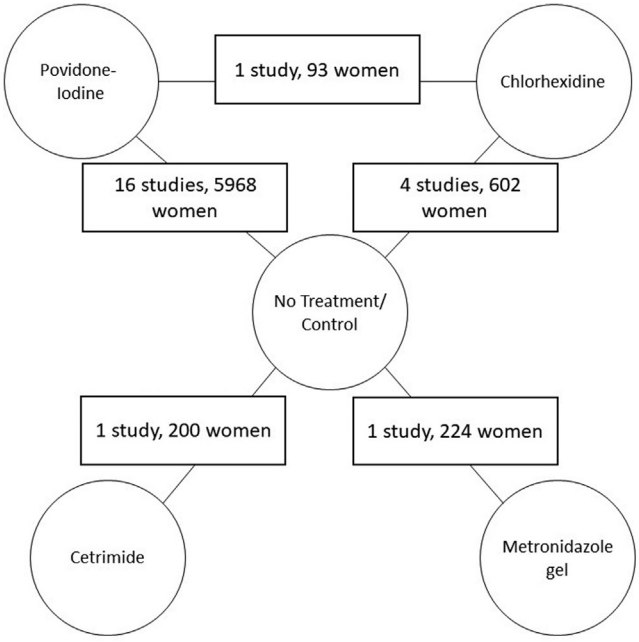
FIGURE 4
Network geometry



Network of randomized controlled trials that compare different vaginal preparations for their efficacy to prevent endometritis.

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95% CI, 0.16−0.90; 224 women; OR, 0.34; 95% CI, 0.13−0.90; 200 women), respectively.

Using endometritis as the primary outcome and the various agents and concentrations of the vaginal preparations, we applied a network meta-analysis framework and SUCRA analysis that allowed all the trials and all the treatments to be compared simultaneously (Figure 4; Appendix 3). When grouped by agent, povidone-iodine had the highest chance of being ranked best, 2nd best, and 3rd best (Table 3; Figure 5, A). Cetrimide was second best. When grouped by agent concentration, povidone-iodine 1% had a 72.7% chance of being the best treatment (Table 4; Figure 5, B). Results of additional analysis that was conducted after we split the placebo node into 2 groups ("no wash" and "placebo wash") did not alter the results (Appendix 4, A−F).

TABLE 3
Network comparisons for prevention of endometritis by agent: league table of different agents for prevention of endometritis (indirect comparisons)

Cetrimide				
0.55 0.11−2.63	Chlorhexidine			
0.89 0.13−6.30	1.63 0.36−7.36	Metronidazole		
0.75 0.17−3.31	1.38 0.65−2.92	0.84 0.21−3.47	Povidone	
0.34 0.08−1.39	0.61 0.31−1.21	0.38 0.10−1.45	0.45 0.29−0.68	No treatment/ placebo

Individual values represent relative risk; ranges represent 95% confidence intervals.

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Reduction of wound infection

For the prevention of wound infection, 21 studies (6920 patients) were included for analysis. Women who received vaginal cleansing with povidone-iodine at various concentrations had a significant reduction in the rate of wound infection (OR, 0.61; 95% CI, 0.48−0.78; 16 studies, 5968 women). As shown in Figure 6, vaginal preparations that used the following agents were not effective in reducing wound infection: chlorhexidine (OR, 0.44; 95% CI, 0.15−1.23; 3 studies, 528 women), cetrimide (OR, 0.53; 95% CI, 0.17−1.65; 1 study, 200 women), and metronidazole gel (OR, 1.70; 95% CI, 0.40−7.28,; 1 study, 224 women).

SUCRA analysis allowed us to rank the various treatments and concentrations. When indirectly compared with each formulation, chlorhexidine had the highest probability (57.4%) of being the best treatment for the prevention of wound infection, followed by povidone-iodine (33.8%). A league table of indirect comparisons and ranking probabilities can be found in the Appendix 4, F.

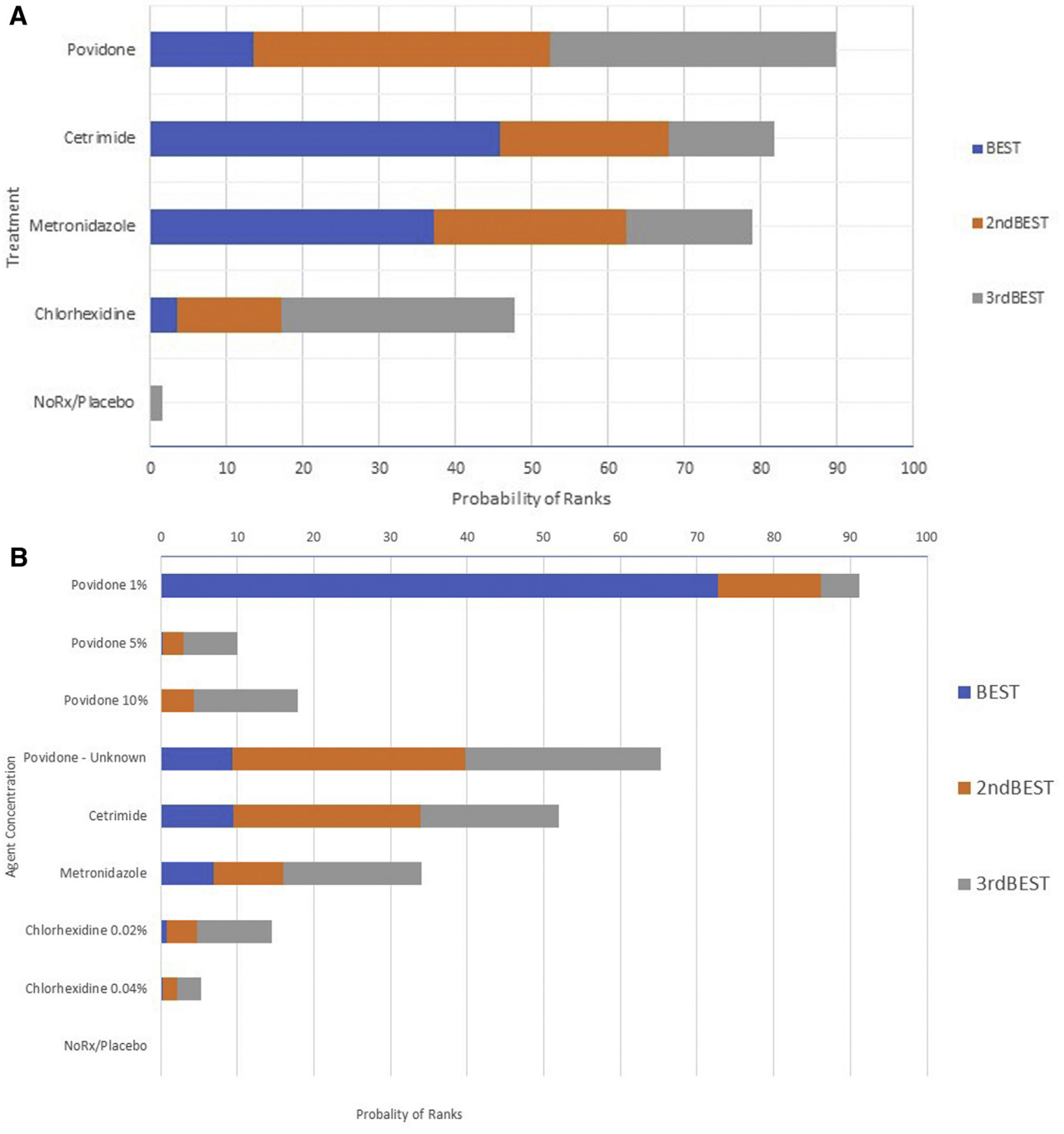
Reduction of postoperative fever

Analysis of the 15 studies that reported postoperative fever found a significant reduction with the 12 trials of povidone-iodine (OR, 0.58; 95% CI, 0.40−0.83; 4667 women) and the single trial of cetrimide (OR, 0.37; 95% CI, 0.17−0.83; 200 women). Studies that assessed metronidazole gel and chlorhexidine did not show a significant reduction in postoperative fever. Forest plots and a league table of the network meta-analysis results can be found in the Appendix 5.

Subgroup analysis

Subgroup analyses that assessed the impact of labor status and fetal membrane status were conducted (Table 5). For patients in labor before cesarean

FIGURE 5
Ranking probabilities



Rankogram indicated the likelihood of different agents being the best agent for the prevention of endometritis. **A,** Ranking probabilities of endometritis by agent. **B,** Ranking probabilities endometritis by agent concentration.

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delivery, the use of vaginal antiseptics significantly reduced the risk of endometritis (OR, 0.42; 95% CI, 0.20−0.88,; 5 studies, 1211 women). For patients in labor, vaginal antiseptics did not significantly reduce wound infection (OR, 0.43; 95% CI, 0.18−1.02; 4 studies, 1095 women).

For patients with ruptured membranes, vaginal antiseptics significantly reduced the risk of endometritis (OR, 0.21; 95% CI, 0.10−0.44; 4 studies, 476

TABLE 4
Network comparisons for prevention of endometritis by agent concentration: league table of different agents for prevention of endometritis (indirect comparisons)

Povidone 1%								
0.12 0.01–1.28	Povidone 5%							
0.16 0.02–1.57	1.36 0.49–3.77	Povidone 10%						
0.27 0.02–3.29	2.22 0.50–9.77	1.64 0.44–6.13	Povidone– unknown					
0.23 0.02–3.18	1.86 0.34–10.30	1.37 0.28–6.67	0.84 0.12–5.65	Cetrimide				
0.20 0.01–2.72	1.66 0.32–8.62	1.22 0.27–5.55	0.75 0.12–4.76	0.89 0.12–6.86	Metronidazole			
0.15 0.01–1.47	1.18 0.37–3.80	0.87 0.36–2.12	0.53 0.13–2.23	0.64 0.12–3.39	0.71 0.14–3.58	Chlorhexidine 0.02%		
0.06 0.01–0.97	0.51 0.08–3.30	0.38 0.07–2.16	0.23 0.03–1.78	0.28 0.03–2.53	0.31 0.04–2.71	0.43 0.07–2.69	Chlorhexidine 0.04%	
0.08 0.01–0.68	0.62 0.26–1.47	0.46 0.26–0.80	0.28 0.08–0.94	0.34 0.08–1.47	0.38 0.09–1.54	0.53 0.24–1.16	1.21 0.23–6.30	No treatment/ placebo

Individual values represent relative risk; ranges represent 95% confidence intervals.
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women) but not the risk of wound infection (OR, 0.55; 95% CI, 0.22–2.50; 4 studies, 476 women). For patients who underwent planned cesarean delivery, we found a significant reduction in endometritis with vaginal antiseptics (OR, 0.39; 95% CI, 0.27–0.57; 8 studies, 1825 women) but no significant reduction in wound infection (OR 0.64; 95% CI, 0.39–1.03; 8 studies, 1825 women).

Comment

Principal findings of the study

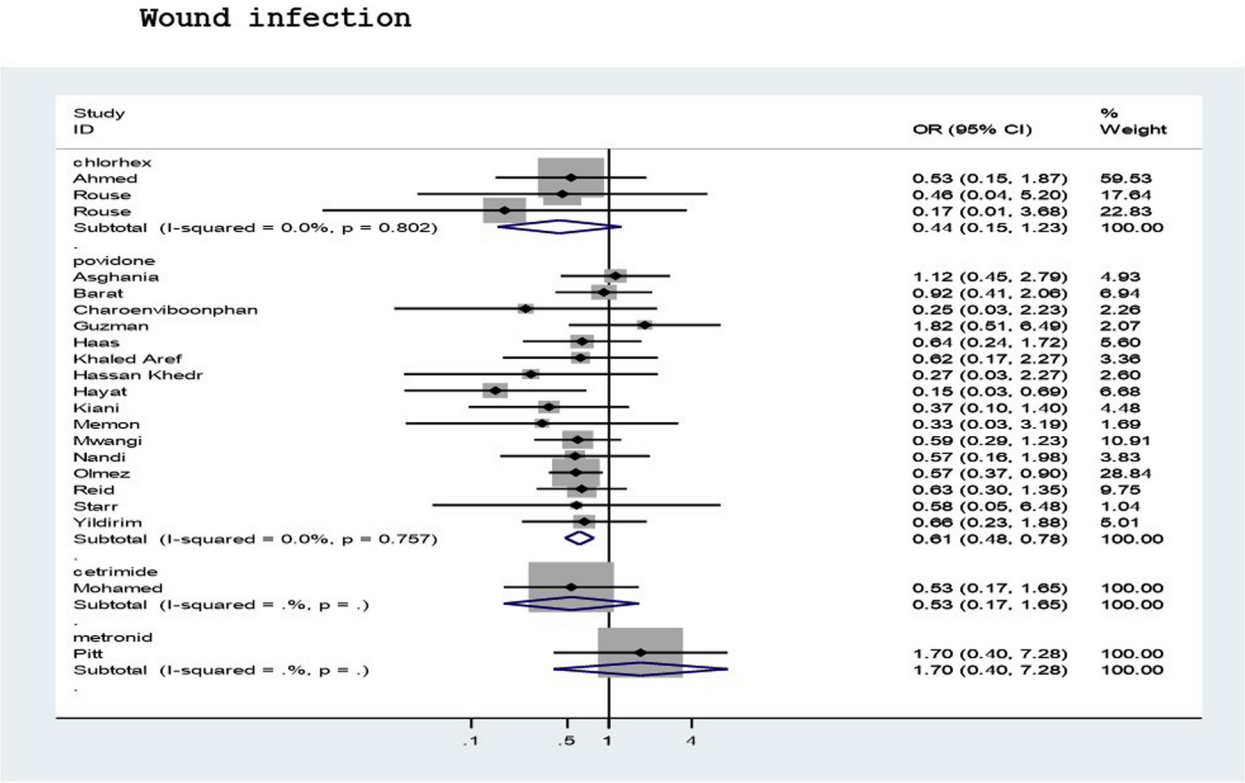
Presurgical vaginal preparation with antiseptic solutions reduces infectious morbidity after cesarean delivery. We found that antiseptic vaginal preparation with povidone-iodine was effective at reducing the rate of endometritis, wound infection, and postoperative fever. Although various treatments and concentrations were beneficial for the reduction of endometritis and wound infection, povidone-iodine 1% appears to be the best treatment. Subgroup analyses found a reduction in endometritis for patients with planned and unplanned cesarean delivery, patients in labor, and patients with ruptured membranes. The SUCRA rankings and indirect comparisons also support povidone-iodine 1% as having the highest likelihood of being the superior treatment.

This network meta-analysis furthers the pairwise metaanalyses by Hass et al[17] (10 RCTs, 3283 women) and Caissutti et al[14] (16 RCTs, 4837 women) by the use of a network meta-analysis to compare various vaginal antiseptics simultaneously. In a direct comparison meta-analysis, Haas et al[17] concluded that povidone-iodine vaginal preparation reduced the risk of postpartum endometritis from 8.7–3.8% (relative risk, 0.36; 95% CI, 0.63–0.97). Although the aforementioned metaanalyses did not find a reduction in the rate of wound infection, we found that the vaginal application of povidone-iodine significantly reduced risk of this adverse outcome. A direct comparison meta-analysis of 5 RCTs (12,154 women) that assessed vaginal chlorhexidine prophylaxis for women in labor did not note a reduction in risk of maternal infections or sepsis.[35] Although that report included patients with vaginal deliveries, it supports our findings that chlorhexidine may not be as effective in reducing the risk of endometritis, wound infection, or fever. Currently, an ongoing clinical trial is investigating the role of chlorhexidine vaginal preparation vs standard treatment at cesarean delivery to reduce endometritis and prevent sepsis.[36]

This network meta-analysis differs substantially from the 2017 meta-analysis[14] in that we found a benefit of preoperative vaginal cleansing in the subgroup of women who were not in labor undergoing planned cesarean delivery. A subgroup analysis in the 2017 meta-analysis found a trend toward a reduction in endometritis in nonlaboring women; however, this finding did not achieve statistical significance (3 studies, 793 women; relative risk, 0.62; 95% CI, 0.34–1.15).[14]

Cesarean delivery in the second stage of labor is associated with increased rates of endometritis.[37] Accordingly, the reduction of ascending infection through a reduction in the load of vaginal bacteria is a plausible mechanism of action to explain the reduction in endometritis achieved by vaginal preparations with antiseptic solutions. Vaginal preparation with povidone-iodine has been shown to decrease the number of vaginal organisms by

FIGURE 6
Forest plot for risk of wound infection by agent



Forest plot shows the pooled effect estimate (odds ratio) for the prevention of wound infection by agent. The *boxes* indicate the point estimate of effect with the area of the box proportional to each study's assigned weight. The *horizontal lines* represent the 95% confidence intervals. The *diamond* and *broken vertical line* represent the overall summary estimate. The *solid vertical line* represents null effect.

CI, confidence interval; *ID*, identification; *OR*, odds ratio.

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>95%.[38] Although chlorhexidine preparations with high doses of alcohol may be caustic to the vagina, low-dose chlorhexidine preparations are available.[9] Because the vaginal bacteria would need to ascend into the uterus, through the hysterotomy site, and into the abdomen to seed the subcutaneous tissue and cause infection, preventing wound infection with the use of vaginal antiseptics may not be an appropriate outcome to assess. This meta-analysis shows that vaginal antiseptic application is associated with fewer benefits for the reduction of wound infection. The subgroup of planned cesarean delivery suggested a reduction in wound infection (OR, 0.64; 95% CI, 0.39–1.03; 8 studies, 1825 women). We were unable to assess potential confounding factors that included operative technique, maternal

TABLE 5
Subgroup analysis

Variable	Labor	Odds ratio (95% confidence interval)[a]	Rupture of membranes[b]	Odds ratio (95% confidence interval)[a]	Planned cesarean delivery[c]	Odds ratio (95% confidence interval)[a]
Endometritis	5 Studies[d]	0.42 (0.20–0.88)	4 Studies	0.21 (0.10–0.44)	8 Studies	0.39 (0.27–0.57)
Wound infection	4 Studies[e]	0.43 (0.18–1.02)	4 Studies	0.55 (0.22–2.50)	8 Studies	0.64 (0.39–1.03)

[a] Random effects model was used; [b] All used povidone-iodine, 1095 women; [c] All used povidone-iodine, 476 women; [d] 4 povidone-iodine, 1 chlorhexidine, 1211 women; [e] 6 povidone-iodine, 1 chlorhexidine, 1 cetrimide, 1825 women.

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body mass index, number of previous cesarean deliveries, and comorbidities.

Guidelines for optimal preoperative, intraoperative, and postoperative care have been published.[39] The results of this network meta-analysis support the addition of preoperative vaginal preparation to the Enhanced Recovery After Surgery (ERAS) Cesarean Delivery Guidelines.[40,41]

Network metaanalyses are useful in the comparison of treatments that have not been compared in head-to-head trials. Although 1 study compared chlorhexidine and povidone-iodine, the number of participants was small (93 women), and no difference was demonstrated between the 2 treatments.[32] After a network meta-analysis, it is useful to rank treatments according to their effectiveness. When ranked by concentration, povidone-iodine 1% had a 72.7% chance of being the best agent. Because our findings regarding cetrimide are based on a single trial, povidone-iodine had a high probability of being ranked first for the prevention of endometritis. In a similar manner, we found that chlorhexidine had the highest probability of being the best treatment to prevent wound infection. It is possible for a treatment to be ranked first when there is no strong evidence (beyond chance) that is more effective than other options.[30] Thus, a treatment being ranked first may or may not be a clinically relevant finding because the confidence intervals of the rankings often overlap. It is also useful to identify which treatment had the lowest probability of being the best treatment. The observation that placebo cleansing/no treatment had the lowest probability of being the best treatment supports the efficacy of the application of vaginal antiseptic before cesarean birth.

Strengths and limitations

Strengths of this systematic review with network meta-analysis include (1) the use of a network framework for indirect comparisons that have not undergone head-to-head trials, (2) an extensive literature search with the use of various computerized databases that included sources of grey literature without language restrictions, (3) a registered review that followed Preferred Reporting Items for Systematic Review and Meta-analysis guidelines, and (4) a study quality assessment that was based on strict predetermined criteria. Administering systemic antibiotics before or during cesarean delivery represents standard of care. Accordingly, we did not include studies in which antibiotics were not administered because this would limit generalizability of our results.

The potential limitations of the work include the challenges in controlling for potential confounding factors and selection bias. Trials varied in their techniques of randomization. Cetrimide and metronidazole had only a single study from which to extract data, increasing the chance of type II error and of falsely inferring the absence of benefit from these vaginal preparations when a benefit may exist if a larger sample or more studies were obtained. Subgroup analyses were limited because many trials included both intrapartum and elective cesarean delivery and ruptured and intact membranes without stratification of these subgroups. Although participants in all studies received systemic antibiotics to prevent infection, the type and timing of the antibiotics, the characteristics of the population studied, the method of placental removal, and the economic resources of the study sites varied. Of note, these trials routinely did not use of azithromycin in laboring patients who underwent cesarean delivery. Also, the definitions of endometritis, wound infection, and postoperative fever that were reported by the trial investigators varied slightly from study to study. To decrease inconsistencies in future trials, we support the use of research design standards, such as the Core Outcome Measures outlined in the CROWN (CoRe Outcomes in WomeN's health) Initiative.[42] We excluded trials of vaginal preparation when the results for patients who underwent cesarean delivery could not be distinguished from patients who underwent vaginal birth.

Implications for practice

Decreasing morbidity after cesarean delivery is of critical importance. Ruptured membranes are a risk factor for ascending infection. Reduction of the vaginal flora through the use of vaginal antiseptics is a plausible mechanism of action to explain the reduction in endometritis. The cost of these agents is low, and the time involved to apply them is minimal. This analysis supports the routine application of povidone-iodine 1% in patients who undergo planned cesarean delivery and cesarean delivery after membranes rupture and/or labor. ■

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Appendix

APPENDIX 1
Detailed search strategy for systematic review

Variable	Search strategy
Databases searched	MEDLINE, EMBASE, CINAHL, and LILACS (all from inception to September 31, 2018), the Cochrane Central Register of Controlled Trials (1960 to October 2018), ISI Web of Science (1960 to October 2018), research registers of ongoing trials (www.clinicaltrials.gov, www.controlledtrials.com, www.centerwatch.com, www.anzctr.org.au, http://www.nihr.ac.uk, and www.umin.ac.jp/ctr), and Google scholar
Search strategy for Pubmed (similar strategies were applied to other databases)	((((((((("Caesarean delivery"[Mesh]) OR "cesarean section") "endometritis" [Mesh]) OR "surgical wound infection"[Mesh]) OR "postoperative infection"[Mesh]) OR "vaginal preparation"[Mesh]) OR "fever"[Mesh]) OR "surgical site infection"[Mesh]) OR "vaginal cleansing" [Supplementary Concept]) AND "Randomized Controlled Trial" [Publication Type]; Cesarean Section AND (Endometritis OR Surgical Wound Infection OR Fever) AND vaginal preparation))))))))
Other sources	The reference lists of selected articles and reviews were hand searched to identify any relevant articles.

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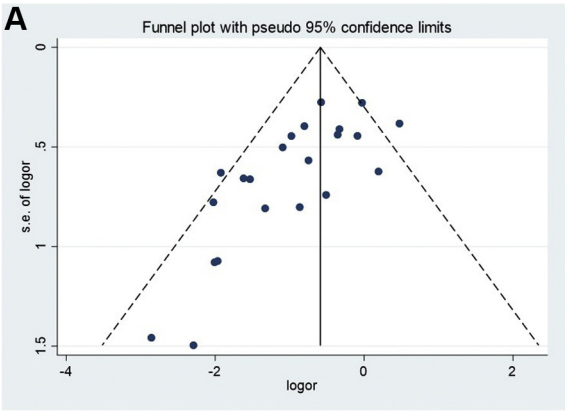
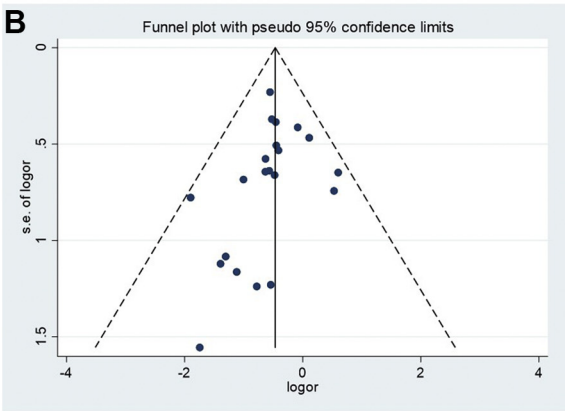
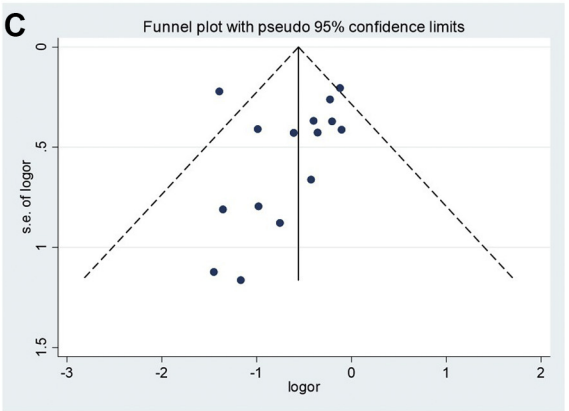
APPENDIX 2
All studies







A, Endometritis. **B,** Wound infections. **C,** Fever.

logor, log odds ratio; *s.e.*, standard error.

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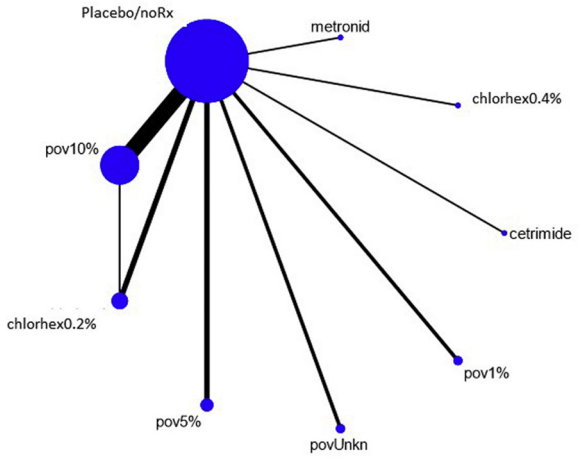
APPENDIX 3
Network diagram for endometritis



Network geometry of randomized controlled trials comparing various vaginal preparations and concentrations for their efficacy to prevent endometritis.

noRX, no treatment; *pov*, povidine iodine; *Unkn*, unknown concentration.

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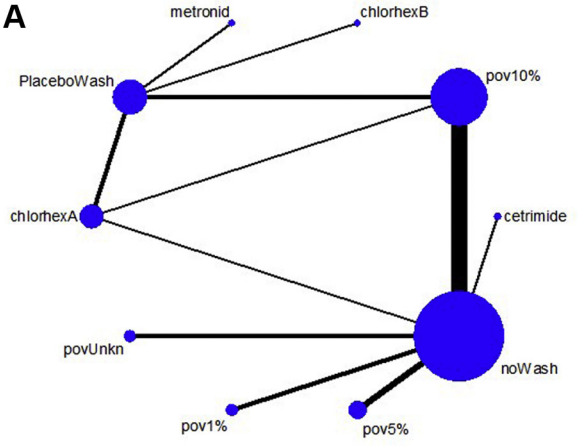
APPENDIX 4
Prevention of endometritis with and without vaginal wash

A



B

study and Rank	Treatment PlaceboWash	cetrimide	chlorhexA	chlorhexB	metronid	noWash	pov1%	pov10%	pov5%	povUnkn
1										
Best	0.0	7.5	1.8	1.3	10.0	0.0	70.1	0.4	0.4	8.5
2nd	0.0	20.1	5.9	2.7	23.0	0.0	13.1	4.4	2.0	28.8
3rd	0.6	17.4	11.1	5.3	16.7	0.0	6.4	13.1	6.3	23.1
4th	1.4	11.9	21.0	3.6	12.1	0.0	2.9	22.5	10.9	13.7
5th	4.6	10.4	19.2	4.9	10.2	0.8	2.4	26.2	13.0	8.3
6th	9.5	9.7	18.0	6.9	7.5	4.1	2.2	18.7	17.1	6.3
7th	16.6	7.0	12.0	9.0	7.6	13.1	1.0	10.6	17.2	5.9
8th	23.7	6.3	7.9	8.8	4.5	26.8	0.4	3.3	15.7	2.6
9th	29.6	5.6	2.9	11.2	5.0	32.0	0.6	0.8	10.5	1.8
Worst	14.0	4.1	0.2	46.3	3.4	23.2	0.9	0.0	6.9	1.0

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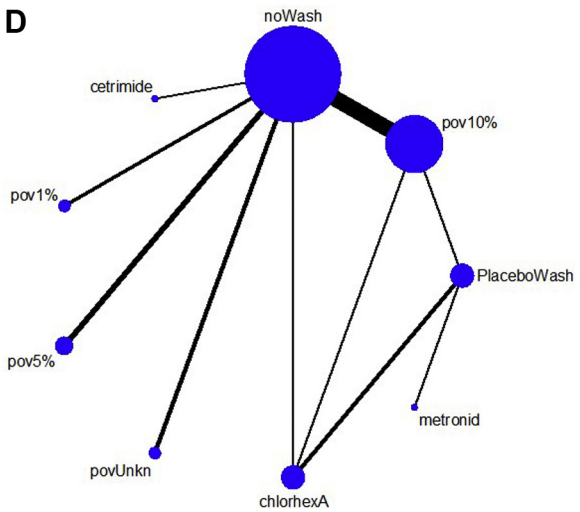
APPENDIX 4
(*Continued*)

C

Table of exponentiated log odds ratio (and its 95% CI) for Treatment vs. Comparator:

Comparator	Treatment: PlaceboWash	cetrimide	chlorhexA	chlorhexB	metronid	noWash	pov1%	pov10%	pov5%	povUnkn
PlaceboWas		0.38 (0.06,2.56)	0.53 (0.22,1.28)	1.21 (0.22,6.65)	0.38 (0.09,1.64)	1.14 (0.37,3.50)	0.09 (0.01,1.03)	0.50 (0.18,1.40)	0.71 (0.17,2.99)	0.32 (0.06,1.69)
cetrimide	2.63 (0.39,17.72)		1.40 (0.21,9.45)	3.19 (0.25,41.10)	0.99 (0.09,11.01)	2.98 (0.64,13.91)	0.23 (0.02,3.34)	1.31 (0.25,6.94)	1.86 (0.31,11.06)	0.83 (0.12,6.03)
chlorhexA	1.88 (0.78,4.54)	0.72 (0.11,4.85)		2.28 (0.34,15.51)	0.71 (0.13,3.94)	2.14 (0.69,6.65)	0.16 (0.01,1.94)	0.94 (0.33,2.71)	1.33 (0.31,5.67)	0.60 (0.11,3.18)
chlorhexB	0.82 (0.15,4.51)	0.31 (0.02,4.04)	0.44 (0.06,2.97)		0.31 (0.03,2.94)	0.94 (0.12,7.20)	0.07 (0.00,1.44)	0.41 (0.06,3.01)	0.58 (0.06,5.42)	0.26 (0.02,2.84)
metronid	2.66 (0.61,11.56)	1.01 (0.09,11.24)	1.41 (0.25,7.83)	3.22 (0.34,30.53)		3.01 (0.47,19.23)	0.23 (0.01,4.09)	1.33 (0.22,8.00)	1.88 (0.24,14.74)	0.84 (0.09,7.82)
noWash	0.88 (0.29,2.72)	0.34 (0.07,1.56)	0.47 (0.15,1.46)	1.07 (0.14,8.23)	0.33 (0.05,2.12)		0.08 (0.01,0.69)	0.44 (0.23,0.83)	0.62 (0.26,1.53)	0.28 (0.08,0.97)
pov1%	11.63 (0.97,139.10)	4.42 (0.30,65.41)	6.18 (0.51,74.14)	14.11 (0.70,285.84)	4.38 (0.24,78.37)	13.20 (1.45,120.40)		5.81 (0.58,57.95)	8.24 (0.76,89.50)	3.68 (0.29,46.56)
pov10%	2.00 (0.71,5.62)	0.76 (0.14,4.02)	1.06 (0.37,3.06)	2.43 (0.33,17.75)	0.75 (0.12,4.54)	2.27 (1.21,4.28)	0.17 (0.02,1.71)		1.42 (0.47,4.25)	0.63 (0.16,2.54)
pov5%	1.41 (0.33,5.96)	0.54 (0.09,3.18)	0.75 (0.18,3.18)	1.71 (0.18,15.90)	0.53 (0.07,4.16)	1.60 (0.65,3.92)	0.12 (0.01,1.32)	0.71 (0.24,2.11)		0.45 (0.10,2.07)
povUnkn	3.16 (0.59,16.86)	1.20 (0.17,8.69)	1.68 (0.31,8.95)	3.83 (0.35,41.70)	1.19 (0.13,11.05)	3.58 (1.03,12.44)	0.27 (0.02,3.43)	1.58 (0.39,6.32)	2.24 (0.48,10.37)	

D



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(continued)

APPENDIX 4
(*Continued*)

E

study and Rank	Treatment								
	PlaceboWash	cetrimide	chlorhexA	metronid	noWash	pov1%	pov10%	pov5%	povUnkn
1									
Best	0.8	30.7	30.8	0.6	0.0	24.7	2.2	7.4	2.8
2nd	2.2	18.1	20.1	2.0	0.0	21.0	10.8	20.3	5.5
3rd	3.0	10.4	14.2	1.5	0.0	14.6	20.8	26.8	8.7
4th	2.2	10.2	9.8	1.9	0.7	11.9	26.5	22.7	14.1
5th	2.7	9.0	8.8	1.8	6.9	10.8	24.9	14.2	20.9
6th	5.1	7.1	7.3	2.5	30.2	8.2	10.5	6.5	22.6
7th	5.9	9.2	7.5	4.5	46.2	5.4	3.0	1.7	16.6
8th	59.0	3.8	1.1	15.0	11.5	1.9	1.2	0.1	6.4
Worst	19.1	1.5	0.4	70.2	4.5	1.5	0.1	0.3	2.4

F

Table of exponentiated log odds ratio (and its 95% CI) for Treatment vs. Comparator:

Comparator	Treatment								
	PlaceboWash	cetrimide	chlorhexA	metronid	noWash	pov1%	pov10%	pov5%	povUnkn
PlaceboWas		0.28 (0.04,1.88)	0.26 (0.06,1.17)	1.70 (0.40,7.28)	0.52 (0.11,2.44)	0.28 (0.05,1.70)	0.34 (0.07,1.58)	0.30 (0.06,1.48)	0.41 (0.08,2.16)
cetrimide	3.62 (0.53,24.56)		0.95 (0.20,4.44)	6.14 (0.55,68.11)	1.88 (0.61,5.82)	1.02 (0.24,4.35)	1.23 (0.38,4.05)	1.08 (0.32,3.60)	1.47 (0.40,5.37)
chlorhexA	3.80 (0.85,16.94)	1.05 (0.23,4.92)		6.46 (0.80,52.01)	1.98 (0.69,5.64)	1.08 (0.27,4.30)	1.30 (0.44,3.79)	1.13 (0.37,3.51)	1.55 (0.45,5.26)
metronid	0.59 (0.14,2.53)	0.16 (0.01,1.81)	0.15 (0.02,1.25)		0.31 (0.04,2.56)	0.17 (0.02,1.68)	0.20 (0.02,1.67)	0.18 (0.02,1.53)	0.24 (0.03,2.20)
noWash	1.92 (0.41,9.04)	0.53 (0.17,1.65)	0.51 (0.18,1.44)	3.27 (0.39,27.34)		0.54 (0.22,1.35)	0.66 (0.45,0.95)	0.57 (0.38,0.87)	0.78 (0.42,1.47)
pov1%	3.54 (0.59,21.24)	0.98 (0.23,4.16)	0.93 (0.23,3.72)	6.01 (0.60,60.47)	1.84 (0.74,4.55)		1.21 (0.45,3.20)	1.06 (0.39,2.86)	1.44 (0.48,4.34)
pov10%	2.94 (0.63,13.64)	0.81 (0.25,2.66)	0.77 (0.26,2.25)	4.98 (0.60,41.37)	1.52 (1.05,2.20)	0.83 (0.31,2.20)		0.88 (0.50,1.53)	1.19 (0.57,2.48)
pov5%	3.35 (0.68,16.64)	0.93 (0.28,3.09)	0.88 (0.28,2.73)	5.69 (0.65,49.60)	1.74 (1.15,2.65)	0.95 (0.35,2.57)	1.14 (0.65,1.99)		1.36 (0.64,2.91)
povUnkn	2.46 (0.46,13.07)	0.68 (0.19,2.48)	0.65 (0.19,2.20)	4.18 (0.46,38.30)	1.28 (0.68,2.40)	0.70 (0.23,2.10)	0.84 (0.40,1.74)	0.73 (0.34,1.56)	

A, Network geometry for endometritis (placebo nodes as "noWash" and "PlaceboWash"). **B,** Ranking for endometritis with "PlaceboWash" and "NoWash." **C,** League table for prevention of endometritis with varying treatments, concentrations, and placebo ("PlaceboWash" and "NoWash"). **D,** Network geometry for wound infection (placebo nodes as "noWash" and "PlaceboWash"). **E,** Ranking for wound infection with "PlaceboWash" and "NoWash." **F,** League table for prevention of wound infection with varying treatments, concentrations, and placebo ("PlaceboWash" and "NoWash").

pov, povidine iodine; *Unkn*, unknown.

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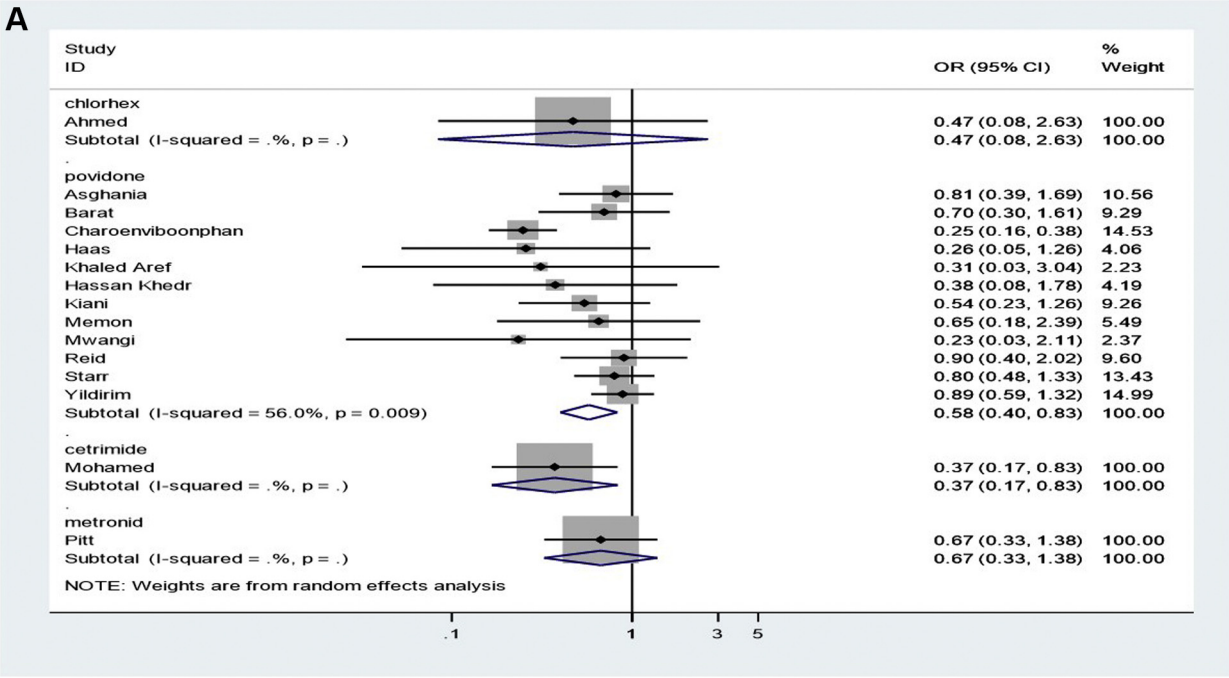
APPENDIX 5
Additional results for prevention of fever

A



B

Cetrimide				
1.70 (0.34-8.56)	Chlorhexidine			
0.56 (0.12-2.59)	0.33 (0.07-1.57)	Metronidazole		
0.63 (0.20-2.02)	0.37 (0.12-1.17)	1.13 (0.37-3.45)	Povidone	
0.37 (0.12-1.14)	0.22 (0.07-0.70)	0.67 (0.23-1.94)	0.59 (0.42-0.83)	No treatment/ placebo

A, Forest plot of fever; **B**, league table of the network meta-analysis results.

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