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Effect of Prophylactic Negative Pressure Wound Therapy vs Standard Wound Dressing on Surgical-Site Infection in Obese Women After Cesarean Delivery
A Randomized Clinical Trial

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IMPORTANCE Obesity increases the risk of both cesarean delivery and surgical-site infection. Despite widespread use, it is unclear whether prophylactic negative pressure wound therapy reduces surgical-site infection after cesarean delivery in obese women.

OBJECTIVE To evaluate whether prophylactic negative pressure wound therapy, initiated immediately after cesarean delivery, lowers the risk of surgical-site infections compared with standard wound dressing in obese women.

DESIGN, SETTING, AND PARTICIPANTS Multicenter randomized trial conducted from February 8, 2017, through November 13, 2019, at 4 academic and 2 community hospitals across the United States. Obese women undergoing planned or unplanned cesarean delivery were eligible. The study was terminated after 1624 of 2850 participants were recruited when a planned interim analysis showed increased adverse events in the negative pressure group and futility for the primary outcome. Final follow-up was December 18, 2019.

INTERVENTIONS Participants were randomly assigned to either undergo prophylactic negative pressure wound therapy, with application of the negative pressure device immediately after repair of the surgical incision (n = 816), or receive standard wound dressing (n = 808).

MAIN OUTCOMES AND MEASURES The primary outcome was superficial or deep surgical-site infection according to the Centers for Disease Control and Prevention definitions. Secondary outcomes included other wound complications, composite of surgical-site infections and other wound complications, and adverse skin reactions.

RESULTS Of the 1624 women randomized (mean age, 30.4 years, mean body mass index, 39.5), 1608 (99%) completed the study: 806 in the negative pressure group (median duration of negative pressure, 4 days) and 802 in the standard dressing group. Superficial or deep surgical-site infection was diagnosed in 29 participants (3.6%) in the negative pressure group and 27 (3.4%) in the standard dressing group (difference, 0.36%; 95% CI, −1.46% to 2.19%, $P = .70$). Of 30 prespecified secondary end points, 25 showed no significant differences, including other wound complications (2.6% vs 3.1%; difference, −0.53%; 95% CI, −1.93% to 0.88%; $P = .46$) and composite of surgical-site infections and other wound complications (6.5% vs 6.7%; difference, −0.27%; 95% CI, −2.71% to 2.25%; $P = .83$). Adverse skin reactions were significantly more frequent in the negative pressure group (7.0% vs 0.6%; difference, 6.95%; 95% CI, 1.86% to 12.03%; $P < .001$).

CONCLUSIONS AND RELEVANCE Among obese women undergoing cesarean delivery, prophylactic negative pressure wound therapy, compared with standard wound dressing, did not significantly reduce the risk of surgical-site infection. These findings do not support routine use of prophylactic negative pressure wound therapy in obese women after cesarean delivery.

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Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 1207

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Cesarean delivery is the most common major surgical procedure among women in the United States.[1] In 2018, 32% (1.2 million) of the 3.8 million births in the United States were by cesarean delivery.[2] Despite significant advances in the use of antiseptics, prophylactic antibiotics, and sterile surgical technique, surgical-site infection remains a significant cause of morbidity.[3,4] In addition to the patient-level effects, surgical-site infections increase hospital length of stay and escalate costs 2-fold at the health care system level.[5] Obesity (body mass index [BMI], calculated as weight in kilograms divided by height in meters squared, ≥30) complicates 25% of pregnancies and exacerbates the problem of surgical-site infection after cesarean delivery.[6] Obese women are more likely than nonobese women to deliver by cesarean and are also at a higher risk of surgical-site infection.[7-10] Therefore, additional interventions are needed to reduce surgical-site infections after cesarean delivery in obese women.

Prophylactic negative pressure wound therapy with closed, portable, single use, battery-powered systems were cleared by the US Food and Drug Administration (FDA) for prophylactic application after wound closure at the time of surgery. Although these devices are increasingly being used after cesarean delivery, evidence of their effectiveness was limited to retrospective cohort studies and small randomized trials with sample sizes ranging from 54 to 440.[11] Moreover, use of these devices adds $200 to $500 per cesarean delivery to health care costs.[12-14] A 2019 Cochrane review of prophylactic negative pressure wound therapy concluded that there is a need for larger, well-designed and well-conducted trials to evaluate the effects of the newer negative pressure products designed for use on closed surgical incisions.[15]

This multicenter randomized clinical trial was conducted to determine the effect of prophylactic negative pressure wound therapy on risks of surgical-site infection and other wound complications in obese women after cesarean delivery. It was hypothesized that in obese women, negative pressure would decrease surgical-site infections compared with standard wound dressing.

Key Points

Question Is prophylactic negative pressure wound therapy initiated immediately after repair of the surgical incision effective in reducing surgical-site infection after cesarean delivery in obese women?

Findings In this randomized clinical trial that included 1608 obese women, there was no significant difference in the risk of surgical-site infection after cesarean delivery with prophylactic negative pressure wound therapy (3.6%) vs standard wound dressing (3.4%).

Meaning These findings do not support routine use of prophylactic negative pressure wound therapy in obese women after cesarean delivery.

Methods

Trial Design

This was an open-label, multicenter trial in which participants were randomly assigned to prophylactic negative pressure wound therapy or standard wound dressing after cesarean delivery. Participants received standard infection prevention measures including preoperative antibiotics (preferentially with cefazolin for all patients and adjunctive azithromycin in laboring patients), skin preparation (preferentially with chlorhexidine-alcohol), closure of subcutaneous layer if the depth was 2 cm or greater, and skin closure with subcutaneous suture. All the study sites agreed to standard infection prevention measures and general approaches to the diagnosis and treatment of surgical-site infections. The full trial protocol is available in Supplement 1. The trial was approved by the institutional review board at each site prior to enrollment. All study participants provided written informed consent.

Patient Selection

Patients were eligible if they had a BMI of 30 or more, at or beyond 23 weeks' gestation, and were undergoing planned or unplanned cesarean delivery. Body mass index was defined by prepregnancy or first prenatal visit weight and height. Women were recruited from February 8, 2017, through November 13, 2019. The final follow-up was completed on December 18, 2019. The study was conducted at 4 academic medical centers (Eskenazi Hospital in Indianapolis, Indiana; Indiana University Health Methodist Hospital, Indianapolis; University of Alabama at Birmingham Medical Center; and Washington University in St Louis Medical Center, Missouri) and at 2 community medical centers (Ochsner Baptist Medical Center in New Orleans, Louisiana, and Mercy Hospital St Louis, Missouri). Women who were not available for postoperative follow-up or had a contraindication to negative pressure use such as a preexisting infection at the incision site, bleeding disorder, therapeutic anticoagulation, or allergy to silicone or adhesive tape were excluded.

Treatment Allocation and Masking

Randomization occurred when the decision was made to perform cesarean delivery. Patients with scheduled cesarean deliveries were randomized on admission to the labor and delivery unit for surgery. Patients undergoing unscheduled cesarean deliveries were randomized once the attending physician made the decision to proceed. Participants were randomized centrally in a 1:1 ratio to prophylactic negative pressure wound therapy or standard wound dressing. A computer-generated randomization sequence was prepared by the study statistician using variable blocks of 4 and 6, stratified by study site, BMI category (30-39.9 and ≥40), and scheduled or unscheduled cesarean delivery.[16] A patient's group assignment was obtained from a secure website after a study number and confirmation of eligibility were entered and locked. The clinical care team could not be blinded to the interventions.

Trial Interventions

Women in the standard dressing group had their closed incisions covered with routine postoperative wound dressing consisting of layers of gauze and adhesive tape. Standard dressing was removed after 24 hours. Women in the negative pressure group had the Prevena (KCI USA, Inc) negative pressure device

applied immediately after repair of the surgical incision and secured with fixation adhesion strips. The device is a battery-powered, lightweight, portable, peel-and-place system designed for single use for up to 7 days. It delivers negative pressure at −125 mm Hg through the dressing to the incision site and contains a 45-mL canister for collection of exudate. All physicians participating in the trial were trained and credentialed to place and manage the negative pressure devices. The device was removed on the day of discharge, typically on postoperative day 4, or by day 7 for patients who remained hospitalized.

Data Collection

Participants were monitored daily until discharge from the hospital. They were then contacted by telephone at approximately 30 days after delivery to assess whether they had symptoms of surgical-site infection or had a physician office visit, emergency department visit, or hospital readmission for wound complications. Postoperative medical records for all participants were obtained from routine postpartum visits, other physician office and emergency department visits, and hospital admissions to determine the diagnosis at each postoperative visit or readmission.

Participant demographics, antepartum, intrapartum, intraoperative, and postpartum course were extracted from the medical record by research staff. Race/ethnicity was collected because adverse pregnancy outcomes including postcesarean delivery complications may be higher among Black women, and it allowed assessment for potential differential effectiveness of negative pressure by race.[17,18] Determination of race/ethnicity was by self-report based on open-ended questions, and the study staff classified the responses. Data abstractors were masked to participants' group assignment during the collection of outcomes data after discharge. Adverse skin reactions were assessed by patient report and confirmed by chart review. Adverse events were monitored and reported to the data and safety monitoring board. When a participant developed an adverse event, their physician in collaboration with the site principal investigator ascertained the safety of continuing the intervention.

Trial End Points

The primary outcome was superficial or deep surgical-site infection, defined according to the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network criteria[19] (see definitions in Supplement 2). The treating physician made the diagnosis of surgical-site infection. Records of all patients with any wound complications were reviewed and validated centrally in a blinded fashion by the principal investigator against the CDC National Healthcare Safety Network definitions of surgical-site infections.

Secondary outcomes included individual components of the primary outcome, organ-space infection, other wound complications (wound dehiscence ≥2 cm, hematoma, cellulitis, and seroma), and a composite of surgical-site infection and other wound complications. Other secondary outcomes were patient-reported pain score on a scale of 0 (no pain) to 10 (worst pain) and satisfaction score on a scale of 0 (least satisfied) to 10 (most satisfied) at discharge and postoperative day 30, and measures of health care resource use (physician office visit, emergency department visit, attendance at a wound clinic, use of antibiotics, and hospital readmission for wound-related problems). Data were collected for other outcomes including types and frequency of different bacteria from wound cultures, including methicillin-resistant *Staphylococcus aureus*, and cost-effectiveness, but the findings are not reported in this article. Data were not collected for one prespecified secondary outcome: satisfaction with aesthetic appearance of the scar.

Adverse events were prespecified and included serious adverse events (maternal death, sepsis, intensive care unit admission, necrotizing fasciitis, and postpartum hysterectomy) and adverse skin reactions (blistering, erythema, wound bleeding, and other skin reactions).

Trial Oversight

The trial was overseen by an independent data and safety monitoring board. Two interim analyses were planned at 50% and 75% of recruitment. The Haybittle-Peto rule was designated as the guide for stopping the trial early for efficacy.[20,21] Under this rule, the interim analyses of the primary outcome had to demonstrate an extreme difference between groups ($P < .001$) to justify stopping the trial. This rule has the advantage that the overall type I error is preserved at .05. No specific stopping rule for futility was designated.

Sample Size

The sample size was calculated assuming a 10% baseline risk of superficial or deep surgical-site infection based on data from a prior study.[22] It was estimated that 2850 participants (1425 in each group) would be sufficient to detect a 30% relative difference (from 10% to ≤7%) in the risk of superficial or deep surgical-site infection with 80% power in a 2-tailed test with a type I error of .05 and 5% adjustment for attrition. A difference of 30% was considered clinically important and plausible, based on prior studies of negative pressure therapy after cesarean delivery.[11,23]

Statistical Analysis

In the primary data analysis, all patients were analyzed in the group to which they were randomized, whether or not they received the assigned intervention.[24] Risks of superficial or deep surgical-site infection and other dichotomous secondary outcomes were compared using the χ^2 or Fisher exact tests. Continuous outcomes were compared using the *t* test or Mann-Whitney *U* test as appropriate. Mixed models with study site as a random effect and BMI category as a fixed effect were used to estimate relative risks and 95% confidence intervals. Generalized estimating equations were used to account for study site and BMI category and to estimate risk differences and 95% confidence intervals using the identity link function for binary outcomes and normal link function for continuous outcomes.

Prespecified subgroup analyses were performed for the primary outcome by study site, BMI category (30-39.9 vs ≥40), scheduled or unscheduled cesarean delivery, skin incision type (low transverse vs nonlow transverse), and diabetes status. Post hoc subgroup analyses were performed by race (Black vs non-Black), category of primary surgeon, and duration of negative pressure therapy (≤4 vs >4 days). The Breslow-Day test was

used to test for homogeneity, which assessed whether the relative effect of negative pressure differed across subgroups.

Time-to-event analysis was performed using Kaplan-Meier curves and Cox regression to assess for differences in the interval to surgical-site infection in the 2 groups. The proportionality assumption was tested by adding a time-dependent covariate for group. Additional prespecified analysis was performed according to the wound dressing actually used, irrespective of the group to which participants were assigned.

There were no missing data for the primary outcome and less than 5% missing data were observed for any variable; thus, no imputation was used. All tests were 2-sided, and the significance level was set at .05. Because of the potential for type I error due to multiple comparisons, findings for the secondary end points should be considered as exploratory. The statistical package SAS version 9.2 was used for all statistical analyses (SAS Institute Inc).

Interim Analysis and Early Trial Termination

After reviewing results of the first planned interim analysis of 1493 participants (approximately 50% of the planned sample size) on September 25, 2019, the data and safety monitoring board was concerned about increased adverse skin reactions in the negative pressure group (6.8% vs 0.7%, respectively, $P < .001$), and requested a conditional power analysis by the study statistician to assist with their decision on further conduct of the trial. At the time of the interim analysis, the risk of superficial or deep surgical-site infection was 2.9% in the negative pressure group and 2.5% in the standard dressing group. After reviewing the analysis on October 30, 2019, that showed a conditional power of only 11% to detect a significant difference in the primary outcome if the planned sample size was enrolled, the data and safety monitoring board recommended that the trial be stopped. Following discussion with the funding agency, the trial was formally stopped on November 13, 2019.

Results

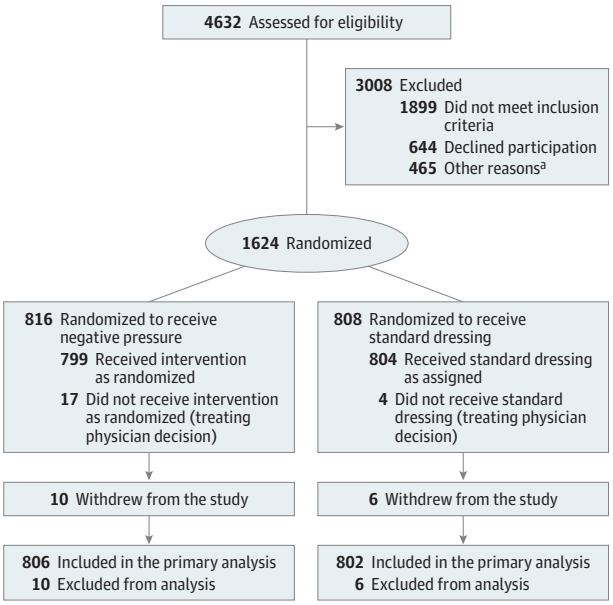
Study Participants

A total of 4632 patients were assessed for eligibility; 3008 were excluded, and the remaining 1624 women were randomized: 816 to negative pressure and 808 to standard dressing (**Figure 1**). Of the 1624 women randomized, 16 (1.0%) withdrew; 10 in the negative pressure group and 6 in the standard dressing group. No participants were lost to follow-up, leaving 1608 patients (806 negative pressure and 802 standard dressing) included in the primary analysis. Most patients received their assigned intervention; 97.9% in the negative pressure group and 99.5% in the standard dressing group. Groups were similar with regards to maternal, pregnancy, labor, and intraoperative characteristics (**Table 1**). In the negative pressure group, the median duration of negative pressure was 4 days (**Table 2**).

Primary Outcome

Superficial or deep surgical-site infection was diagnosed in 29 participants (3.6%) in the negative pressure group and 27 (3.4%) in the standard dressing group (**Table 3**). The risk of superficial or deep surgical-site infection was not significantly different between groups (difference, 0.36%; 95% CI, −1.46% to 2.19%, $P = .70$).

Figure 1. Flow of Study Participants in a Trial of Negative Pressure Wound Therapy After Cesarean Delivery



[a] Other reasons for exclusion include patients not approached because study staff were unavailable (n = 354), missed by staff (n = 60), emergency delivery (n = 40), and physician refusal (n = 11).

In prespecified subgroup analyses, the primary outcome results did not significantly differ by study site, BMI category, type of cesarean, skin incision type, or diabetes status (**Figure 2**). Similarly, the results did not significantly differ by race and category of primary surgeon in post hoc subgroup analyses. The risk of superficial or deep surgical-site infection was 6.5% (6 of 23) among those who wore the device for more than 4 days compared with 3.4% (23 of 708) among those who wore the device for 4 days or less (difference, 3.06%; 95% CI, −2.81% to 8.93%; $P = .31$)

Taking time to infection into account, the risk of superficial or deep surgical-site infection was not significantly different between the 2 groups (hazard ratio, 0.92; 95% CI, 0.54 to 1.57; $P = .76$) (eFigure in Supplement 2). The proportional assumption was met ($P = .48$).

Secondary Outcomes

Risks of the individual components of the primary outcome were not significantly different between the 2 groups. The risk of superficial infection was 2.2% (n = 18) in the negative pressure group and 2.0% (n = 16) in the standard dressing group (difference, 0.34%; 95% CI, −0.86% to 1.53%; $P = .58$). The risk of deep infection was 1.4% (n = 11) in each group (difference, −0.18%; 95% CI, −1.20% to 0.84%; $P = .73$). The risk of organ-space infection was not different between groups: 2 patients (0.3%) in each group (difference, 0.00%; 95% CI, −0.49% to

Table 1. Baseline Participant Characteristics of Women

Characteristics	No. (%) of patients	
	Negative pressure (n = 806)	Standard dressing (n = 802)
Study site		
Washington University Medical Center	243 (30.2)	239 (29.8)
Mercy Hospital, St Louis	35 (4.3)	39 (4.9)
University of Alabama Birmingham	393 (48.8)	392 (48.9)
Ochsner Baptist, New Orleans	102 (12.7)	103 (12.8)
Indiana University-Methodist	20 (2.5)	16 (2.0)
Indiana University-Eskenazi	13 (1.6)	13 (1.6)
Maternal age, mean (SD), y	30.2 (5.6)	30.5 (6.1)
Gestational age, mean (SD), y	37.3 (3.1)	37.4 (2.9)
BMI, mean (SD)	39.6 (7.7)	39.5 (8.1)
>30-39.9	494 (61.3)	508 (63.3)
≥40	312 (38.7)	294 (36.7)
Race		
Black	453 (56.2)	452 (56.4)
White	331 (41.1)	330 (41.2)
Other[a]	22 (2.7)	20 (2.5)
Hispanic/Latina ethnicity	34 (4.2)	27 (3.4)
Insurance		
Government	488 (60.6)	457 (57.0)
Private	303 (37.6)	331 (41.3)
None	15 (1.9)	14 (1.8)
Tobacco use[b]	87 (10.8)	90 (11.2)
Alcohol use[b]	10 (1.2)	10 (1.3)
Recreational drug use[b]	34 (4.2)	32 (4.0)
Group B streptococcus positive	209 (25.9)	208 (25.9)
Medical complications		
Chronic hypertension	171 (21.2)	180 (22.4)
Gestational diabetes	96 (11.9)	99 (12.3)
Pregestational diabetes	72 (8.9)	66 (8.2)
Obstetric complications		
Preeclampsia/eclampsia	150 (18.6)	173 (21.6)
Gestational hypertension	79 (9.8)	73 (9.1)
Indication for cesarean delivery		
Repeat cesarean delivery	368 (45.7)	405 (50.5)
Failure to progress	95 (11.8)	86 (10.7)
Nonreassuring fetal heart tones	119 (14.8)	118 (14.7)
Breech/malpresentation	65 (8.1)	65 (8.1)
Genital herpes simplex	4 (0.5)	3 (0.4)
Primary elective	13 (1.6)	10 (1.3)
Multiple gestation	24 (3.0)	11 (1.4)
Previa/accreta	10 (1.2)	12 (1.5)
Failed forceps	1 (0.1)	0
Prior uterine surgery	8 (1.0)	8 (1.0)
Other[c]	99 (12.3)	84 (10.5)

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[a] Includes Asian, American Indian, Alaska Native, and Pacific Islander.

[b] Tobacco, alcohol, and recreational drug use were assessed by chart abstraction from records of routine care.

[c] Includes hypertensive disease of pregnancy, cord prolapse, fetal anomalies, fetal growth restriction, fetal macrosomia, and prior shoulder dystocia.

0.49%; $P > .99$). There were no significant differences in the risks of other wound complications: 21 patients (2.6%) in the negative pressure group vs 25 (3.1%) in the standard dressing group for a difference of 0.53% (95% CI, −1.93% to 0.88%; $P = .46$). Fifty-two patients (6.5%) in the negative pressure group vs 54 (6.7%) in the standard dressing group experienced the composite of surgical-site infection and other wound complications (difference, −0.27%; 95% CI, −2.71% to 2.25%; $P = .83$) (Table 3).

Patient-reported pain scores on a scale of 0 (no pain) to 10 (worst pain) were not significantly different at discharge and postoperative day 30 between the groups. Patient satisfaction scores on a scale of 0 (least satisfied) to 10 (most satisfied) were significantly higher in the negative pressure group at discharge. The median score was 10 (interquartile range [IQR], 8-10) vs 9 (IQR, 7-10; difference, 0.79 95% CI; 0.25 to 1.32; $P < .001$), but the median postoperative day 30 score was the same: 10 (IQR, 9-10) vs 10 (IQR, 8-10; difference, 0.19; 95% CI, −0.01 to 0.39; $P = .07$).

The proportion of participants using health care resources for wound care including physician office visits, emergency department visits, wound clinic visits, antibiotic use, and hospital readmission were not significantly different between groups: 130 patients (16.4%) in the negative pressure group vs 132 patients (16.2%) in the standard dressing group (difference, −0.04%; 95% CI, −4.29% to 4.21%; $P = .99$).

Adverse Events

Risks of serious adverse events were not significantly different between the 2 groups: 4 patients (0.5%) in the negative pressure group vs 5 patients in the standard dressing group (0.6%) (difference, −0.13%; 95% CI, −0.86% to 0.60%). There were no cases of maternal death or necrotizing fasciitis, and risks of maternal sepsis, intensive care unit admission and postpartum hysterectomy were not significantly different (**Table 4**).

The risk of adverse skin reactions was significantly higher in the negative pressure group than the standard dressing group with 56 events (7.0%) in the former experiencing an adverse reaction compared with the 5 events (0.6%) in the latter (difference, 6.95%; 95% CI, 1.86%-12.03%; $P < .001$). Risks of individual adverse events including skin blisters, bleeding, erythema, and other skin reactions were also significantly higher in the negative pressure group (Table 4).

Additional Analyses

Predominantly similar results were seen in the analysis of the 798 participants who received negative pressure and the 810 who had standard wound dressing (eTable 1 and eTable 2 in Supplement 2).

Discussion

This multicenter randomized clinical trial of obese women undergoing cesarean delivery found no significant difference in the risk of surgical-site infection with the use of prophylactic negative pressure therapy compared with standard wound dressing. Furthermore, no significant differences were found

Table 2. Characteristics of Treatment and Experience of Women During Cesarean Delivery

Characteristics	No. (%) of patients	
	Negative pressure (n = 806)	Standard dressing (n = 802)
Chorioamnionitis	26 (3.2)	29 (3.6)
Skin antiseptic		
Chlorhexidine-alcohol	656 (81.4)	639 (79.7)
Iodine-alcohol	36 (4.5)	39 (4.9)
Chlorhexidine	113 (14.0)	120 (15.0)
Iodine	1 (0.1)	2 (0.3)
Other	0	2 (0.3)
Skin incision type		
Low transverse	779 (96.7)	778 (97.0)
High transverse	2 (0.3)	1 (0.1)
Midline vertical	20 (2.5)	16 (2.0)
Other	5 (0.6)	7 (0.9)
Duration of surgery, median (IQR), min	59.0 (48.0-73.0)	58.5 (47-72)
Type of cesarean		
Scheduled	417 (51.7)	414 (51.6)
Unscheduled	253 (31.4)	256 (31.9)
Urgent	90 (11.2)	96 (12.0)
Emergency	46 (5.7)	36 (4.5)
Primary surgeon		
Postgraduate y		
1	141 (17.5)	132 (16.5)
2	319 (39.6)	281 (35.0)
3	41 (5.1)	52 (6.5)
4	146 (18.1)	174 (21.7)
Fellow	144 (17.9)	155 (19.3)
Attending	15 (1.9)	7 (0.9)
Other, not otherwise specified	0	1 (0.1)
Vaginal cleansing	258 (32.0)	254 (31.7)
Preincision antibiotics	802 (99.5)	799 (99.6)
Type of preincision antibiotics		
Cefazolin	727 (90.2)	720 (89.8)
Ampicillin	7 (0.9)	9 (1.1)
Azithromycin	438 (54.3)	448 (55.9)
Gentamicin	53 (6.6)	54 (6.73)
Clindamycin	60 (7.4)	70 (8.7)
Other	8 (1.0)	4 (0.5)
Cefazolin dose, g		
1	16 (2.2)	9 (1.3)
2	497 (68.4)	494 (68.6)
3	214 (29.4)	217 (30.1)
Skin closure type[a]		
Subcuticular suture	787 (97.6)	778 (97.0)
Staples	19 (2.4)	24 (3.0)
Subcutaneous depth, median (IQR), cm[b]	3.0 (2.0-3.5)	3.0 (2.0-3.5)
Subcutanous layer closure	521 (64.6)	525 (65.5)
Antibiotics prior to discharge[c]	36 (4.5)	57 (7.1)
Estimated blood loss, median (IQR), mL	800 (600-900)	800 (600-900)
Duration of negative pressure, median (IQR), d	4 (3-4)	

Abbreviation: IQR, interquartile range.

[a] Skin closure was generally performed by resident or fellow under the supervision of the attending physicians.

[b] Subcutaneous tissue depth measured as distance from the fascia to the skin, reflecting each woman's abdominal wall thickness.

[c] Antibiotics prior to discharge denote prophylactic postoperative antibiotics prescribed by some physicians or for other infections such as urinary tract infection.

in other wound complications, pain scores at discharge or postoperative day 30, or health care resource use. Patient satisfaction was high overall, and minimally higher at discharge with negative pressure therapy, but not at postoperative day 30. The risk of adverse skin reactions was significantly higher in the negative pressure group.

Table 3. Primary and Secondary Outcomes by Randomization Group

Outcome	No. (%)		Absolute risk difference (95% CI)[a]	Relative risk (95% CI)[b]	*P* value[c]
	Negative pressure (n = 806)	Standard dressing (n = 802)			
Primary outcome					
Superficial or deep surgical-site infection	29 (3.6)	27 (3.4)	0.36 (−1.46 to 2.19)	1.05 (0.63 to 1.76)	.70
Prespecified secondary outcomes					
Infection type					
Superficial surgical site	18 (2.2)	16 (2.0)	0.34 (−0.86 to 1.53)	1.12 (0.57 to 2.18)	.58
Deep surgical-site[d]	11 (1.4)	11 (1.4)	−0.18 (−1.20 to 0.84)	0.96 (0.42 to 2.20)	.73
Organ space surgical-site[d]	2 (0.3)	2 (0.3)	0.00 (−0.49 to 0.49)	0.97 (0.14 to 6.84)	>.99
Other wound complications	21 (2.6)	25 (3.1)	−0.53 (−1.93 to 0.88)	0.83 (0.47 to 1.47)	.46
Skin separation	11 (1.4)	9 (1.1)			
Seroma	5 (0.6)	6 (0.8)			
Hematoma	4 (0.5)	8 (1.0)			
Cellulitis	1 (0.1)	4 (0.1)			
Surgical site infection or other wound complication	52 (6.5)	54 (6.7)	−0.27 (−2.71 to 2.25)	0.95 (0.66 to 1.37)	.83
Patient pain score (0-10), median (IQR)[e]					
Discharge	3 (0 to 5)	3 (0 to 5)	−0.15 (−0.39 to 0.09)		.23
Postoperative day 30	0 (0 to 2)	0 (0 to 2)	0.02 (−0.34 to 0.38)		.90
Patient satisfaction score (0-10), median (IQR)[e]					
Discharge	10 (8 to 10)	9 (7 to 10)	0.79 (0.25 to 1.32)		<.001
Postoperative day 30	10 (9 to 10)	10 (8 to 10)	0.19 (−0.01 to 0.39)		.07
Health care resource use	132 (16.4)	130 (16.2)	−0.04 (−4.29 to 4.21)	1.0 (0.87 to 1.19)	.99
Physician visit for wound	4 (0.5)	14 (1.8)			
ED visit for wound	20 (2.5)	30 (3.7)			
Wound clinic	91 (11.3)	83 (10.3)			
Antibiotics prescribed[f]	63 (7.9)	64 (8.1)			
Hospital readmission for wound	2 (0.3)	0			

Abbreviations: ED, emergency department; IQR, interquartile range.

[a] Absolute risk differences estimated using generalized estimating equations accounting for study site and body mass index category, with the identity link function for binary outcomes and normal link function for continuous outcomes.

[b] Relative risks estimated using mixed models with study site as a random effect and body mass index category as a fixed effect.

[c] *P* values refer to the statistical significance of the relative risks.

[d] Deep surgical site infection does not include organ space infection.

[e] See the Methods section for pain score ranges.

[f] Antibiotics prescribed for suspected surgical site infections and other infections such as urinary tract infection.

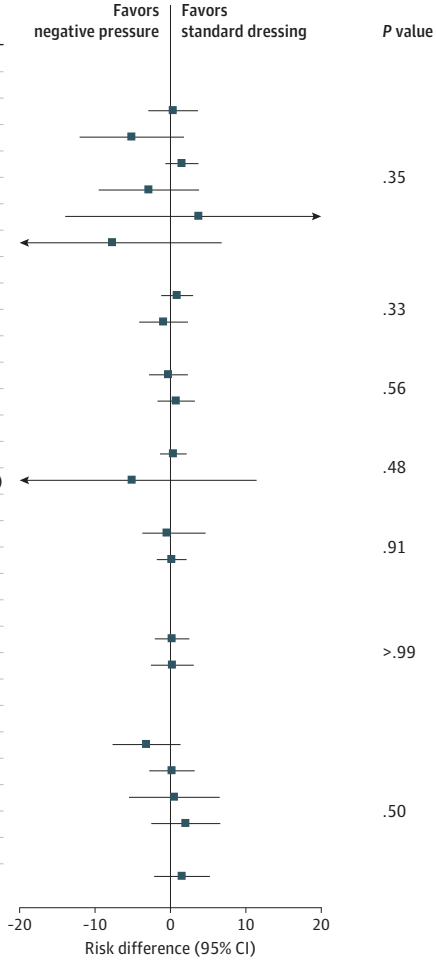
Experimental evidence suggests that negative pressure wound therapy reduces bacterial contamination, edema, and exudates; increases microvascular blood flow; and promotes granulation tissue by inducing mechanical stress that promotes cell growth.[25-28] Coincidentally, the increased risk of surgical-site infections in obese women is thought to be in part due to increased thickness of the subcutaneous space that allows accumulation of exudate, increases lateral tension on the wound edges, promotes growth of bacteria, and leads to wound infection and dehiscence.[29] Therefore, it was anticipated that negative pressure therapy would be particularly effective in this population.

Prior studies of negative pressure after cesarean delivery were limited largely to retrospective cohort studies and small randomized trials with sample sizes ranging from 54 to 440.[11] Although some demonstrated a reduction in surgical-site infection and other wound complications, they were limited by their small sample sizes, selection bias, and confounding by indication. Two systematic reviews and meta-analyses of these studies reached conflicting conclusions regarding the effectiveness of negative pressure in reducing surgical-site infection after cesarean.[11,23]

A recent trial in Denmark comparing negative pressure to standard dressing after cesarean delivery that involved 876 obese, nearly all White women showed a significant reduction in surgical-site infection from 9.2% with standard dressing to 4.6% with negative pressure.[30] The use of negative pressure also reduced wound exudates but had no effect on endometritis and wound dehiscence. The trial reported herein differs from that study in enrolling a racially diverse sample, using a different negative pressure device, and 4 days' duration of use compared with 5 to 6 days, respectively. It is unclear that any of these differences in design explain the disparate findings. The device used in this trial exerts −125 mm Hg pressure and has a canister for collecting exudate, while the device used in the prior trial exerted −80 mm Hg and had no

Figure 2. Subgroup Analysis of the Primary Outcome[a]

Subgroup	No. of women/total No. (%) Negative pressure	Standard dressing	Risk difference (95% CI)	P value
Prespecified				
Study site				
Washington University Medical Center	9/243 (3.7)	8/239 (3.4)	0.36 (-2.94 to 3.65)	
Mercy Hospital, St Louis	0/35 (0)	2/39 (5.1)	-5.13 (-12.05 to 1.79)	
University of Alabama Birmingham	13/393 (3.3)	7/392 (1.8)	1.52 (-0.68 to 3.72)	
Ochsner Baptist, New Orleans	5/102 (4.9)	8/103 (7.8)	-2.87 (-9.52 to 3.79)	.35
Indiana University—Methodist	2/20 (10.0)	1/16 (6.3)	3.75 (-13.96 to 21.46)	
Indiana University—Eskenazi	0/13 (0)	1/13 (7.7)	-7.69 (-22.18 to 6.79)	
BMI category				
>30-39.9	17/494 (3.4)	13/508 (2.6)	0.88 (-1.23 to 3.00)	
≥40	12/312 (3.9)	14/294 (4.8)	-0.92 (-4.15 to 2.32)	.33
Cesarean type				
Scheduled	15/417 (3.6)	16/414 (3.9)	-0.27 (-2.84 to 2.31)	
Nonscheduled	14/389 (3.6)	11/388 (2.8)	0.76 (-1.72 to 3.24)	.56
Skin incision type				
Low transverse	27/779 (3.5)	24/778 (3.1)	0.38 (-1.39 to 2.15)	
Nonlow transverse	2/27 (7.4)	3/24 (12.5)	-5.09 (-21.60 to 11.42)	.48
Diabetes				
Yes	7/168 (4.2)	6/162 (3.7)	-0.46 (-3.73 to 4.66)	
No	22/638 (3.5)	21/640 (3.3)	0.17 (-1.81 to 2.14)	.91
Post hoc				
Race				
Black	15/453 (3.3)	14/452 (3.1)	0.21 (-2.08 to 2.51)	
Non-Black	14/353 (4.0)	13/350 (3.7)	0.25 (-2.59 to 3.09)	>.99
Primary surgeon				
Postgraduate y				
1	3/141 (2.1)	7/132 (5.3)	-3.18 (-7.68 to 1.33)	
2	12/319 (3.8)	10/281 (3.6)	0.20 (-2.81 to 3.21)	
3	1/41 (2.4)	1/52 (1.9)	0.52 (-5.50 to 6.53)	
4	8/146 (5.5)	6/174 (3.5)	2.03 (-2.55 to 6.61)	.50
Fellow	0/15 (0)	0/7 (0)		
Attending	5/144 (3.5)	3/155 (1.9)	1.54 (-2.16 to 5.23)	



[a] Prespecified (site, BMI category, scheduled vs unscheduled cesarean delivery, skin incision type, diabetes status) and post hoc (race, primary physician). *P* values for interaction are from the Breslow-Day test.

BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared.

Table 4. Adverse Events by Randomization Group

	No. (%) Negative pressure (n = 806)	Standard dressing (n = 802)	Risk difference (95% CI)
Serious adverse event[a]	4 (0.5)	5 (0.6)	−0.13 (−0.86 to 0.60)
Maternal death	0	0	
Maternal ICU admission	1 (0.1)	2 (0.3)	−0.13 (−0.55 to 0.30)
Maternal sepsis	3 (0.4)	2 (0.3)	0.12 (−0.42 to 0.67)
Necrotizing fasciitis	0	0	
Postpartum hysterectomy	1 (0.1)	1 (0.1)	0 (−0.35 to 0.34)
Adverse skin reactions[a]	56 (7.0)	5 (0.6)	6.95 (1.86 to 12.03)
Blisters	27 (3.4)	2 (0.3)	3.66 (0.16 to 7.17)
Bleeding	9 (1.1)	0	1.12 (0.39 to 1.84)
Erythema	10 (1.2)	3 (0.4)	0.85 (0.03 to 1.68)
Other[b]	14 (1.7)	1 (0.1)	1.61 (0.68 to 2.55)

Abbreviation: ICU, intensive care unit.

[a] Summing the individual types of events does not equal the total event counts because some participants had more than 1 type of event.

[b] Other adverse skin reactions include skin abrasion, rash, and superficial epithelial peel.

canister. Systematic reviews showed no differential effectiveness of the 2 types of negative pressure devices.[11,31] Although it has been suggested that longer duration of use may increase the effectiveness of negative pressure, no difference was seen in the risk of surgical-site infection by duration of use in this trial. Similarly, there was no differential effect by race,

category of obesity or diabetes status. Results of this trial are consistent with another recent large trial involving patients undergoing surgery for major trauma-related lower limb fractures that showed no reduction in surgical-site infections.[32]

This multicenter trial included a diverse sample of obese patients undergoing cesarean delivery in the United States. Patients were enrolled from both tertiary care and community hospitals, increasing the external validity and generalizability of the findings. Patients were analyzed in the group to which they were randomized, whether or not they received the assigned intervention, producing findings that reflect anticipated outcomes with a strategy of routine use of negative pressure or standard dressing.

Limitations

This study has several limitations. First, the baseline risk of the primary outcome (3.4%) was significantly lower than the 10% based on data from a study prior to widespread implementation of evidence-based preventive measures.[22] This lower risk was seen across the 6 study sites, despite enrolling a high-risk study sample including women with mean BMI higher than 39, 48% unscheduled, urgent or emergency cesarean deliveries, and prevalence of comorbidities similar to prior studies in which infection risks were higher.[3,33,34] Active postdischarge surveillance was also used to maximize ascertainment.[3,34] The low risk of surgical-site infection likely reflects the effect of recent widespread implementation of evidence-based interventions including skin cleansing with chlorhexidine-alcohol, universal preoperative cefazolin, adjunctive azithromycin in women undergoing unscheduled cesarean, and subcuticular suture (rather than staples) for skin closure.[4,33,35,36] In fact, the baseline surgical-site infection risk in the current trial is consistent with a 3.7% risk noted at one of the study sites with the use of evidence-based interventions that did not include negative pressure wound therapy.[37]

Second, the trial was stopped following a planned interim analysis after 1624 of the planned 2850 patients were recruited, raising the possibility that it may be underpowered. However, the decision by the data and safety monitoring board to stop the trial for futility was based on a conditional power analysis showing only an 11% probability of detecting a significant difference in the primary outcome if the planned sample size was recruited. This suggests that a clinically important beneficial effect of negative pressure is unlikely. Moreover, this study is, to our knowledge, the largest randomized clinical trial to date of prophylactic negative pressure wound therapy after any type of surgical procedure.[15,31]

Third, the clinical team could not feasibly be blinded to the intervention, raising the possibility of bias. However, standard infection prevention measures were used for all participants irrespective of group assignment. In addition, data collection for the primary outcome was performed masked to group assignment, and records of all patients with suspected infections or wound complications were reviewed blindly and diagnoses validated using objective criteria.[19] Fourth, no adjustment was made for multiple comparisons, raising the possibility that significant differences in secondary end points as in patient satisfaction scores at discharge could have occurred by chance.

Conclusions

Among obese women undergoing cesarean delivery, prophylactic negative pressure wound therapy, compared with standard wound dressing, did not significantly reduce the risk of surgical-site infection. These findings do not support routine use of prophylactic negative pressure wound therapy in obese women after cesarean delivery.

ARTICLE INFORMATION

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