ORIGINAL ARTICLE

A Randomized Trial Comparing Skin Antiseptic Agents at Cesarean Delivery

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ABSTRACT

BACKGROUND

Preoperative skin antisepsis has the potential to decrease the risk of surgical-site infection. However, evidence is limited to guide the choice of antiseptic agent at cesarean delivery, which is the most common major surgical procedure among women in the United States.

METHODS

In this single-center, randomized, controlled trial, we evaluated whether the use of chlorhexidine–alcohol for preoperative skin antisepsis was superior to the use of iodine–alcohol for the prevention of surgical-site infection after cesarean delivery. We randomly assigned patients undergoing cesarean delivery to skin preparation with either chlorhexidine–alcohol or iodine–alcohol. The primary outcome was superficial or deep surgical-site infection within 30 days after cesarean delivery, on the basis of definitions from the Centers for Disease Control and Prevention.

RESULTS

From September 2011 through June 2015, a total of 1147 patients were enrolled; 572 patients were assigned to chlorhexidine–alcohol and 575 to iodine–alcohol. In an intention-to-treat analysis, surgical-site infection was diagnosed in 23 patients (4.0%) in the chlorhexidine–alcohol group and in 42 (7.3%) in the iodine–alcohol group (relative risk, 0.55; 95% confidence interval, 0.34 to 0.90; P=0.02). The rate of superficial surgical-site infection was 3.0% in the chlorhexidine–alcohol group and 4.9% in the iodine–alcohol group (P=0.10); the rate of deep infection was 1.0% and 2.4%, respectively (P=0.07). The frequency of adverse skin reactions was similar in the two groups.

CONCLUSIONS

The use of chlorhexidine–alcohol for preoperative skin antisepsis resulted in a significantly lower risk of surgical-site infection after cesarean delivery than did the use of iodine–alcohol. (Funded by the National Institutes of Health and Washington University School of Medicine in St. Louis; ClinicalTrials.gov number, NCT01472549.)

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This article was published on February 4, 2016, at NEJM.org.

N Engl J Med 2016;374:647-55.
DOI: 10.1056/NEJMoa1511048

Cesarean delivery is the most common major surgical procedure among women in the United States.[1] In 2013, more than 32.7% (1.3 million) of the 3.9 million births were by cesarean section.[2] Surgical-site infections complicate 2 to 5% of all surgical procedures and 5 to 12% of cesarean deliveries.[3-6] Infection occurring after delivery places an extra burden on the new mother and may impair mother–infant bonding and breast-feeding. The average attributable hospital cost per surgical-site infection after cesarean delivery is estimated to be $3,529.[7]

The skin is a major source of pathogens that cause surgical-site infections. Therefore, preoperative skin antisepsis has the potential to decrease the risk of surgical-site infection.[8] Unfortunately, there is a paucity of evidence to guide the choice of antiseptic agent at cesarean delivery.[9] Three small trials, involving a total of 189 participants, have been published comparing antiseptic agents for preoperative skin preparation at cesarean delivery; these trials showed no significant between-group differences in the rate of surgical-site infection.[10-12] Moreover, data from observational studies are conflicting.[13-15] The current guidelines on strategies to prevent surgical-site infection recommend the use of an alcohol-containing preoperative skin-preparatory agent, but they note that the most effective disinfectant to combine with alcohol is unclear.[3]

Randomized trials that have predominantly involved patients undergoing general surgical procedures have suggested the superiority of chlorhexidine-based antiseptic agents over iodine-based antiseptic agents for the prevention of surgical-site infection.[16-18] However, most trials compared a chlorhexidine–alcohol combination with iodine alone, which raises the question of whether the apparent superiority of chlorhexidine–alcohol is attributable to the chlorhexidine, the alcohol, or the combination.[19,20] The unique dual microbial source of pathogens from both skin and vaginal origins in surgical-site infections after cesarean delivery and the immune modulation in pregnancy raise questions about whether the results of trials of preoperative skin antisepsis for general surgical procedures can be extrapolated to cesarean delivery.[21] Therefore, we designed this pragmatic randomized, controlled trial to test the hypothesis that preoperative skin antisepsis with chlorhexidine–alcohol would be superior to iodine–alcohol for the prevention of surgical-site infection after cesarean delivery.

Methods

Trial Design

Patients were randomly assigned to preoperative skin antisepsis with chlorhexidine–alcohol or iodine–alcohol in a pragmatic trial to determine the comparative effectiveness of the two preoperative skin preparations for the prevention of surgical-site infection after cesarean delivery. We used broad inclusion criteria and routine clinical procedures, and we analyzed outcomes according to the intention-to-treat principle.[22] The full trial protocol is available with the full text of this article at NEJM.org.

The funders had no role in the design or conduct of the study, the collection, management, analysis, or interpretation of the data, or the preparation, review, or approval of the manuscript. The decision to submit the manuscript for publication was made by all the authors. All the authors take responsibility for the accuracy and completeness of the reported data and analyses and for the fidelity of the report to the trial protocol.

Patient Selection and Study-Group Assignment

All the participants provided written informed consent. Pregnant women undergoing cesarean delivery at Washington University Medical Center in St. Louis from September 2011 through June 2015 were eligible. We excluded women who had known allergy to chlorhexidine, alcohol, iodine, or shellfish or who had a skin infection adjacent to the operative site.

Once the decision was made to perform a cesarean section, enrolled patients underwent randomization, in a 1:1 ratio, with the use of a computer-generated random sequence produced by the study statistician. Patients were assigned to receive one of two antiseptic regimens for skin preparation: a chlorhexidine–alcohol combination (2% chlorhexidine gluconate with 70% isopropyl alcohol) or an iodine–alcohol combination (8.3% povidone–iodine with 72.5% isopropyl alcohol).

Trial Procedures

Skin preparation was performed by the circulating nurse following the manufacturer's instruc-

tions, which were similar for the two antiseptic agents. In brief, the prepackaged antiseptic applicator was opened and used to scrub the operative site. A wait time of 3 minutes was allowed between the application of the antiseptic agent and skin incision except in emergency cases in which this step was skipped. Patients also received standard infection-prevention measures, including body weight–based preoperative antibiotic prophylaxis.

Patients were followed daily until discharge from the hospital. They were then contacted by telephone within 30 days after delivery to assess whether they had symptoms of surgical-site infection and inquire whether they had had a physician office or emergency department visit for wound complications. Medical records were obtained from physician office or emergency department visits or hospital admissions and were reviewed by the principal investigator, who was unaware of the study-group assignments, to determine the diagnosis at each postoperative visit or readmission. We collected demographic information, obstetrical and medical history, and details of the surgical procedure. Data were collected by means of direct interview with the patients and were supplemented with data abstracted from the patients' charts.

TRIAL OVERSIGHT

The study was approved by the institutional review board at the Washington University in St. Louis and was overseen by an independent data and safety monitoring board. Two interim analyses were conducted, after 50% and 75% of the participants were evaluated. The principal investigator was not informed of the results of the interim analyses. The Haybittle–Peto rule was used as a guide for stopping the trial early for efficacy[23,24]; it required a P value of less than 0.001 for the difference between groups to justify stopping early. This rule has the advantages that the exact number and timing of interim analyses need not be specified and that the type I error at the end of the trial is preserved at 0.05.

TRIAL OUTCOMES

The primary outcome was superficial or deep surgical-site infection within 30 days after cesarean delivery, on the basis of the National Healthcare Safety Network definitions of the Centers for Disease Control and Prevention (CDC)[25] (see the Supplementary Appendix, available at NEJM.org). The diagnosis was made by the treating physician and verified by means of chart review by the principal investigator, who was unaware of the study-group assignments. Prespecified secondary outcomes were length of hospital stay, physician office visits and hospital readmissions for infection-related complications, endometritis, positive wound culture, skin irritation, and allergic reaction. We also assessed, post hoc, other wound complications (including skin separation, seroma, hematoma, and cellulitis), emergency department visits for wound complications, additional wound surgery, use of home health services or services of a wound clinic, and duration of wound care.

STATISTICAL ANALYSIS

We estimated the sample size for the trial assuming a baseline rate of surgical-site infection of 8%, on the basis of a prior study conducted at our institution,[5] and we anticipated a clinically significant 50% lower risk of surgical-site infection in the chlorhexidine–alcohol group than in the iodine–alcohol group. We estimated that the study needed to enroll 1084 participants, 542 in each group, in order to have 80% power to detect a 50% difference in the rates of surgical-site infection (at a two-tailed alpha level of 0.05). To accommodate a 10% loss to follow-up, we anticipated enrolling at most 1192 participants.

The primary data analyses followed the intention-to-treat principle, in which data from all the participants were analyzed in the group to which the participants were randomly assigned, regardless of whether they received the assigned intervention.[26] Descriptive and univariable statistics were used to characterize the study participants and to compare the baseline characteristics of the two groups.

We compared the primary outcome and other categorical outcomes between groups and calculated relative risks with 95% confidence intervals. We conducted four prespecified subgroup analyses of the primary outcome in subgroups defined according to status with respect to cesarean delivery (scheduled vs. unscheduled), status with respect to obesity (obese vs. nonobese), skin-closure type (subcuticular suture vs. staple closure), and presence or absence of chronic medical conditions (diabetes, chronic hypertension, or renal disease). Obesity was defined

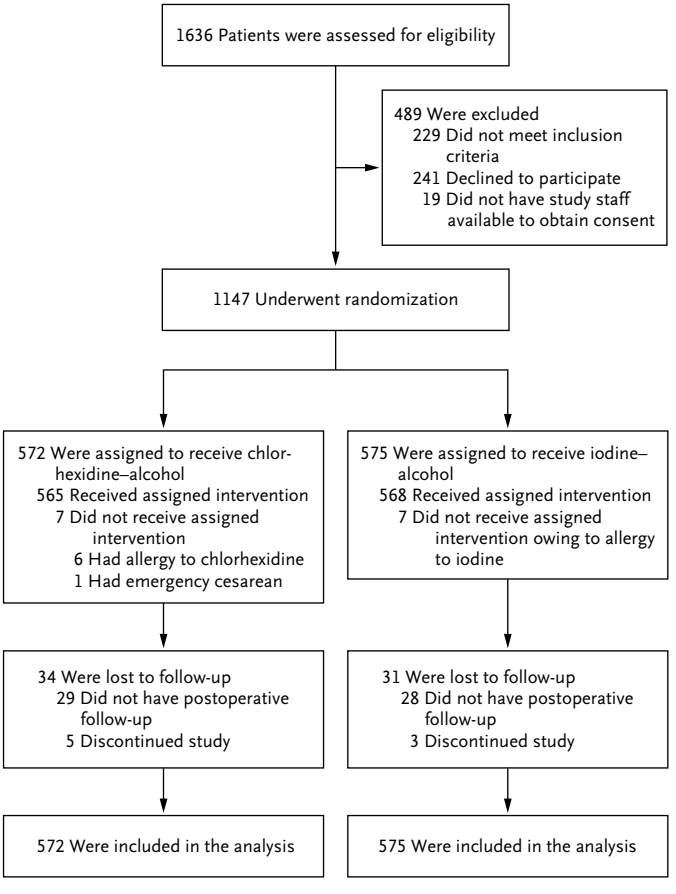

Figure 1. Randomization and Follow-up of Study Participants.

as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more. We also performed one post hoc subgroup analysis involving patients with diabetes versus those without diabetes. All the patients with diabetes (pregestational or gestational) were considered as a single group. We used the Mantel–Haenszel test of homogeneity to test for interaction; this test assessed whether the relative effectiveness of the antiseptic agents differed across subgroups. We also conducted a prespecified analysis in which we included only patients who completed the 30 days of follow-up.

Two-sided P values of less than 0.05 were considered to indicate statistical significance. Data analysis was conducted with the use of Stata software, version 12.1 (StataCorp).

RESULTS

TRIAL PARTICIPANTS

A total of 1636 pregnant women were screened for eligibility; 489 women were excluded from the study because they did not meet the inclusion criteria, they declined to participate, or study staff were not available to obtain informed consent. The remaining 1147 women were randomly assigned to receive preoperative skin preparation with either chlorhexidine–alcohol (572 women) or iodine–alcohol (575) and were included in the primary intention-to-treat analysis (Fig. 1). All the patients except for 14 (7 patients [1.2%] in each group) received their assigned intervention. The most common reason in either group that the assigned intervention was not received was the discovery after randomization that the participant had an allergy to the antiseptic agent. A similar number of participants in each group — 34 (5.9%) in the chlorhexidine–alcohol group and 31 (5.4%) in the iodine–alcohol group — were lost to follow-up. There were no significant differences between the two groups in the characteristics at baseline (Table 1, and Table S1 in the Supplementary Appendix).

PRIMARY OUTCOME

A total of 23 patients (4.0%) in the chlorhexidine–alcohol group and 42 (7.3%) in the iodine–alcohol group received a diagnosis of surgical-site infection (relative risk, 0.55; 95% confidence interval [CI], 0.34 to 0.90; P=0.02) (Table 2). The absolute difference in the rate of surgical-site infection between the chlorhexidine–alcohol group and the iodine–alcohol group was −3.3 percentage points (95% CI, −6.0 to −0.6). The rate of superficial infection was 3.0% in the chlorhexidine–alcohol group and 4.9% in the iodine–alcohol group (P=0.10); the rate of deep infection was 1.0% and 2.4%, respectively (P=0.07).

In the subgroup analyses, four prespecified and one post hoc, the risks of surgical-site infection were lower in the chlorhexidine–alcohol group than in the iodine–alcohol group in all subgroups. The reductions in risk were not materially affected by whether cesarean delivery was scheduled versus unscheduled, by the presence or absence of obesity, by the type of skin closure, by the presence or absence of chronic

medical conditions, or by status with respect to diabetes (Fig. 2).

A total of 1082 patients (94.3%) completed the 30 days of follow-up (538 patients in the chlorhexidine–alcohol group and 544 in the iodine–alcohol group). Among the patients with complete follow-up, the rate of surgical-site infection was significantly lower among those who had preoperative skin preparation with chlorhexidine–alcohol than among those who had preoperative skin preparation with iodine–alcohol (4.3% vs. 7.7%; relative risk, 0.55; 95% CI, 0.34 to 0.91; P=0.02) (Table S2 in the Supplementary Appendix).

SECONDARY OUTCOMES

Key Secondary Outcomes

There were no significant differences between patients who were randomly assigned to the chlorhexidine–alcohol group and those randomly assigned to the iodine–alcohol group with respect to rates of endometritis, hospital readmission for infection-related complications, or length of hospital stay (Table 2). Patients assigned to the chlorhexidine–alcohol group were significantly less likely than those assigned to the iodine–alcohol group to have physician office visits for wound concerns (7.9% vs. 12.5%; relative risk, 0.63; 95% CI, 0.44 to 0.90; P=0.009).

Wound Cultures

Specimens for culture were obtained from 32 of the 65 patients with surgical-site infection, and in 27 of these 32 patients (84%) the cultures were positive for bacterial growth. A total of 14 of 27 positive cultures (52%) were polymicrobial. There was no significant difference in the rate of positive bacterial growth between patients assigned to chlorhexidine–alcohol and those assigned to iodine–alcohol (6 of 8 patients [75%] and 21 of 24 [88%], respectively; P=0.58). *Staphylococcus aureus* was the most common isolate (in 10 of 27 patients [37%]). Methicillin-resistant *S. aureus* was present in 1 of 8 cultures (12%) in the chlorhexidine–alcohol group and in 4 of 24 (17%) in the iodine–alcohol group (P=0.10).

Adverse Skin Reactions

Overall, the rates of adverse skin reactions were low. Erythema at the operative site was the most common skin reaction, and the rate did not differ significantly between the chlorhexidine–alcohol group and the iodine–alcohol group (2.3% and 1.9%, respectively; P=0.67). The rates of skin irritation and allergic skin reactions also did not differ significantly between the two groups (Table 2).

Table 1. Characteristics of the Study Participants at Baseline.*

Characteristic	Chlorhexidine–Alcohol (N=572)	Iodine–Alcohol (N=575)
Maternal age — yr	28.3±5.8	28.4±5.8
Gestational age at delivery — wk	37.6±2.8	37.7±3.1
Race — no. (%)†		
Black	324 (56.6)	312 (54.3)
White	224 (39.2)	238 (41.4)
Other	24 (4.2)	25 (4.3)
Insurance — no. (%)		
Public insurance or Medicaid	376 (65.7)	339 (59.0)
Private insurance	178 (31.1)	216 (37.6)
None	18 (3.2)	20 (3.5)
Body-mass index‡	35.1±8.9	34.1±8.1
Current tobacco use — no. (%)	92 (16.1)	98 (17.0)
Chronic hypertension — no. (%)	69 (11.9)	49 (8.5)
Renal disease — no. (%)	3 (0.5)	1 (0.2)
Diabetes mellitus — no. (%)	55 (9.6)	65 (11.3)
Prior MRSA infection — no. (%)	3 (0.5)	1 (0.2)
Primiparous — no. (%)	151 (43.9)	240 (41.7)
Chorioamnionitis — no. (%)	17 (3.0)	24 (4.2)
Type of cesarean delivery — no. (%)		
Scheduled	334 (58.4)	335 (58.3)
Unscheduled	238 (41.6)	240 (41.7)
Median duration of surgery (IQR) — min	55 (42–70)	55 (43–70)
Preincision prophylactic antibiotics — no. (%)	567 (99.1)	572 (99.5)
Skin-closure type — no./total no. (%)		
Staples	108/572 (18.8)	107/574 (18.6)
Subcuticular suture	464/572 (81.2)	467/574 (81.4)
Estimated blood loss — ml	848.6±258.0	859.3±258.8

* Plus–minus values are means ±SD. There were no significant between-group differences in the characteristics at baseline. IQR denotes interquartile range, and MRSA methicillin-resistant *Staphylococcus aureus*.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Prespecified Primary and Secondary Outcomes and Post Hoc Additional Outcomes, According to Treatment Group, in the Intention-to-Treat Analysis.

Outcome	Chlorhexidine–Alcohol (N=572)	Iodine–Alcohol (N=575)	Relative Risk (95% CI)	P Value*
Primary outcome				
Surgical-site infection — no. (%)	23 (4.0)	42 (7.3)	0.55 (0.34–0.90)	0.02
Superficial incisional	17 (3.0)	28 (4.9)	0.61 (0.34–1.10)	0.10
Deep incisional	6 (1.0)	14 (2.4)	0.43 (0.17–1.11)	0.07
Secondary outcomes				
Median length of hospital stay (IQR) — days	4 (3–4)	4 (3–4)	—	0.24
Physician office visit — no. (%)	45 (7.9)	72 (12.5)	0.63 (0.44–0.90)	0.009
Hospital readmission — no. (%)	19 (3.3)	25 (4.3)	0.76 (0.43–1.37)	0.37
Endometritis — no. (%)	8 (1.4)	11 (1.9)	0.73 (0.30–1.80)	0.49
Adverse skin reaction — no. (%)				
Erythema at operative site	13 (2.3)	11 (1.9)	1.19 (0.54–2.63)	0.67
Skin irritation	0	3 (0.5)	—	0.08
Allergic skin reaction	2 (0.3)	1 (0.2)	2.02 (0.18–22.11)	0.56
Skin irritation or allergic skin reaction	2 (0.3)	4 (0.7)	0.51 (0.09–2.73)	0.42
Additional outcomes				
Other wound complication — no. (%)				
Skin separation	66 (11.5)	66 (11.5)	1.01 (0.73–1.39)	0.97
Seroma	24 (4.2)	28 (4.9)	0.87 (0.51–1.47)	0.58
Hematoma	7 (1.2)	5 (0.9)	1.41 (0.45–4.41)	0.56
Cellulitis	5 (0.9)	10 (1.7)	0.50 (0.17–1.46)	0.20
Fire or chemical skin burn — no.	0	0	—	—

* P values are based on chi-square tests or Fisher's exact test for categorical variables and on the Mann–Whitney U test for continuous variables.

ADDITIONAL OUTCOMES

In a post hoc analysis, the use of other health care services (including emergency department visits, additional wound surgery, and use of home health services or the services of a wound clinic) did not differ significantly between the chlorhexidine–alcohol group and the iodine–alcohol group (Table S3 in the Supplementary Appendix). Skin separation was the most common wound complication (assessed post hoc) and occurred in 11.5% of the patients in each group (P=0.97). The groups also did not differ significantly with respect to the rates of other wound complications (including seroma, hematoma, and cellulitis). The median duration of wound care did not differ significantly between the two groups (5 weeks in each group, P=0.55). There were no cases of fire or chemical skin burn in either group.

DISCUSSION

In this randomized, controlled trial, we found that the risk of surgical-site infection after cesarean delivery was significantly lower when chlorhexidine–alcohol was used for preoperative skin preparation than when iodine–alcohol was used. The rates of surgical-site infection were low overall, and the absolute difference between groups was relatively modest.

In addition, patients who were assigned to chlorhexidine–alcohol were significantly less likely than those who were assigned to iodine–alcohol to have physician office visits for wound

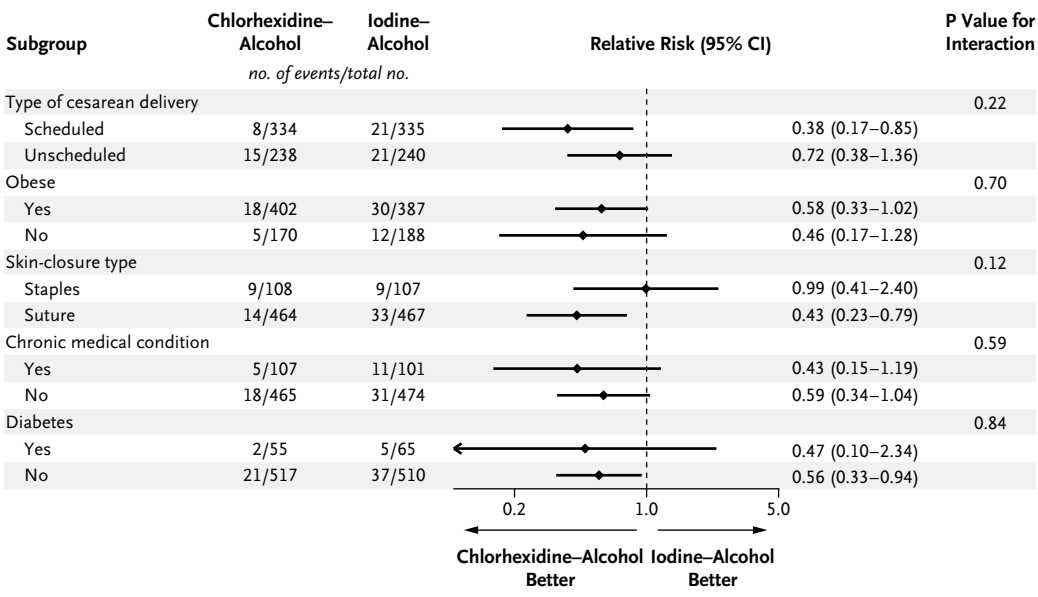

Figure 2. Risk of Surgical-Site Infection in Subgroups.

The analyses were performed according to the intention-to-treat principle. Four subgroup analyses were prespecified: scheduled versus unscheduled cesarean delivery, obese (body-mass index [the weight in kilograms divided by the square of the height in meters], ≥30) versus nonobese, subcuticular suture versus staple closure, and presence versus absence of chronic medical condition (diabetes, chronic hypertension, or renal disease). One subgroup analysis was post hoc (diabetes vs. no diabetes). Estimates for the relative effect of chlorhexidine–alcohol versus iodine–alcohol on the risk of surgical-site infection in each subgroup are presented as relative risks with 95% confidence intervals. P values for interaction are from the Mantel–Haenszel test of homogeneity. Data on the skin-closure type were missing for one patient in the iodine–alcohol group. The arrow indicates that the lower limit of the 95% confidence interval is less than 0.2.

complications. The length of hospital stay and the rates of hospital readmission for infection-related complications, endometritis, and adverse skin reactions were similar in the two groups, as were the rates of other wound complications.

The results of this trial can be compared only with trials involving nonobstetrical patients, because none of the three small randomized trials comparing antiseptic agents for the prevention of surgical-site infection after cesarean delivery compared chlorhexidine–alcohol with iodine–alcohol.[10-12] One trial involving 79 women that compared alcohol scrub and iodophor drape with iodophor scrub only showed no wound infection in either group.[10] Another trial involving 50 women compared parachlorometaxylenol plus iodine with iodine alone and showed no significant difference in the risk of wound infection.[11] A recent trial that was designed primarily to test the effects of antiseptic agents on skin culture randomly assigned 60 women to chlorhexidine gluconate or povidone–iodine and showed no significant difference in surgical-site infection.[12]

Several studies involving patients undergoing general surgical procedures have shown the superiority of chlorhexidine–alcohol over povidone–iodine for the prevention of surgical-site infection. A multicenter, randomized trial comparing these agents in adults undergoing clean-contaminated surgery (defined by the investigators as colorectal, small intestinal, gastroesophageal, biliary, thoracic, gynecologic, or urologic operations performed under controlled conditions without substantial spillage or unusual contamination) showed a significantly lower risk of surgical-site infection with chlorhexidine–alcohol than with povidone–iodine (9.5% vs. 16.1%; relative risk, 0.59; 95% CI, 0.41 to 0.85; P=0.004)[17]; risks were lower with chlorhexidine–

alcohol for superficial and deep incisional infections but not for organ or space infections.[17] A subsequent meta-analysis that included this trial and five other trials showed a significantly lower risk of surgical-site infection with chlorhexidine-based antiseptics than with iodine-based antiseptics.[16] Although these data suggested the superiority of chlorhexidine-based antiseptics, it remained unclear whether the superiority was attributable to the chlorhexidine, the alcohol, or the combination and whether these results would apply to cesarean delivery.

Our results are consistent with those of the prior studies that suggested the superiority of chlorhexidine-based antiseptics over iodine-based antiseptics for the prevention of surgical-site infection. However, our findings differ from the results of a large, nonrandomized, sequential-implementation study that showed a lower rate of surgical-site infection with iodine–alcohol than with chlorhexidine–alcohol.[27] The reasons for the different findings in that trial are unclear, but differences in the types of surgical procedures and potential confounding by unmeasured variables are plausible explanations.

Chlorhexidine has a number of properties that may lead to greater effectiveness than iodine as an antiseptic. It has strong affinity for binding to skin, high antibacterial activity against gram-positive and gram-negative bacteria including methicillin-resistant *S. aureus*, and longer residual effects than are observed with iodine.[28,29] Unlike iodine, chlorhexidine is not inactivated by organic matter such as bodily fluids and does not require a wait time between application and surgical incision. However, chlorhexidine is more expensive than iodine and has been linked to allergic reactions.[16,29] We found no differences in the rates of pruritus or allergic reactions between patients randomly assigned to chlorhexidine–alcohol and those assigned to iodine–alcohol, a finding that is consistent with the results of a prior trial.[17]

This trial has several limitations. First, we conducted the trial at a single site, which raises a question about the potential generalizability of our findings. However, the study population was racially and socioeconomically diverse; 55% of the participants were black, and 62% had public insurance. The obstetrical providers were also diverse (academic specialists and subspecialists, private physicians, and resident physicians), and we included scheduled as well as unscheduled cesarean deliveries. Subgroup analyses suggested a consistent superiority of chlorhexidine–alcohol across subgroups, which increases the generalizability of our findings.

Second, the lack of blinding among the participants and providers could potentially have introduced bias. However, any such bias would be expected to be nondirectional. Furthermore, we used similar standard skin-preparation procedures for the patients in the two groups. We used active surveillance, including telephone calls, to minimize loss to follow-up and to track the incidence of surgical-site infection; this point is important because most infections after cesarean delivery occur after discharge from the hospital.[6] We reviewed medical records in a blinded fashion to verify the primary outcome and used the CDC National Healthcare Safety Network definitions to ensure objective ascertainment.[25]

In conclusion, this randomized, controlled trial showed that the use of chlorhexidine–alcohol for preoperative skin antisepsis at cesarean delivery was associated with a significantly lower risk of surgical-site infection than was the use of iodine–alcohol.

The views expressed in this article are those of the authors and do not necessarily represent the official views of the National Institutes of Health or Washington University School of Medicine in St. Louis.

Supported by a Women's Reproductive Health Research Career Development grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (1K12HD063086-01, to Drs. Tuuli and Macones), and the Department of Obstetrics and Gynecology, Washington University School of Medicine in St. Louis.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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