Prophylactic Negative Pressure Wound Therapy for Obese Women After Cesarean Delivery

A Systematic Review and Meta-analysis

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OBJECTIVE: To summarize available studies on wound complication outcomes after prophylactic negative pressure wound therapy for obese women (body mass index 30 or greater).

DATA SOURCES: We conducted a systematic review and meta-analysis using electronic database search (PubMed, Cumulative Index to Nursing and Allied Health Literature, EMBASE, Google scholar, and Web of Science), Cochrane, and trial registries including ClinicalTrials.gov.

METHODS OF STUDY SELECTION: We conducted an electronic search of research articles from 1966 to January 2017 for randomized controlled trials (RCTs), prospective cohort, and retrospective cohort studies of negative pressure wound therapy compared with standard dressing after cesarean delivery among obese women. Our primary outcome was defined as a composite of wound complication, including wound or surgical site infection, cellulitis, seroma, hematoma, wound disruption, or dehiscence. For cohort studies and RCTs, we performed a descriptive systematic review. For available RCTs, we performed a meta-analysis and pooled risk ratios using a random-effects model. We assessed for heterogeneity using χ^2 test for heterogeneity and I^2 test. We assessed for publication bias using a funnel plot.

TABULATION, INTEGRATION, AND RESULTS: Of 10 studies meeting eligibility criteria, five were RCTs and five were cohort studies. Results of cohort studies were varied; however, all had a high potential for selection bias. In the meta-analysis, there was no difference in primary composite outcome among those women with negative pressure wound therapy (16.8%) compared with those who had standard dressing (17.8%) (risk ratio 0.97, 95% CI 0.63–1.49). There was no statistically significant heterogeneity (χ^2 test 4.80, P=.31, I^2=17%).

CONCLUSION: Currently available evidence does not support negative pressure wound therapy use among obese women for cesarean wound complication prevention.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO: International prospective register of systematic reviews, 42016033948.

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Obesity, defined as body mass index (BMI, calculated as weight (kg)/[height (m)]^2) 30 or greater, is a common medical comorbidity of pregnancy affecting one third of reproductive-aged women.[1] Maternal obesity is also a well-recognized risk factor for dysfunctional labor and cesarean delivery.[2–5] Although 11% of nulliparous normal-weight women deliver by cesarean delivery, 33% of obese (BMI 30 or greater) and 43% of nulliparous women with BMIs of 40 or greater deliver by cesarean.[6] Obesity is directly associated with increased risk for postoperative

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wound complication with rates among obese women ranging from 10% to 50%.[7–11] Because obese women are at high risk of wound complications, novel risk-reducing approaches including negative pressure wound therapy for wound complication prophylaxis have been proposed.[12]

Negative pressure wound therapy is a device placed at the time of wound closure to promote healing by primary intention using suction (negative pressure). However, effectiveness data for these devices are limited for women undergoing cesarean delivery. The objective of this study was to conduct a systematic review and meta-analysis to estimate whether negative pressure wound therapy compared with standard surgical wound care is associated with a reduced risk of postcesarean wound complications among obese women.

Before the initiation of this systematic review and meta-analysis, we developed a protocol identifying the population, intervention, comparison group, and outcome to address the research question. We included studies with women undergoing cesarean delivery who were obese, defined as BMI 30 or greater. All studies included calculated BMI at the time of cesarean delivery. The intervention was defined as placement of a negative pressure wound therapy over a closed cesarean incision at the time of surgery (ie, prophylactic). The comparison group was use of any standard sterile wound dressing placed over a closed cesarean incision at the time of surgery. Our primary outcome was defined as a composite of wound complications including wound or surgical site infection, cellulitis, seroma, hematoma, wound disruption, or dehiscence. Our secondary outcome was wound or surgical site infection. We included in wound infection those outcomes described as wound infection, surgical site infection, or cellulitis. We excluded studies assessing negative pressure wound therapy after cesarean wound complication, those studies that had no comparison group, and those that did not include data on maternal BMI. We developed a plan for data extraction and analysis before the initiation of the study and we registered our systematic review on PROSPERO, an international prospective register of systematic reviews (registration number 42016033948). We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analyses Of Observational Studies in Epidemiology publication guidelines in our methods. This study was unfunded.

SOURCES

A trained clinical health sciences librarian (S.T.W.) performed our comprehensive electronic search of publications using the following databases: PubMed, Cumulative Index to Nursing and Allied Health Literature via EBSCO, EMBASE via Elsevier, Cochrane Central Register of Controlled Trials, and Web of Science Core Collection. Our search was not restricted by language. We also searched unpublished literature from clinical trial registries using the search terms "cesarean" and "negative pressure wound therapy" including Clinicaltrials.gov, European Union Clinical Trials Register (Clinicaltrialsregister.eu), and the Australia New Zealand clinical trial registry (http://www.anzctr.org.au).

All database results were collected from the inception of the database through January 2017. Search terms were used to retrieve articles addressing the three main concepts of the search strategy: 1) negative pressure wound therapy; 2) obesity; and 3) cesarean delivery. The exact search strategy used in each of the electronic databases is reported in Appendix 1, available online at http://links.lww.com/AOG/A994. We also manually searched the reference lists from selected articles to ensure comprehensive review of the literature. The search strategy was conducted in PubMed using keyword and MeSH combinations. Results were downloaded to EndNote and duplicates were removed. All references were uploaded to Covidence Systematic Review software (https://www.covidence.org), a web-based tool designed to facilitate and track each step of the abstraction and review process.

STUDY SELECTION

Two authors (M.C.S., S.K.D.-K.) reviewed the reference lists to identify relevant studies. Titles and abstract were screened and full-text articles were obtained if articles were relevant or if relevance was uncertain. Full-text research publications were assessed for inclusion and exclusion criteria. Those articles meeting inclusion criteria were critically assessed using standard data form collection sheets.

All randomized controlled trials (RCTs) as well as prospective cohort and retrospective cohort studies comparing wound complication outcomes of negative pressure wound therapy compared with a standard dressing, defined as any sterile dressing placed on a primarily closed cesarean skin incision, were eligible. We excluded case series, case reports, case–control studies, reviews, cost analyses, comments, and editorials. For unpublished data, data in abstract form only, and cohort studies that included women with BMIs less than 30, one author (M.C.S.) contacted authors to obtain detailed information about

methodology and obese population-specific study outcomes.

One author (M.C.S.) reviewed each of the eligible study and extracted data. Other authors (M.G., S.K. D.-K, M.S.V., A.H.-F.) reviewed eligible studies such that two authors reviewed each study. Data were extracted systematically and included number of participants, closure technique, type of negative pressure wound therapy, number of composite wound complications, and number of wound infections. Two reviewers each assessed study quality using standardized tools specific to study design.

The quality of cohort studies was assessed using Newcastle-Ottawa Quality Assessment Scale.[13] This scale assigns a star and point system to assess selection and attrition bias (4 points), intergroup comparability (2 points), and exposure bias (3 points) for a maximum of 9 points. Because a wound complication cannot precede a surgical wound,[14–15] we omitted one of the questions of the scale ("demonstration that outcome of interest was not present at the start of the study"); therefore, the maximum score for cohort studies was 8 points in our study. In the Newcastle-Ottawa Quality Assessment Scale, a higher score denotes a higher quality study. Randomized controlled trials were assessed using the Physiotherapy Evidence Database tool, which uses a validated 11-point scale for critical assessment of RCTs.[16] Studies with scores of 6–11 are deemed "high quality," 4–5 score "fair quality," and 3 or less "poor quality." In the Physiotherapy Evidence Database scale, adequate follow-up is defined as 85% or greater of participants had follow-up for at least one key outcome. The senior author (D. M.S.) resolved discrepancies about study selection, data extraction, and quality assessments.

For the systematic review, we report the results of each study for the primary and secondary outcomes for RCTs and cohort studies. Our meta-analysis included only RCTs in an effort to minimize selection and information bias of pooled estimates. For meta-analysis, abstracted data were analyzed using RevMan 5.3. We performed a meta-analysis when there were at least two studies reporting the primary wound composite outcome or secondary wound infection outcome. We used the χ^2 test for heterogeneity to assess statistical heterogeneity and estimated the magnitude of heterogeneity using I^2 calculated as $([Q-df]/Q)\times 100\%$. We considered the potential for analytically important heterogeneity to be minimal if I^2 0–40%, moderate if 30–60%, and substantial if 50–90%, and if 75–100%, this represents "considerable heterogeneity."[17] We calculated pooled relative risk (RR) and 95% CIs using the Mantel-Haenszel method and random-effect model.[18,19] We chose to use the more conservative analytic approach of a random-effects model as opposed to a fixed-effects model, as a result of apparent clinical heterogeneity. We assessed the potential for publication bias using a funnel plot, primarily relying on visual inspection of symmetry because a statistical test of bias is insensitive as a result of the few number of trials included.

RESULTS

From our initial search, we identified and screened 702 abstracts and included 24 for full-text review (Fig. 1). After exclusion of full-text articles not meeting inclusion and exclusion criteria, 10 studies were included in the systematic review.[20–29] Only RCTs were included in the meta-analysis. There were no additional references found on review of reference lists of each study. Cochrane database review yielded one study on techniques and material for skin closure at time of cesarean delivery but did not include any studies on negative pressure wound therapy placement.[30]

We identified 10 RCTs meeting our inclusion and exclusion criteria (Appendix 2, available online at http://links.lww.com/AOG/A994). We included five RCTs in our meta-analysis, four of which were identified in the U.S. clinical trial registry (clinicaltrials.gov) (Tuuli et al 2017 NCT02578745; Ruhstaller et al, 2017 NCT02128997; Guntilake et al 2014 NCT01450631; Stitely et al 2012 NCT00654641) and one in the Australian Clinical Trials Registry (Chaboyer et al, ACTRN12615000286549). Of the five RCTs included, one is published in full,[22] one included data available from clinicaltrials.gov and information obtained from the principal investigator,[19] three are available in abstract form[23,25,26] On our request, additional information needed to assess study quality and perform meta-analysis was provided by the investigators in each of the unpublished three RCTs. One study (NCT01637870) was subsequently published as a cohort study and is included in the descriptive portion of our systematic review but not the meta-analysis.[27]

A total of 10 studies are included in our descriptive systematic review, including five cohort studies (n=1,830) and the previously mentioned five RCTs (n=494) (Table 1). A variety of negative pressure wound therapy devices are included including Prevena, PICO, and the KCI VAC system. All studies except one[22] were conducted in the United States. Of the five cohort studies, two were available in abstract form,[28,29] one included unpublished data for obese women that we were able to obtain from the authors,[27] and one was published in full.[24] In the

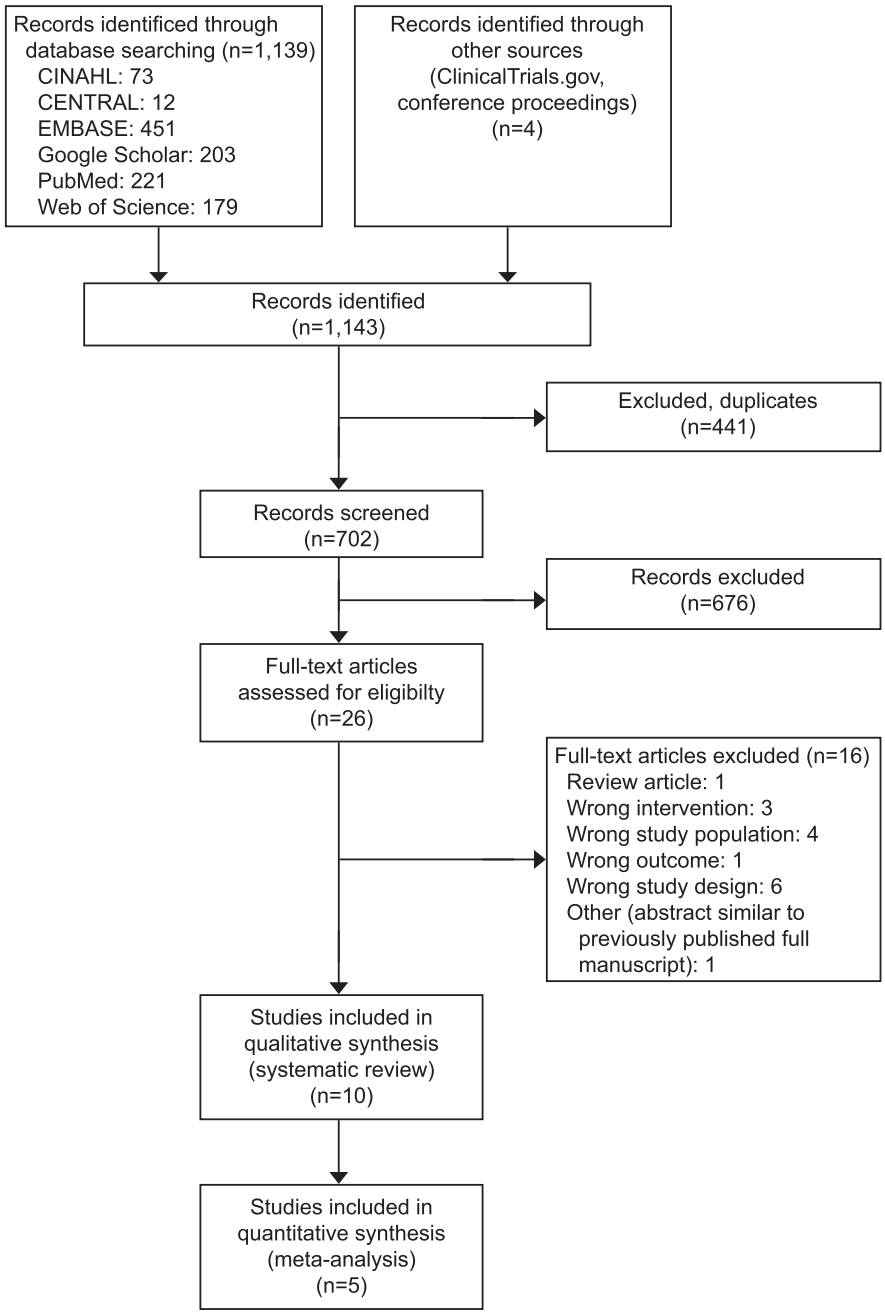

Fig. 1. Flow diagram of studies included in systematic review and meta-analysis. CINAHL, Cumulative Index to Nursing and Allied Health Literature; CENTRAL, Cochrane Central Register of Controlled Trials.

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descriptive portion of the systematic review, we include the result of one retrospective study for completeness.[20] However, although the majority of women (64%) included in this cohort were obese, the outcome data stratified by the presence of obesity are not available for this study.[20] Of the 10 studies reviewed, we contacted seven authors and received additional information from six authors.

We report the quality assessment of the five cohort studies by the Newcastle–Ottawa Scale (Appendix 3, available online at http://links.lww.com/AOG/A994). All of the cohort studies selected women with BMIs of at least 30 or greater undergoing cesarean delivery from large single-center retrospective reviews. Two studies had higher BMI cutoff inclusion criteria.[24,28] None of the studies controlled for important confounders including BMI and medical comorbidities.[24,27,28] All of the cohort studies used hospital records. Swift et al[27] assessed their controls (sterile dressing) through chart review retrospectively

from April to September 2011 and prospectively assessed cases (negative pressure wound therapy) from August 2012 to January 2013. Sources of "other bias" in cohort studies included inadequate assessment of other potential confounders including maternal medical comorbidities, unclear length of sterile wound dressing, and negative pressure wound therapy device in situ.[28] Additionally, studies do not report if women received increased or weight-specific dosage of antibiotics,[31,32] estimated blood loss,[33,34] type of skin preparation,[35] or length of surgery,[36] all of which are risk factors for wound complication among obese women.

Physiotherapy Evidence Database scores for the five RCTs ranged from 6 to 9 points (Appendix 4, available online at http://links.lww.com/AOG/A994). All studies described eligibility criteria and random allocation to treatment group. One lacked information about important baseline characteristics of study participants.[21] In all five RCTs, neither the participants nor the clinicians were blinded to treatment allocation. Only one RCT included outcome assessors who were blinded to treatment allocation.[25] All of the studies had adequate follow-up. All five RCTs used intention-to-treat analysis. All five studies were deemed "high"-quality studies by the Physiotherapy Evidence Database scale.

In the five cohort studies reviewed, participants varied on important maternal characteristics including BMI and medical comorbidities between the treatment and control groups (Table 2). In four of five cohort studies reviewed, the proportion of women who had the primary composite outcome was lower among those who received negative pressure wound therapy compared with standard dressing (Table 2). The point estimates of relative risk in each of these four studies are in the same direction and of similar magnitude in each of these four cohort studies.[24,27–29] In one study, the proportion of women who had a wound complication was higher among women who received negative pressure wound therapy; however, the study population was heterogeneous with regard to obesity and outcome data were only available for the entire cohort, which included approximately one third of women (n=352) who had BMIs less than 30.[20]

All five RCTs evaluated the primary composite outcome, which is any wound complication, and the secondary outcome of wound infection (Table 2). In the meta-analysis, there was no difference in primary wound composite outcome among those women with negative pressure wound therapy (16.8%) compared with those who had sterile dressing (17.8%) (pooled RR 0.97, 95% CI 0.63–1.49) (Fig. 2). There was no significant heterogeneity (χ^2 test 4.80, P=.31, I^2=17%). There was also no significant difference for wound infection among those with negative pressure wound therapy (8.3%) compared with those who sterile dressing (10.8%) (pooled RR 0.79, 95% CI 0.44–1.41) without evidence of heterogeneity (χ^2 test 1.47, P=.69, I^2=0%) (Fig. 3). In sensitivity analysis for any wound complication, there was no significant difference in pooled RR and 95% CI when individual studies were removed. Based on the funnel plot symmetry (Appendix 5, available online at http://links.lww.com/AOG/A994), there does not appear to be evidence for marked publication bias.

DISCUSSION

Our systematic review of negative pressure wound therapy cohort studies demonstrates that cohort studies currently available have a high degree of study design heterogeneity and potential for selection bias including differences in important maternal characteristics such as BMI, medical comorbidities, and surgical technique. Our review of RCTs demonstrated that there are five high-quality RCTs with data currently available. In each of these trials, the major potential area of bias was lack of blinding among outcome assessors. Our meta-analysis indicated that based on currently available data, there is no detectable difference in wound complication or wound infections between negative pressure wound therapy and standard dressing among obese women.

Although meta-analysis improves the power and precision for estimating differences between negative pressure wound therapy and standard treatment compared with individual RCTs, our meta-analysis is still somewhat limited by sample size given the relatively low frequency of outcomes. We are limited in detecting smaller reductions in risk if they exist. Using the primary outcome as an example, our meta-analysis has adequate power to detect a 50% reduction in the outcome with negative pressure wound therapy if it truly existed. Our analysis will not reliably discern smaller differences (less than 50%) if they exist. Similarly, the detectable difference of our meta-analysis for wound infection is 70%; therefore, we may not detect risk reductions smaller than 70% with negative pressure wound therapy if they truly exist. Arguably, smaller risk reductions are less clinically important, but our results may reflect one of two possibilities: 1) negative pressure wound therapy does not offer clinically significant risk reduction for wound complications; or 2) negative pressure wound therapy provides smaller risk reductions that are not

Table 1. Summary of Characteristics of Clinical Trials and Cohort Studies Assessing Wound Complications Among Obese Women With Negative Pressure Wound Therapy Compared With Sterile Dressing

Author, Year	Location	Publication Status	Sample Size			Inclusion Criteria	Exclusion Criteria
			Total	Negative Pressure Wound Therapy	Control		
Randomized controlled trials							
Stitely, 2012	Morgantown, WV	ClinicalTrials.gov	54	28	26	Age 18 y or older Weight greater than 199 pounds Subcutaneous tissue depth (fascia to epidermis) 4 cm or greater	Age younger than 18 y Weight less than 199 pounds Unable to consent Unable to follow-up for 2 postoperative visits (7–14 d and 4–6 wk)
Chaboyer et al, 2014	Australia	Full text	92	46	46	Elective cesarean delivery Prepregnancy BMI (kg/m^2) 30 or greater Informed consent	Urgent or emergency delivery Previous participation Existing infection before cesarean delivery Unable to speak English
Gunatilake et al, 2014	Durham, NC	Abstract	92	46	46	Age 18 y or older BMI 35 or greater	Skin or systemic infection, chorioamnionitis, critical illness, high anesthesia risk (ASA class P4, P5, P6)
Ruhstaller et al, 2017	Philadelphia, PA	Abstract	136	67	69	BMI 30 or greater at less than 22 wk of gestation 4 cm or greater dilated during unscheduled, intrapartum cesarean delivery	Diabetes, non-English speaker, chronic steroids, active malignancy, undergoing scheduled cesarean delivery, allergic to silver
Tuuli et al, 2017	St Louis, MO	Abstract	120	60	60	BMI 30 or greater	Nonavailability for follow-up Contraindication to negative pressure wound therapy Pre-existing skin infection Bleeding disorder Therapeutic anticoagulation Allergy to any component of dressing (silicone, adhesive tape)
Cohort studies							
Orth et al, 2016	Kansas City, MO	Full text	970	103	867	BMI 30 or greater	—
			618	Obese women only 95	523		
Mark et al, 2014	Baltimore, MD	Full text	63	21	42	BMI 45 or greater	—
Swift et al, 2015	Iowa City, IA	Full text	319	110	209	18 y old English-speaking	—
				Obese women only BMI 30 or greater			
			235	95	140	1 or more risk factors: BMI 30 or greater, preeclampsia, HELLP, rupture of membranes for greater than 4 h, chorioamnionitis, diabetes, current anticoagulation, multiple gestation, hypertension	
Looby et al, 2016	Minneapolis, MN	Abstract	245	123	122	BMI 40 or greater BMI 35 or greater with obesity-related comorbidity	—
Villers et al, 2017	Durham, NC	Abstract	317	210	117	BMI 40 or greater	—

CDC, Centers for Disease Control and Prevention; BMI, body mass index; ASA, American Society of Anesthesiologists; ICD-9, International Classification of Diseases, 9th Revision; HELLP, hemolysis, elevated liver enzymes, low platelet count; SSI, surgical site infection.

Type of Device	Control	Suction Amount (mm Hg)	Duration	Follow-up	Primary Outcome
Noncommercial	Subcutaneous absorbable suture and skin staples	125	72 h	2 visits: 7–14 d, 4–6 wk	Superficial or deep space surgical site infection or any type of wound disruption, including wound hematoma or seroma
PICO	Comfeel Plus sterile dressing in place for 4 d	50–125	4	28 d	Surgical site infection by CDC criteria
Prevena	Sutured incision with sterile gauze and nonpenetrable barrier (eg, Tegaderm) for 1–2 d	125	5	42±10 d	Surgical site outcome composite (local inflammatory response, wound infection, seroma, hematoma, wound dehiscence, need for surgical or antibiotic intervention)
Prevena	Skin closed with staples	125	3 d	4 wk	Wound morbidity composite (surgical site infection, wound opening requiring packing)
PICO	Standard dressing removed after 1 d	80	4 d	30 d	Composite of superficial or deep SSI, separation 2 cm or greater, hematoma, or seroma
Prevena	Standard dressing	125	7	1–6 wk postpartum	Wound complication (seroma, hematoma, separation, infection)
KCI VAC	Standard dressing	125	2–4	6 wk postpartum	Wound complication (ICD-9) 670.02 or 670.04 major puerperal infection 998.3 disruption of surgical wound 998.5 postoperative infection not elsewhere classified 998.59 other postoperative infection 998.83 nonhealing surgical wound 674.1 disruption of cesarean wound 674.32 surgical complication
Prevena	Standard dressing	125	3 d	6 wk postpartum	All wound complications
KCI VAC	Standard dressing	125	3–4 d (day of discharge)	10 wk postpartum	Surgical site infection
PICO or Prevena	Standard dressing	125	7–10 d	6 wk postpartum	Surgical site infection (CDC)

Table 2. Data on Wound Complication and Wound Infection From Included Studies Comparing Negative Pressure Wound Therapy and Sterile Dressing After Cesarean Delivery Among Obese Women

Study	Any Wound Complication		Wound Infection	
	Negative Pressure Wound Therapy	Control	Negative Pressure Wound Therapy	Control
Randomized controlled trials				
Stitely, 2012	15/28 (53.6)	10/26 (38.4)	—	—
Ruhstaller et al, 2017	3/61 (4.9)	4/58 (6.9)	2/61 (3.3)	4/58 (6.9)
Chaboyer et al, 2014	14/44 (31.8)	17/43 (39.5)	10/44 (22.7)	12/43 (27.9)
Guntilake et al, 2014	2/39 (5.1)	7/43 (16.3)	4/43 (9.3)	1/39 (2.6)
Tuuli et al, 2017	5/60 (5.0)	3/60 (8.3)	2/60 (3.3)	3/60 (5.0)
Total for RCTs	39/232 (16.8)	41/230 (17.8)	18/208 (8.7)	20/200 (10.0)
Retrospective cohort studies				
Swift et al, 2015 (BMI [kg/m^2] 30 or greater)	6/95 (6.1)	26/140 (18.6)	3/95 (3.2)	18/140 (12.9)
Mark et al, 2014 (BMI 45 or greater)	0/43 (0)	5/21 (10.4)	—	—
Looby et al, 2016 (BMI 40 or greater)	—	—	12/123 (9.4)	16/122 (13.4)
Villers et al, 2017 (BMI 40 or greater)	16/100 (16.0)	24/113 (21.2)	9/100 (9.0)	22/113 (19.5)
Orth et al, 2016 (includes women with BMIs less than 30)	13/103 (12.6)	37/837 (4.4)	—	—

RCTs, randomized controlled trials; BMI, body mass index.
Data are n/N (%).

detectable in this analysis and may or may not reflect a clinically significant effect.

Strengths of our study include the a priori definition of women with a common risk factor for wound complication–BMI 30 or greater and the use of a well-defined and discrete composite wound complication outcome. By combining five RCTs, we are able to provide a larger sample size. Challenges in our study include both lack of information on and variation in surgical practices known to affect wound complication risk in this population including skin closure technique (skin compared with subcuticular suture),[37–39] subcutaneous adipose tissue closure,[40] incision type (Pfannenstiel compared with vertical skin incision),[41] antibiotic type and dosing,[32,33,42] and barrier retractors.[43] The lack of blinding of the participant and physician is likely unachievable in any study of this nature. However, the lack of outcome assessors blinded to study allocation in any of the RCTs has potential to introduce bias.

Among available RCTs, the pooled data are underpowered to assess less than 50% risk reduction in wound complications with negative pressure wound therapy compared with standard dressing in this population. Assuming a 10% risk of wound complication among obese women undergoing cesarean delivery and 30% risk reduction with 80% power and α 0.05, the number needed to enroll in an RCT that is adequately powered is 2,712. Based on our review of current clinical trials, there are two large trials (NCT03009110 and ACTRN12615000286549) presently registered. The U.S. trial (NCT03009110) began recruitment in January 2017 and aims to recruit 2,850 women and the Australian trial

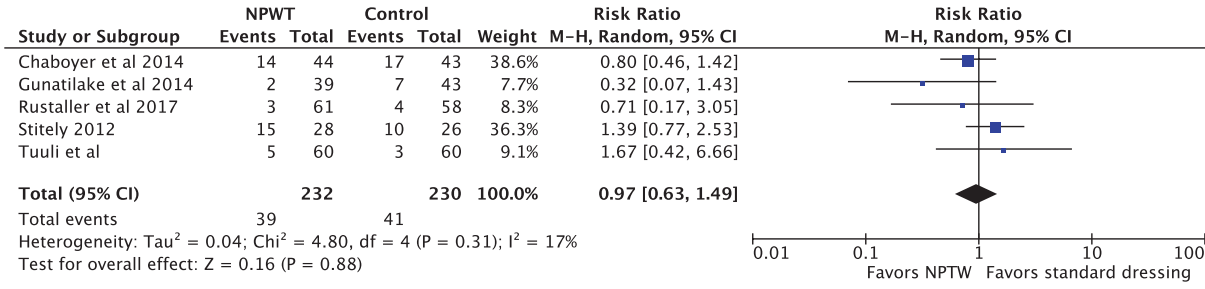

Fig. 2. Forest plot of the composite outcome of wound complications in selected randomized controlled trials comparing negative pressure wound therapy and sterile dressing after cesarean delivery among obese women. NPTW, negative pressure wound therapy; M-H, Mantel-Haenszel test; df, degrees of freedom.

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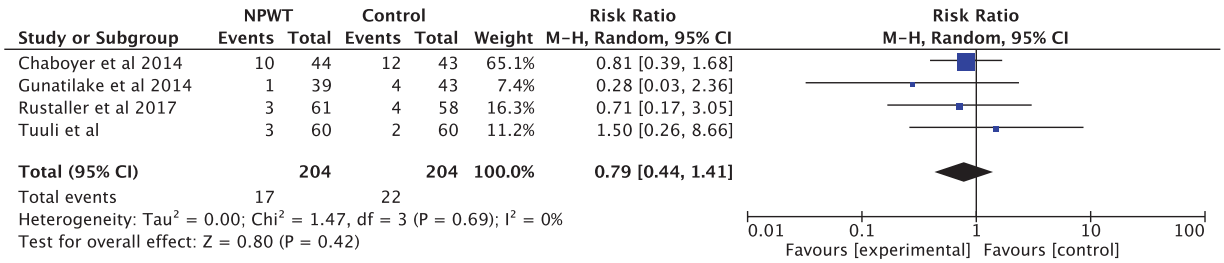

Fig. 3. Forest plot of the composite outcome of wound infections in selected randomized controlled trials comparing negative pressure wound therapy and sterile dressing after cesarean delivery among obese women. NPTW, negative pressure wound therapy; M-H, Mantel-Haenszel test; df, degrees of freedom.

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(ACTRN12615000286549) is currently enrolling and aims to recruit 2,100 women. The U.S. trial anticipates study completion in August 2021, with last outcome data collection in January 2020 and the Australian trial anticipates last study participant enrollment in March 2019.

The cost of negative pressure wound therapy devices is substantial and range from $150 to $1,700[44,45] and efficacy should be demonstrated before widespread use. We urge health care providers considering the use of negative pressure wound therapy in obese women to discuss the lack of definitive evidence supporting its use and encourage health care providers to assist in the enrollment of eligible women in RCTs to assess negative pressure wound therapy efficacy where available.

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