BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.15413
www.bjog.org

General obstetrics

Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: a pragmatic randomised clinical trial

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Accepted 9 July 2018. Published Online 8 September 2018.

Objective To evaluate the reduction of surgical site infections by prophylactic incisional negative pressure wound therapy compared with standard postoperative dressings in obese women giving birth by caesarean section.

Design Multicentre randomised controlled trial.

Setting Five hospitals in Denmark.

Population Obese women (prepregnancy body mass index (BMI) ≥30 kg/m^2) undergoing elective or emergency caesarean section.

Method The participants were randomly assigned to incisional negative pressure wound therapy or a standard dressing after caesarean section and analysed by intention-to-treat. Blinding was not possible due to the nature of the intervention.

Main outcome measures The primary outcome was surgical site infection requiring antibiotic treatment within the first 30 days after surgery. Secondary outcomes included wound exudate, dehiscence and health-related quality of life.

Results Incisional negative pressure wound therapy was applied to 432 women and 444 women had a standard dressing. Demographics were similar between groups. Surgical site infection occurred in 20 (4.6%) women treated with incisional negative pressure wound therapy and in 41 (9.2%) women treated with a standard dressing (relative risk 0.50, 95% CI 0.30–0.84; number needed to treat 22; $P = 0.007$). The effect remained statistically significant when adjusted for BMI and other potential risk factors. Incisional negative pressure wound therapy significantly reduced wound exudate whereas no difference was found for dehiscence and quality of life between the two groups.

Conclusion Prophylactic use of incisional negative pressure wound therapy reduced the risk of surgical site infection in obese women giving birth by caesarean section.

Keywords Caesarean section, incisional negative pressure wound therapy, obesity, surgical site infection.

Tweetable abstract RCT: prophylactic incisional NPWT versus standard dressings postcaesarean in 876 women significantly reduces the risk of SSI.

Linked article This article is commented on by M Tuuli, p. 635 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.15572.
This article has journal club questions by BD Einerson, p. 636 in this issue. To view these visit https://doi.org/10.1111/1471-0528.15610.

Please cite this paper as: Hyldig N, Vinter CA, Kruse M, Mogensen O, Bille C, Sorensen JA, Lamont RF, Wu C, Heidemann LN, Ibsen MH, Laursen JB, Ovesen PG, Rorbye C, Tanvig M, Joergensen JS . Prophylactic incisional negative pressure wound therapy reduces the risk of surgical site infection after caesarean section in obese women: a pragmatic randomised clinical trial. BJOG 2019;126:628–635.

Trial registration: ClinicalTrials.gov (NCT 01890720)

Introduction

Maternal obesity is associated with a higher risk of caesarean section and surgical site infection.[1–3] Surgical site infection occurs in about 10% of obese women undergoing caesarean section despite prophylactic strategies (e.g. antibiotics).[2,4] This can be explained partly by a decreased blood flow in adipose tissue and an obesity-associated inflammation causing vascular dysfunction, which results in a local hypoxic response.[5] Hypoxia impairs oxidative bacterial killing and leads to an increased risk of surgical site infection.[6]

Incisional negative pressure wound therapy (iNPWT) increases blood flow[7] and has been shown to reduce the risk of surgical site infection after nonobstetric surgery.[8] Furthermore, iNPWT reduces the risk of haematoma/seroma due to improved lymphatic drainage[9] and reduces the risk of wound dehiscence[10] by decreasing the lateral and shear stress on sutures. However, iNPWT is relatively expensive as compared with standard postoperative dressings. Therefore, it should be considered judiciously for patients at high risk of surgical site complications or if the consequences of a surgical site complication are high. Only a few cohort and pilot studies have investigated the effect of prophylactic iNPWT after caesarean section.[11,12] No firm recommendations can be made from these studies due to heterogeneity and risk of bias. Further investigation of iNPWT in the prophylactics of surgical site infections after caesarean section is therefore warranted.

The objective of our study was to investigate the effectiveness of prophylactic iNPWT after caesarean section in obese women. Our hypothesis was that iNPWT would be associated with fewer surgical site infections and other wound complications (i.e. wound exudate and dehiscence) compared with standard postoperative dressings. We chose to focus on obese women as they have a higher risk of surgical site infection.

Methods

This study was an unblinded pragmatic randomised multicentre study conducted in two tertiary referral centres and three Danish teaching hospitals between 2013 and 2016. The Regional Scientific Ethical Committee of Southern Denmark (S-20130010) and the Danish Data Protection Agency (2008-58-0035) approved the study. The study was overseen by the local ethics committee and an independent data safety monitoring committee. The study was registered at ClinicalTrials.gov (NCT 01890720) and includes a parallel economic evaluation and a cosmetic evaluation that are reported separately.

Participants

Eligible participants were pregnant women undergoing elective or emergency caesarean section, aged ≥18 years, who had a prepregnancy body mass index (BMI) ≥30 kg/m^2, and could read and understand Danish. Midwives and doctors recruited the women and obtained written informed consent during pregnancy. Women who had given informed consent were excluded if they subsequently delivered vaginally.

Intervention

In the operating theatre, women were randomly assigned to iNPWT (PICO, size 10 × 30 cm or 10 × 40 cm, Smith & Nephew, Hull, UK) or a standard postoperative dressing (Table S1). The dressing was applied immediately after skin closure. Prior to incision, the skin was prepared with chlorhexidine–alcohol, except in extreme emergency cases in which this step was skipped. All skin incisions were transverse lower abdominal incisions. Two surgeons, usually a trainee supervised by an experienced resident or a specialist, performed the surgical procedure. A single dose of intravenous cefuroxime (1.5 or 3.0 g according to local standard procedures) was administered during surgery. The choice of suture material or staples was according to the surgeon's preference. All women received uniform care according to local hospital guidelines. The iNPWT dressing was left *in situ* for approximately 5 days, corresponding to the day of removal of staples, and the standard postoperative dressing was left *in situ* for at least 24 hours. Any malfunction or dressing changes of iNPWT during hospitalisation were recorded. On average, women were discharged 3 days after caesarean section and were followed up 5–6 days postpartum by a trained nurse who removed the iNPWT dressing and the staples, and evaluated the incision.

Data collection

Data were collected from a questionnaire, national Danish registers and medical records. An electronic questionnaire was sent to all participants 30 days after caesarean section to collect data on postsurgical wound complications within the period of 30 days after surgery. The questionnaire asked about demographics, wound complications, contacts with the healthcare system, antibiotic treatment and health-related quality of life (the EQ-5D-5L questionnaire).[13,14] A reminder to complete the questionnaire was sent to nonresponders.

Individual healthcare data were extracted from three linked national registers. In Denmark, all citizens are provided with a unique social security number, which is used as the key identifier in all Danish health and social care registers. Data from the following national registers were used to extract baseline characteristic and to identify postpartum maternal antibiotic use and diagnosis codes related to postsurgical wound complications:

- the Danish Medical Birth Registry,[15] which comprises all births in Denmark including detailed maternal information on (e.g. prepregnancy BMI and mode of delivery).
- the Danish National Patient Register,[16] which comprises all somatic inpatient admissions and outpatient visits including diagnosis codes.
- the Danish National Prescription Registry,[17] which contains individual information on all dispensed prescription pharmaceuticals sold in Danish community pharmacies.

Outcomes

The primary outcome, surgical site infection, was defined as surgical site infection requiring antibiotic treatment within the first 30 days after caesarean section. The outcome comprised data from the Prescription Registry[17] (dispensed prescriptions), the Patient Register[16] (hospitalisation and diagnosis codes), medical records and the questionnaire. Medical records were reviewed to identify antibiotic treatment during hospitalisation if a woman was hospitalised for more than 4 days, was readmitted or registered with a diagnostic code that could be related to a complication after caesarean section, or responded 'yes' to the question 'Have you received any antibiotic treatment after your caesarean section?' but did not redeem an antibiotic prescription. For participants who did not respond to the questionnaire, data on antibiotics and diagnostic codes related to postpartum complications were extracted from the registers and medical charts.

Secondary outcomes were deep surgical site infection defined as an infection requiring surgery, and patient-reported wound exudate, minor dehiscence (defined as a gap between the sides of the wound) and health-related quality of life (EQ-5D-5L). The EQ-5D-5L questionnaire covers five dimensions of health status (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a 0–100 visual analogue scale (EQ VAS) to describe overall self-rated health status.[13] Each EQ-5D dimension has five levels, ranging from no problems to extreme problems. The composite health status can subsequently be converted into a country-specific index value between 0 and 1 (where 1.0 represents full health) to calculate quality-adjusted life years for economic evaluation of healthcare interventions.[14]

Randomisation

Participants were randomised in the operating theatre during surgery using a web-based randomisation programme with a 1:1 allocation ratio and random block sizes of 4–6, stratified by centre and type of caesarean section (emergency versus elective). The random allocation sequence was generated by an external data manager with no clinical involvement in the study. Blinding was not possible due to the nature of the intervention.

Statistical analyses

A sample size of 870 was necessary to ascertain a reduction in surgical site infection of 50% in the intervention group compared with an expected baseline event rate of 10% in the control group, with a two-sided 5% significance level and a power of 80%.

The outcomes were estimated by crude and weighted relative risks (RR) with 95% confidence intervals (95% CI). A significance level of 0.05 (two-sided) was chosen. The number needed to treat to prevent one outcome was calculated as 1/the absolute risk reduction. The primary outcome was analysed on an intention-to-treat basis, meaning that all patients stayed in their allocated group.[18] Imputation for missing secondary outcome data was not applied, as there was no difference in the prognostic characteristics at baseline of those with and those without questionnaire data (Table S2).[19] Accordingly, women with missing outcome data were excluded from the analyses of secondary outcomes.

To investigate whether any potential confounders affected the observed results, we used logistical regression to estimate odds ratios with 95% CI for surgical site infection. The odds ratios were adjusted for potential risk factors identified in the literature,[3,20] including BMI (<35 and ≥35 kg/m^2), age (continuous variable), diabetes (yes/no), smoking (yes/no), blood loss (intervals of 100 ml), rupture of membranes (yes/no), duration of procedure (continuous variable) and wound closure method (staples/sutures).

Core outcome set and patient involvement

No core outcome set was used when designing the trial. The study design was discussed with women giving birth at the primary investigator site (Odense University Hospital) prior to the conduct of the study, with specific focus on information material, questionnaire and patient follow-up.

Results

Trial participants

Between September 2013 and October 2016, 876 obese women were treated after caesarean section with an iNPWT dressing (n = 432) or a standard postoperative dressing (n = 444). Follow up was concluded in November 2016. A total of 827 women responded to the questionnaire (response rate 94.4%) (Figure 1). Baseline demographics and perioperative patient characteristics were similar between groups (Table 1). The participating women were aged 18–46 years, 49.4% had a prepregnancy BMI of 30–35 kg/m^2 and 53.0% had an elective caesarean section. There were some cases of nonadherence to the protocol: 39 women (15 intervention and 24 control) had a prepregnancy BMI <30 kg/m^2 and in 12 cases the iNPWT dressing was removed earlier than scheduled due to malfunction. In

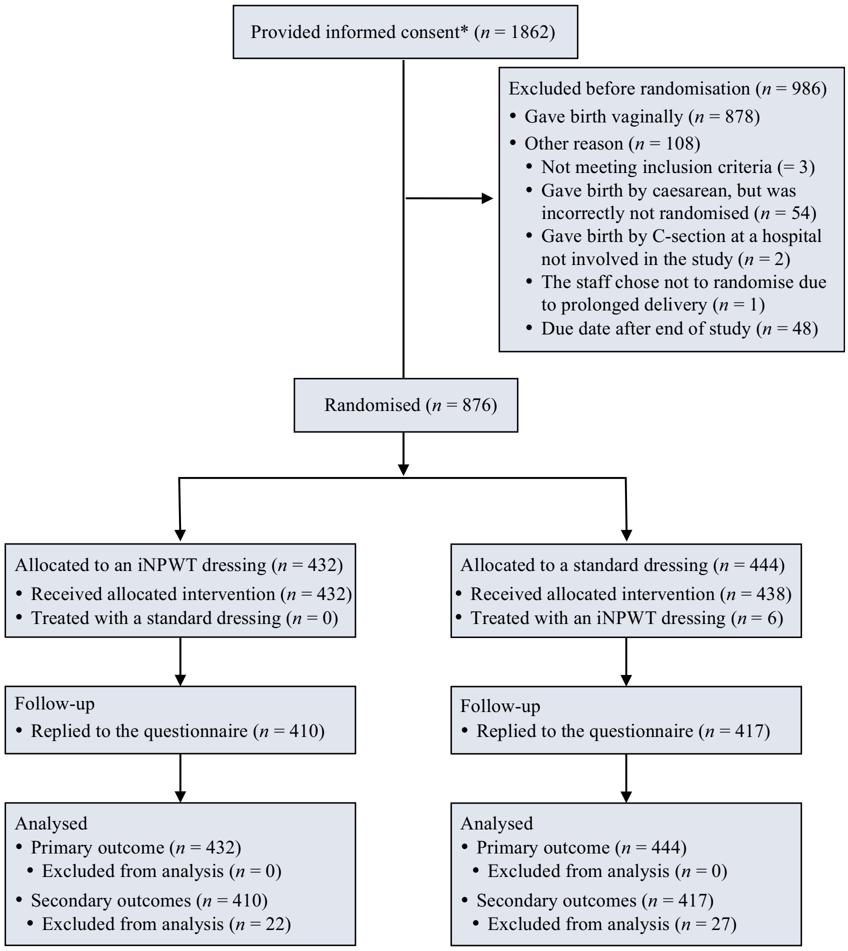

Figure 1. CONSORT diagram for study participation. *Women assessed for eligibility were not accounted for.

addition, six women in the control group were erroneously treated with an iNPWT dressing. All were analysed as allocation at time of randomisation.

Primary outcome

Surgical site infection was identified in 20/432 women (4.6%) in the intervention group and 41/444 women (9.2%) in the control group. Accordingly, iNPWT reduced the relative risk of surgical site infection by 50% (RR 0.50, 95% CI 0.30–0.84; $P = 0.007$) with an absolute risk reduction of 4.6% (95% CI 1.2–7.9%). The number needed to treat was 22 (95% CI 12–80) (Table 2). Adjusting the analysis for potential risk factors did not change the relative risk or 95% CI (Table 3).

Secondary outcomes

The number of deep surgical site infections requiring surgery was similar in both groups, with eight women (1.9%) in the intervention group and nine women (2.0%) in the control group. Wound exudate was reported by 92 of 410 women (22.4%) in the intervention group and 137 of 417 women (32.9%) in the control group, corresponding to a relative risk reduction of 31% (RR 0.69, 95% CI 0.55–0.86; $P = 0.001$) with an absolute risk reduction of 10.3% (95% CI 4.2–16.4%) and number needed to treat of 10 (95% CI 6–24). Minor wound dehiscence was reported by 15.8% of women, with no difference between the groups (Table 2).

The composite health status (EQ index value; mean = 0.86, 95% CI 0.85–0.87, versus mean = 0.86, 95% CI 0.84–0.87) and the overall self-rated health status (EQ VAS; mean = 83, 95% CI 82–85, versus mean = 82, 95% CI 80–83) did not differ between the groups ($P = 0.33$ and $P = 0.25$, respectively). In all the participating women, the EQ-5D-5L health profile showed that the women reported most problems with pain/discomfort 1 month post-CS.

Discussion

Main findings

To the best of our knowledge, this is the largest randomised controlled trial randomly allocating obese women

Table 1. Baseline characteristics and perioperative information in women treated with either incisional negative pressure wound therapy (iNPWT) or standard postoperative dressing (SPD) after caesarean section

Characteristics	**iNPWT (*n* = 432)**	**SPD (*n* = 444)**
Maternal age*	32 ± 5	32 ± 5
Prepregnancy BMI, kg/m^2**	34.7 (31.5–38.2)	34.2 (31.6–38.1)
Diabetes		
Prepregnancy diabetes	11 (2.6%)	11 (2.5%)
Gestational diabetes	65 (15.1%)	69 (15.5%)
Nonspecific diabetes	4 (0.9%)	10 (2.3%)
Smoking during pregnancy	30 (6.9%)	37 (8.3%)
Nulliparous	177 (41.0%)	179 (40.3%)
Singleton pregnancy	418 (96.8%)	428 (96.4%)
Rupture of membranes		
Prelabour (PROM)	33 (7.6%)	30 (6.8%)
During labour	22 (5.1%)	34 (7.7%)
Prior caesarean section	188 (43.5%)	191 (43.0%)
Type of caesarean section		
Elective	229 (52.9%)	235 (53.0%)
Emergency	203 (47.1%)	209 (47.0%)
Uterus closure		
One layer	312 (72.2%)	319 (71.8%)
More than one layer	120 (27.8%)	125 (28.2%)
Closure of the subcutaneous layers***	274 (63.4%)	279 (62.8%)
Skin closure		
Skin staples	260 (60.2%)	264 (59.5%)
Absorbable sutures	172 (39.8%)	180 (40.5%)
Estimated perioperative blood loss in ml**	450 (300–700)	500 (300–700)
Duration of surgery in minutes**	36 (30–45)	36 (29–45)

BMI, body mass index.
*Mean ± standard deviation;
**Median (interquartile range).
***3% in the intervention group and 5% in the control group had missing data for this variable.

to a prophylactic iNPWT dressing or a standard postoperative dressing after caesarean section. The iNPWT dressing significantly reduced the risk of surgical site infection and the effect remained statistically significant after controlling for potential risk factors, including prepregnancy BMI. Wound exudate was significantly reduced but no effect was found for minor wound dehiscence. Likewise, the study was not able to demonstrate a statistically significant difference in quality-adjusted life years between the two groups.

Strengths and limitations

The strengths of the study are its pragmatic randomised design and large sample size, which increase the validity and generalisability.[18] A limitation is the inevitable unblinded design, which in general can introduce observer and patient bias.[21–23] The primary outcome was defined an infection that occurred at the incision site within 30 days of caesarean section and treated with antibiotics. No gold standard for reporting surgical site infection exists,[24] and at present no core outcome set related to postcaesarean surgical site infection exists or is in development at the CROWN database (www.crown-initiative.org). Several studies refer to the US Centers for Disease Control and Prevention definitions[25,26] of surgical site infection, as follows: superficial incisional—involving only skin and subcutaneous tissue, indicated by localised signs such as redness, pain, heat or swelling at the site of the incision or by the drainage of pus or microbiological evidence or diagnosis by the surgeon or attending physician; deep incisional—affecting the facial and muscle layers, indicated by the presence of pus or an abscess, fever with tenderness of the wound or a separation of the edges of the incision exposing the deeper tissues.[26,27] Because the diagnosis of surgical site infection is to a certain extent based on the physician's subjective judgement, it carries a risk of some wounds being false-positive treated with antibiotics on suspicion on surgical site infection. There is no reason to believe that the risk of false-positive diagnosis is different in the two groups. The secondary outcomes (i.e. wound dehiscence, wound exudate and health-related quality of life) were self-reported and the patient's judgement may have introduced bias.[21] There were some cases of nonadherence to the protocol (including BMI <30). However, the nature of the protocol deviation did not justify excluding participants after randomisation according to the intention-to-treat approach.[18] The intervention was evaluated in young obese women in good health and the results may differ for elderly patients with more co-morbidity.

Interpretation

The prevention of surgical site infections is complex and comprises several strategies.[28] Different interventions have been shown to be beneficial in the prevention of maternal infection risk after caesarean section, including timing of prophylactic antibiotics,[29] choice of antibiotic[30] and antiseptic skin preparation.[31] In 2016, the World Health Organization guidelines for prevention of surgical site infection included a recommendation of prophylactic iNPWT in high-risk closed surgical incisions.[24] The current knowledge of iNPWT after caesarean section is, however, limited to a few cohort and pilot studies summarised in two recent systematic reviews.[11,12] One review concluded that iNPWT was associated with a decreased risk of surgical site infection,[12] whereas the other found that the current evidence did not support a positive effect of iNPWT after caesarean section.[11] These diverging results probably are due to the cohort and pilot designs, which carry a high risk of bias and uncertainty about the results. However, the

Table 2. Postoperative complications after caesarean section using either incisional negative pressure wound therapy (iNPWT) or standard postoperative dressing (SPD)

Outcome	Number (%)		Relative risk (95% CI)	Weighted relative risk* (95% CI)	*P* value**
	iNPWT	SPD			
Primary outcome	*n* = 432	*n* = 444			
Surgical site infection	20 (4.6)	41 (9.2)	0.50 (0.30–0.84)	0.51 (0.30–0.84)	0.007
Secondary outcomes	*n* = 410	*n* = 417			
Wound exudate	92 (22.4)	137 (32.9)	0.69 (0.55–0.86)	0.68 (0.55–0.86)	0.001
Minor wound dehiscence	62 (15.1)	69 (16.6)	0.91 (0.67–1.25)	0.90 (0.66–1.24)	0.66
Other types of postpartum infections					
Endometritis	8 (2.0)	8 (1.9)	1.02 (0.39–2.68)	1.02 (0.38–2.72)	0.97
Urinary tract infection	24 (5.9)	17 (4.1)	1.44 (0.78–2.63)	1.43 (0.78–2.60)	0.25
Mastitis	20 (4.9)	17 (4.1)	1.20 (0.64–2.25)	1.22 (0.65–2.31)	0.58

CI, confidence interval.
*Adjusted for stratification variables (hospital and type of caesarean section).
***P* value of crude relative risk.

Table 3. Logistical regression analysis model adjusting for potential risk factors for surgical site infection identified in the literature

Potential risk factor	Crude OR (95% CI)	Adjusted OR (95% CI)
Group	0.48 (0.27–0.83)	0.46 (0.26–0.80)
BMI ≥35 kg/m^2		1.93 (1.11–3.37)
Age (years)*		1.00 (0.95–1.06)
Diabetes		2.21 (0.62–2.38)
Smoking during pregnancy		2.40 (1.21–4.74)
Emergency caesarean section		1.57 (0.88–2.81)
Bleeding during surgery (per 100 ml)		0.98 (0.91–1.05)
Rupture of membranes		1.66 (0.68–4.00)
Duration of surgery (minutes)*		1.02 (1.00–1.03)
Skin closed with staples		0.84 (0.48–1.47)

BMI, body mass index; CI, confidence interval; OR, odds ratio.
*Continuous variable.

present large-scale randomised controlled trial demonstrates that prophylactic iNPWT reduces surgical site infections in obese women after caesarean section.

The decreased risk of surgical site infection may be explained by the increased microvascular blood flow introduced by iNPWT, leading to a decreased hypoxia response and thereby an improved oxidative bacterial killing mechanism in the adipose tissue.[6,32] We observed a decreased amount of wound exudate in the iNPWT arm, which might be explained by a combination of reduction in tissue oedema, increased blood flow and lymph clearance.[7,9] No difference in wound dehiscence was demonstrated. A caesarean section incision is without stretch or tension and does not carry a high risk of dehiscence. Our finding is in accordance with a cohort study where minor wound dehiscence was equally distributed between iNPWT and control groups.[33]

The health-related quality of life did not differ between the iNPWT and the standard arm. However, the study was not empowered to demonstrate a statistically significant difference in quality-adjusted life years.

Conclusion

Prophylactic iNPWT reduces the risk of surgical site infection compared with standard postsurgical dressings in women with a prepregnancy BMI >30 kg/m^2 giving birth by caesarean section.

Disclosure of interests

NH, JAS and CB have received funding or honoraria from the company Smith & Nephew. PGO was funded by The Novo Nordisk Foundation. The Novo Nordisk Foundation did not have any influence on this work. Full disclosure of interests available to view online as supporting information.

Contribution to authorship

NH, OM, CAV, MK, CB, JAS, RFL, CW and JSJ made substantial contributions to the design and drafting of this article. NH, CAV, LNH, MHI, JBL, PGO, CR and MT carried out the study. NH, MK and CW contributed to the analysis of the data. All authors revised and approved this final version for publication. NH is guarantor for the trial report.

Details of ethics approval

The study was approved by the Regional Scientific Ethical Committees for Southern Denmark on April 9, 2013 (S-20130010) and the Danish Data Protection Agency on

March 13, 2013 (2008-58-0035) and was registered at ClinicalTrials.gov (NCT 01890720).

Funding

Funding for this peer-reviewed, investigator-initiated clinical trial was provided by grants from the University of Southern Denmark, Odense University Hospital, the Region of Southern Denmark, Lundbeckfonden, and an unrestricted grant from the iNPWT device manufacturer Smith & Nephew (devices and operating funding). None of these sources of funds had an influence on study design, data collection, data analyses, interpretation of results or writing of the report.

Acknowledgements

We thank the women who participated in this randomised trial, which was made possible by the collaborative efforts of nurses, midwives and physicians at the recruiting hospitals. The authors also thank the independent data monitoring committee, (Professor Jesper Hallas and Professor Aleksander Krag) for their contribution and Professor Asbjørn Hróbjartsson for his comments on the manuscript.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Procedures during surgery according to participating centres.

Table S2. The distribution of prognostic variables for surgical site infection between respondents and non-responders of the study questionnaire. ■

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Prophylactic negative pressure wound therapy at caesarean: are we there yet?

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Linked article: This is a mini commentary on N Hyldig et al., pp. 628–635 in this issue. To view this article visit https://doi.org/10.1111/1471-0528.15413

Prophylactic negative pressure wound therapy (NPWT) has emerged as a promising intervention in patients at high risk for surgical site infection (SSI). One such group is obese gravidae, a growing population worldwide who are at high risk for both caesarean delivery and SSI. Although the precise mechanism by which NPWT aids incisional wound healing is unclear, experimental evidence suggests that it reduces bacterial contamination, oedema and exudate, increases microvascular blood flow, promotes formation of granulation tissue and reduces lateral tensile and shear stress. Data on NPWT after caesarean section have hitherto been limited to retrospective cohort and small pilot randomised controlled trials (RCT). Although some studies demonstrated benefit in reducing SSI and other wound complications, they were limited by small sample sizes, selection bias and confounding.

Hyldig et al. conducted a multicentre RCT comparing NPWT with the PICO™ device (n = 432) to standard dressing (n = 444) in obese (body mass index ≥30 kg/m^2) women after caesarean delivery in five hospitals in Denmark (Hyldig et al. *BJOG* 2018 (2018-RCT-21679)). The primary outcome, SSI within the first 30 days, was reduced by 50% from 9.2% with standard dressing to 4.6% with NPWT. The use of NPWT also reduced wound exudates, with no impact on endometritis and wound dehiscence. In an accompanying trial-based economic evaluation, NPWT appeared to possibly be cost saving, particularly for women with a body mass index ≥35 kg/m^2 (Hyldig et al. *BJOG* 2019; 126:628–35.

These data are an important contribution to the evidence-base for the use of NPWT after caesarean delivery. The multicentre randomised design and sample size of over 800 women are strengths of the study. Given that the current US Food and Drug Administration-cleared prophylactic single-use NPWT devices cost between $200 (PICO™) and $500 (Prevena™) on average per unit, cost is an important consideration. The economic analysis presented here is a significant improvement upon the model-based cost-effectiveness analyses that were conducted before the availability of RCT data on the efficacy of NPWT after caesarean delivery (Echebiri et al. *Obstet Gynecol* 2015;125:299–307; Tuffaha et al. *J Surg Res* 2015;195:612–12). However, although the sample size of over 800 is the largest to date, it remains modest. Moreover, the patient population of largely young obese Caucasian women without comorbidities limits the generalisability of the findings to other settings.

So are we there yet? A meta-analysis of four small RCTs with sample sizes ranging from 87 to 535 suggested that use of NPWT after caesarean delivery in high-risk patients significantly reduced the risk of SSI (pooled relative risk 0.55; 95% CI 0.35–0.87; Yu et al. *Am J Obstet Gynecol* 2018;218:200–10.e1). Together with data from the RCT by Hyldig et al., the evidence in support of NPWT after caesarean is increasing. However, the studies are clinically heterogeneous with small to moderate sample sizes and limited generalisability. Results of ongoing large multicentre RCTs in the USA and Australia enrolling a more diverse range of participants will help clarify the role of NPWT after caesarean delivery (NCT03009110; ACTRN12615000286549).

Disclosure of interests

Dr Tuuli is supported by a National Institutes of Health grant R01HD086007 and supplemental funding from Acelity for an ongoing multicentre trial testing the effectiveness of prophylactic negative pressure wound therapy after caesarean delivery in obese women. A completed disclosure of interests form is available to view online as supporting information. ■