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Cost-effectiveness of single-layer versus double-layer uterine closure during caesarean section on postmenstrual spotting: economic evaluation alongside a randomised controlled trial

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ABSTRACT

Objective To evaluate the cost-effectiveness of double-layer compared with single-layer uterine closure after a first caesarean section (CS) from a societal and healthcare perspective.

Design Economic evaluation alongside a multicentre, double-blind, randomised controlled trial.

Setting 32 hospitals in the Netherlands, 2016–2018.

Participants 2292 women ≥18 years undergoing a first CS were randomly assigned (1:1). Exclusion criteria were: inability for counselling, previous uterine surgery, known menstrual disorder, placenta increta or percreta, pregnant with three or more fetuses. 1144 women were assigned to single-layer and 1148 to double-layer closure. We included 1620 women with a menstrual cycle in the main analysis.

Interventions Single-layer unlocked uterine closure and double-layer unlocked uterine closure with the second layer imbricating the first.

Main outcome measures Spotting days, quality-adjusted life-years (QALYs), and societal costs at 9 months of follow-up. Missing data were imputed using multiple imputation.

Results No significant differences were found between single-layer versus double-layer closure in mean spotting days (1.44 and 1.39 days; mean difference (md) −0.056, 95% CI −0.374 to 0.263), QALYs (0.663 and 0.658; md −0.005, 95% CI −0.015 to 0.005), total healthcare costs (€744 and €727; md €−17, 95% CI −273 to 143), and total societal costs (€5689 and €5927; md €238, 95% CI −624 to 1108). The probability of the intervention being cost-effective at willingness-to-pay of €0, €10 000 and €20 000/QALY gained was 0.30, 0.27 and 0.25, respectively, (societal perspective), and 0.55, 0.41 and 0.32, respectively, (healthcare perspective).

Conclusion Double-layer uterine closure is not cost-effective compared with single-layer uterine closure from both perspectives. If this is confirmed by our long-term reproductive follow-up, we suggest to adjust uterine closure technique guidelines.

Trial registration number NTR5480/NL5380.

Strengths and limitations of this study

► This study has been performed alongside a large multicentre randomised controlled trial, which is considered the best vehicle for economic evaluations.
► We prospectively collected data regarding costs and effect, and we used patient level information.
► All relevant costs for decision making were included in the analysis, to conduct an analysis from a societal perspective.
► Possible recall bias due to retrospective self-reported questionnaire over 3-month and 6-month period.
► Generalisability of the results to other populations may be limited, as other healthcare practices and payment systems may exist.

INTRODUCTION

Caesarean section (CS) rates rise globally and is the mode of delivery for approximately one in five live births globally.[1 2] As a consequence, a rise in morbidity related to CS is observed as well.[3] Severe morbidity associated with a subsequent pregnancy includes caesarean scar pregnancy, placenta accreta spectrum disorders and uterine rupture. However, less severe but more prevalent gynaecological morbidity related to a CS have recently gained more interest as well. Chronic maternal morbidity after CS includes dysmenorrhoea and abnormal uterine bleeding, which are both associated with a sonographically visible indentation at the site of the previous uterine incision.[4–6] This indentation is called a niche and is seen in approximately 60% of women after CS.[7 8] Of them, 30% develops abnormal uterine bleeding and more specifically, postmenstrual spotting.[5 6] This is brownish

discharge at the end of the menstruation or blood loss in between two menstruations that is limiting women in daily life.[5] Over the last years, an increase in the development of medical treatments and surgical procedures to treat or remove the niche is observed, primarily aiming to reduce spotting.[9]

CS is the most common major surgical intervention.[10] However, there is no international guideline on the most optimal way to close the uterine incision while the specific closure technique may influence healing of the uterine wound. A specific issue on which no consensus exists is whether to use single-layer or double-layer closure of the uterine layers.[11 12] When comparing these techniques, no differences were found at short-term except for longer operation time after double-layer closure.[13 14] Nevertheless, previous studies also suggested that double-layer closure may result in better uterine scar healing and lower prevalence of large niches thereby possibly leading to lower medical costs than single-layer closure.[13 15] There is, however, a lack of studies on uterine closure techniques and their impact on maternal health outcomes related to gynaecological symptoms.[14] The impact of different uterine closure techniques on healthcare utilisation, informal care and lost productivity costs has never been investigated previously. As decision-makers increasingly demand evidence of cost-effectiveness (CE) of healthcare interventions, conducting economic analysis alongside clinical trials is desirable because it allows the prospective collection of cost and effect data and the use of patient level information for drawing inferences about additional costs and benefits of interventions.[16] In addition, regulatory and reimbursement agencies of many countries consider evidence of economic value along with clinical effectiveness.[16]

Therefore, the aim of this study was to perform a CE analysis of double-layer compared with single-layer uterine closure after a first CS from both a societal and healthcare perspective. We hypothesised that double-layer closure would reduce postmenstrual spotting and total societal and healthcare costs compared with single-layer closure as a result of less morbidity, despite slightly higher intervention costs of double-layer closure.

METHODS
Study design
An economic evaluation was performed alongside a multi-centre randomised controlled superiority trial comparing double-layer closure and single-layer uterine closure after a first CS. The study protocol and the effect paper have been published elsewhere[17 18] No substantial changes were made to the protocol after commencement of the trial.[17] This trial-based economic evaluation is reported according to the Consolidated Health Economic Evaluating Reporting Standards statement.[19]

Target population
All women who underwent a first CS, planned or unplanned, at one of the participating hospitals were asked to participate in the study. Inclusion criteria were sufficient command of the Dutch or English language, age 18 years or older and written informed consent. Exclusion criteria were: inadequate possibility for counselling (eg, indication for emergency CS without being informed about the study previously, women in severe pain without adequate therapy), previous major uterine surgery (eg, laparoscopic or laparotomic fibroid resection, septum resection), women with known causes of menstrual disorders (eg, cervical dysplasia, communicating hydrosalpinx, uterine anomaly or endocrine disorders disturbing ovulation), placenta increta or percreta during the current pregnancy, or three or more fetuses during the current pregnancy. After informed consent had been signed and a CS was indicated, participants were randomly allocated to receive single-layer (control) or double-layer (intervention) closure of the uterine incision in a 1:1 ratio. Due to the nature of the treatment, surgeons performing the CS were not masked to the allocated method. Participants and sonographers were blinded to the allocation, researchers and statisticians were not. Detailed information about study design and randomisation can be found in the study protocol.[17]

Choice of health outcomes
For this trial-based economic evaluation, two main health outcomes were used: postmenstrual spotting (referred to as spotting days in this paper) and quality-adjusted life-years (QALYs) at nine months after CS. Spotting days was chosen because it has been strongly related to a niche[5 6] (ie, an indentation at the site of the caesarean scar with a depth of at least 2 mm[20]), which may be influenced by uterine closure technique.[8] QALY is routinely used as a summary outcome measure of health in economic evaluations, because it incorporates the impact of interventions on both the quantity and quality of life,[21] and allows decision-makers to compare the effectiveness and CE of a range of interventions for different health conditions.[22]

Study perspective and time horizon
This trial-based economic evaluation was performed from a societal and a healthcare perspective over a time horizon of nine months. Therefore, discounting of costs and effects was not necessary. When a healthcare perspective is adopted, only the intervention costs and costs related to healthcare utilisation are included in the analysis.[23] For the societal perspective, costs related to informal care and productivity losses are included in addition to intervention and healthcare utilisation costs.[23]

Setting and location
In total, 32 hospitals in the Netherlands, both academic (n=6) and non-academic (n=26), collaborating within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (Consortium 2.0, www.zorgevaluatienederland.nl), participated in this study.[17] In the Netherlands, a CS is only performed in a hospital setting. In most cases, without maternal or

neonatal complications, women will be discharged from the hospital after a CS after two or three days. All costs regarding the CS and admission days are standard care and are paid by an individual's health insurance. Maternity leave of at least ten weeks is regulated through the Employee Insurance Agency. Paternity leave is limited to one week. The first eight days after delivery, a maternity nurse visits the family at least three hours a day.

Control and intervention condition

The control group underwent single-layer closure of the uterus using unlocked continuous running multifilament sutures, which is the usual care provided by hospitals in the Netherlands.[17] In the intervention group, double-layer closure of the uterine incision was performed using unlocked multifilament continuous running sutures for both layers and the endometrial layer was included in the first layer. The second layer was a continuous running suture that imbricated the first. A mandatory online instruction video was shown to all surgeons in participating hospitals prior to participation for the intervention group. The exact procedures in both study arms regarding uterine closure are described in the study protocol.[17]

At baseline, data were collected on sociodemographic characteristics for all participants.[17]

Outcomes

Health outcomes

Spotting days was the primary outcome of the trial, and was defined as number of days with brownish discharge for more than two days at the end of the menstruation, with a total duration (menstruation and spotting) of more than seven days, or intermenstrual blood loss that started after the end of the menstruation.[5] Spotting days were self-reported by participants through a digital questionnaire at nine months after CS, including a calendar on which women could record daily blood loss during one month. Women who reported that they had no blood loss were classified as amenorrhoeic.

Health-related quality of life was measured using the EuroQol five dimensions five levels (EQ-5D-5L) at baseline, and at three and nine months after CS.[24] The EQ-5D-5L has five dimensions of quality of life (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) using five response levels (ie, no problems, slight problems, moderate problems, severe problems or extreme problems) describing 3125 health states.[24] The participants' health states obtained from EQ-5D-5L responses were converted into utility values using the Dutch tariff.[25] The utility values were used to calculate QALYs by means of the area under the curve method (ie, the duration of a health state is multiplied by the utility related to that health state).

Cost outcomes

Intervention costs

The average costs of performing a CS reported by the participating hospitals was €5360. The intervention incurred additional suture material and additional operation time (3.9 minutes on average). The costs of additional resources were obtained from the academic and non-academic hospitals using a bottom-up approach. On average, the intervention resulted in additional costs of €95.79 per participant in academic hospitals and €71.14 per participant in non-academic hospitals (online supplemental table S1).

Healthcare utilisation and informal care costs

A specifically adapted version of the iMTA Medical Cost Questionnaire (iMCQ)[26] was used to measure healthcare utilisation and care provided by family and/or friends (ie, informal care) using 3-month and 6-month recall periods at three and nine months of follow-up, respectively. The iMCQ is a standardised generic instrument for measuring medical costs including questions related to healthcare utilisation and informal care.[26] Healthcare utilisation was valued using prices from the Dutch costing guideline.[27] Healthcare utilisation costs included primary care costs (eg, costs of visits to general practitioners, health professionals and complementary healthcare providers), secondary care costs (eg, costs of ambulatory hospital visits, visits to other healthcare organisations and admissions to the hospital), and medication costs. Secondary care costs were recorded after discharge from the hospital. The average costs of performing the CS included the operation and hospital stay until discharge and were, therefore, not included in the secondary care costs to avoid double counting.

The informal care costs were based on the amount of time the participant needed help in performing household tasks or received care from family and/or friends, because of health problems. Dutch standard prices were used for informal care costs.[27] Medication use was valued using data from the Dutch Healthcare Institute (www.medicijnkosten.nl).[28]

Lost productivity costs

The iMTA Productivity Cost Questionnaire (iPCQ)[29] was used to measure self-reported sickness absenteeism from paid and unpaid work, and presenteeism using 3-month and 6-month recall periods at three and nine months of follow-up, respectively. The iPCQ is a standardised generic questionnaire to measure productivity costs and it is applicable to national and international studies.[29] The friction cost approach (FCA) was used to calculate sickness absenteeism costs from paid work.[30] The FCA assumes that sickness absenteeism costs are limited to the period needed to replace an absent, sick worker (the friction period), which has been estimated to be 12 weeks (85 days) in the Netherlands.[27] Gender-specific estimates of the mean wages of the Dutch population were used to calculate sickness absenteeism costs from paid work.[27]
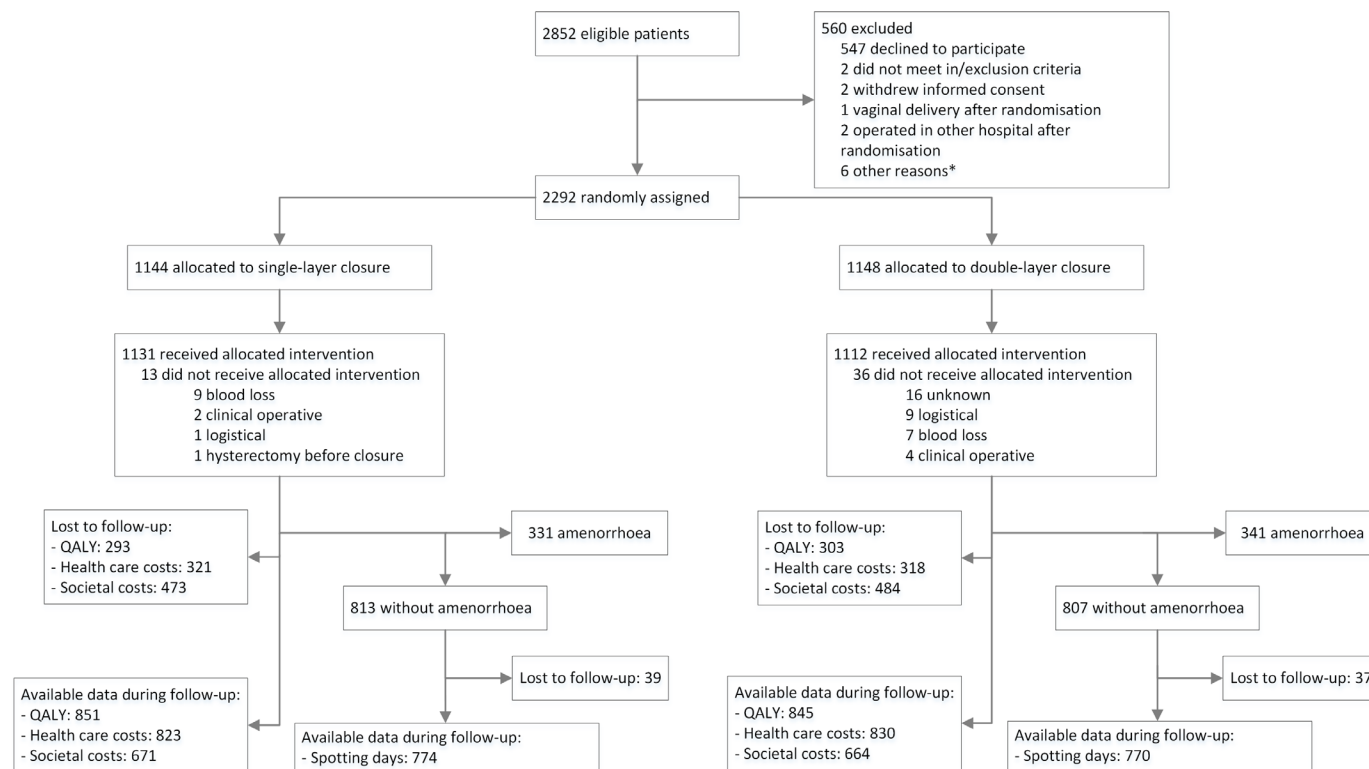
Figure 1 Trial profile. *Logistical reasons, computer randomisation issues, passing through the allocated method to operating gynaecologist, or participant not traceable after randomisation. QALYs, quality-adjusted life-years.

To measure sickness absenteeism from unpaid work, the participants were asked whether they had difficulty in performing unpaid work activities due to sickness (eg, household tasks, childcare, voluntary work), and if that was the case, for how many hours.[29] Costs related to sickness absenteeism from unpaid work were valued using a shadow price for legally employing a domestic assistant.[29] To measure participants' level of presenteeism, participants rated how efficiently they worked while suffering from health complaints on a scale from 0 (I was unable to do anything) to 10 (I was able to do as much as usual). The resulting efficiency score was used to calculate presenteeism costs: Presenteeism costs=number of days working with complaints * [1 - (efficiency score / 10)] * number of working hours per day * gender-specific mean wage rates.[31]

Statistical analysis

The main analyses included all participants with a menstrual cycle (ie, participants with amenorrhoea for any reason were excluded) at nine months follow-up.

Analyses were performed according to the intention-to-treat principle using StataSE V.16 (Stata). Multiple imputation by chained equations, stratified by group allocation, was used to impute missing data. Variables associated with missingness and outcomes as well as potential confounders were included in the imputation model such as age, body mass index, level of education, parity, previous miscarriage, gestational age at CS, hypertension, diabetes, use of contraception and breast feeding.

Predictive mean matching was used in the imputation procedure to account for the skewed distribution of the costs.[32] The number of imputations was increased until there was a loss of efficiency of ≤5%, resulting in 20 imputed datasets.[32 33] The 20 datasets were analysed separately and estimates were pooled using Rubin's rules.[34] After multiple imputation, amenorrhoeic women were excluded from the analyses as a priori decided, because the outcome spotting days could not be evaluated in these women.[17]

Differences in costs and effects between treatment groups at 9 months follow-up were estimated using seemingly unrelated regression analyses, which accounts for the correlation between costs and effects.[35] The intraclass correlation coefficient (ICC, ie, the variation around the subjects belonging to the same hospital cluster divided by the total variance between hospitals)[36] was small (ICC=0.004). This means that hardly any of the variance in the outcome measure was accounted for by clustering at the level of the hospital. In addition to the small ICC, patients were randomised at the individual level and not at the hospital level. Therefore, multilevel analysis was not necessary. Incremental cost-effectiveness ratios were calculated by dividing the difference in costs (ie, total societal costs and total healthcare costs) between groups by the difference in effects.

Bias-corrected accelerated bootstrapping with 5000 replications was used to estimate the joint uncertainty surrounding differences in costs and effects.

Bootstrapped cost-effect pairs were plotted on CE planes.[37] Cost-effectiveness acceptability curves were estimated that show the probability of double-layer closure being cost-effective compared with single-layer closure for a range of willingness-to-pay (WTP) thresholds (ie, the maximum amount of money society is willing to pay for a unit of effect gained).[38] For spotting days, we used a maximum WTP threshold of €253 per one day reduction. This threshold was based on the value of 8 hours of paid work given the average productivity costs per working hour for women in the Netherlands (ie, €31.6 per hour). For QALYs, we used a WTP threshold of €20 000/QALY gained recommended by the Dutch Healthcare Institute[27] and €23 420/QALY (equivalent of £20 000/QALY) recommended by the National Institute for Health and Clinical Excellence.[39]

Sensitivity analysis

Four sensitivity analyses (SA) were performed to assess the robustness of the results. SA1 consisted of a cost-effectiveness analysis (CEA) including all women randomised (ie, without excluding amenorrhoeic women) from both a societal and healthcare perspective for the QALY outcome. SA2 consisted of a complete case analysis from both a societal and healthcare perspective including only women without amenorrhoea for both spotting days and QALYs. Third, we performed per protocol analyses for both outcomes from both a societal and healthcare perspective (SA3). Finally, we performed a SA in which we adjusted for hormonal contraception and breast feeding

(exclusively or combined with formula) at nine months of follow-up (SA4).

Patient and public involvement

The Dutch gynaecological patients' association agreed on the design of the study and the grant proposal for funding. They were not involved in outcome measures or recruitment, and they were not asked to give advice in the interpretation of the results. We will disseminate the study results to all participants, and to the public through popular science articles.

RESULTS

Participants

In total, 2292 women undergoing a first CS were included. Of them, 1144 participants were randomised to single-layer and 1148 participants to double-layer closure of the uterine incision. In the single-layer group, 694 (60.7%) participants underwent planned CS, and in the double-layer group this was done in 705 (61.4%) participants.

In total, 672 women reported amenorrhoea (n=331 in control and n=341 in intervention group), resulting in 1620 women reported having menstrual blood loss over 9 months of follow-up and were included in the main analyses (n=813 in control and n=807 in intervention group) (figure 1). Of all women included in the main analysis (n=1620), 95% had completed follow-up data for spotting days (n=1544, 774 in control group and 770 in intervention group). Within the total group (n=2292), complete follow-up data were available for 74% of QALYs (n=1696, 851 in control group and 845 in intervention group), for 72% of total healthcare costs (n=1653, 823 in control group and 830 in intervention group), and for 58% of total societal costs (n=1335, 671 in control group and 664 in intervention group) (figure 1). At baseline, no meaningful differences were found between both groups (table 1). At nine months follow-up, 12.1% of women in the single-layer arm and 17.1% of women in the double-layer arm were breastfeeding their children. In the single-layer arm, 40.3% of the participants used hormonal contraceptives at nine months follow-up, and in the double-layer arm this was 38.2%. Participants with complete follow-up were more likely to be nulliparous and to have a higher education level compared with participants without complete follow-up.

Effectiveness

There were no statistically significant differences between groups in spotting days (mean difference −0.056, 95% CI −0.374 to 0.263) and QALYs (mean difference −0.005, 95% CI −0.015 to 0.005) at nine months follow-up (table 2).

Costs

The main contributors to total societal costs in both groups were lost productivity costs (€5689 in control group and €5927 in intervention group) and healthcare

Table 1	Baseline characteristics of women without amenorrhoea in the control group and intervention group	
	Single layer (n=813)*	Double layer (n=807)†
Age, years	32.1 (4.7)	32.0 (4.6)
Level of education		
Low	50 (6.5)	54 (7.1)
Middle	263 (34.2)	242 (31.8)
High	452 (58.8)	457 (60.0)
Nulliparous women	568 (73.9)	578 (75.9)
BMI (kg/m^2)	26.4 (4.5)	26.7 (4.9)
Smoking habit	44 (5.7)	37 (4.9)
Hypertension	146 (19.0)	127 (16.7)
Diabetes mellitus	89 (11.6)	66 (8.7)
Gestational age	38.6 (2.4)	38.6 (2.3)
Previous miscarriage	255 (33.2)	221 (29.0)
Previous ectopic pregnancy	10 (1.3)	12 (1.6)
Planned CS	504 (62.0)	503 (62.3)

Data are mean (SD) or n (%). N is equal to the total number of patients in the group.
*5.5% missing data for all variables, except 'planned CS' (0%).
†5.9% missing data for all variables, except 'planned CS' (0%).
BMI, body mass index; CS, caesarean section.

Table 2 Multiply imputed mean effects and costs by group and mean difference at 9 months follow-up in women without amenorrhoea

	Single layer (n=813)	Double layer (n=807)	Mean difference* (95% CI)
Effects			
Spotting days	1.44 (0.11)	1.39 (0.11)	−0.056 (−0.374 to 0.263)
QALYs gained	0.663 (0.003)	0.658 (0.004)	−0.005 (−0.015 to 0.005)
Costs			
Intervention costs†	0	76 (0.31)	76 (75 to 76)
Primary care costs	255 (16)	250 (17)	−5 (−49 to 40)
Secondary care costs	400 (75)	317 (44)	−83 (−292 to 38)
Medication costs	89 (84)	84 (23)	−5 (−103 to 70)
Total healthcare costs‡	744 (112)	727 (58)	−17 (−273 to 143)
Informal care costs	77 (18)	124 (33)	47 (−10 to 141)
Absenteeism costs at paid work	1052 (122)	1009 (110)	−42 (−34 to 261)
Absenteeism costs at unpaid work	3525 (226)	3810 (263)	284 (−360 to 964)
Presenteeism costs	290 (26)	256 (24)	−34 (−98 to 28)
Total lost productivity costs	4857 (280)	5076 (299)	208 (−574 to 999)
Total societal costs§	5689 (321)	5927 (324)	238 (−624 to 1108)

Data are mean (SE). Multiple imputation model consisted of age, education level, parity, body mass index, smoking habit, hypertensive disorder, diabetic status, gestational complications, gestational age, previous miscarriage or ectopic pregnancies, use of contraception, breastfeeding and self-reported menstrual blood loss.
Primary care: costs of visits to general practitioners, health professionals, and complementary healthcare providers. Secondary care: costs of ambulatory hospital visits, visits to other healthcare organisations and hospital admissions. Medication costs: costs of medication use after discharge from the hospital. Informal care costs: costs of received care from family and/or friends due to health problems. Absenteeism costs at paid work: costs of sickness absenteeism from paid work. Absenteeism costs at unpaid work: costs of absenteeism from unpaid work activities (eg, household tasks, childcare, voluntary work). Presenteeism costs: costs of working while suffering from health complaints.
*Cost and effect differences at nine months follow-up were estimated using seemingly unrelated regression analyses.[35]
†Additional intervention costs to perform double-layer, excluding the average costs for performing a caesarean section (€5360,-).
‡The sum of intervention, primary care, secondary care and medication costs.
§The sum of total healthcare costs, informal care costs and lost productivity costs.
QALY, quality-adjusted life-years.

costs (€744 in control group and €727 in intervention group, table 2). There were no differences in days of hospital stay between the groups.[18] Costs associated with absenteeism from unpaid work due to sickness (ie, costs related to getting help to perform household tasks, childcare, voluntary work) was the largest contributor to lost productivity costs in both groups (€3525 in control group and €3810 in intervention group). Secondary care costs were the largest contributor to total healthcare costs in both groups (€400 in control, group and €317 in intervention group). During the follow-up, there were no statistically significant differences between groups in total healthcare costs (€−17, 95% CI −273 to 143) and total societal costs (€238, 95% CI −624 to 1108, table 2). Presenteeism costs were not statistically significantly different in the intervention group compared with the control group (€−34, 95% CI −98 to 28, table 2).

CE analysis

From a societal perspective, most bootstrapped cost-effect pairs (44%) were in the North East Quadrant of the CE-plane for spotting days (table 3, figure 2A). The probability of double-layer closure being cost-effective compared with single-layer was 0.30 at a WTP of €0/ spotting day less and 0.31 at €253/spotting day less (figure 2B). For QALYs, most of the bootstrapped cost-effect pairs (62%) was in the North West Quadrant of the CE-plane (table 3, figure 2C). The probability of double-layer closure being cost-effective compared with single-layer at both the Dutch WTP threshold of €20 000/QALY gained, and the UK WTP threshold of €23 420/QALY gained, was 0.25 from a societal perspective (figure 2D, online supplemental table S2).

From a healthcare perspective, bootstrapped cost-effect pairs were equally distributed among the Eastern and Western quadrants of the CE-plane for spotting days (table 3, figure 2E). This shows that uncertainty around costs and effects is large. The CEAC presented in figure 2E2F shows that if the WTP for one spotting day less is €0, the probability of double-layer closure being cost-effective in comparison with single-layer was 0.55. This probability increases to 0.59 if the WTP is €253/spotting day less (online supplemental table S2). For QALYs, from

Table 3 Results of the cost-effectiveness analysis

Effect outcome*	Cost difference, € (95% CI)	Effect difference (95% CI)	ICER €/ effect gained	Distribution of the cost-effectiveness plane			
				North East	South East	South West	North West
Main analysis—societal perspective							
Spotting days	238 (−624 to 1108)	0.056 (−0.263 to 0.374)	4281	44%	20%	10%	26%
QALY	238 (−624 to 1108)	−0.005 (−0.015 to 0.005)	−49699	8%	9%	21%	62%
Main analysis—healthcare perspective							
Spotting days	−17 (−283 to 146)	0.056 (−0.263 to 0.374)	−311	30%	34%	18%	18%
QALY	−17 (−283 to 146)	−0.005 (−0.015 to 0.005)	3614	6%	10%	42%	42%
SA1—including all women randomised—societal perspective							
QALY	150 (−764 to 944)	−0.006 (−0.014 to 0.002)	−25696	4%	6%	30%	60%
SA1—including all women randomised—healthcare perspective							
QALY	−235 (−1230 to 84)	−0.005 (−0.014 to 0.004)	46765	3%	10%	66%	21%
SA2—complete-case analysis—societal perspective							
Spotting days	346 (−641 to 1394)	0.149 (−0.452 to 0.138)	2324	69%	18%	3%	10%
QALY	313 (−671 to 1382)	0.006 (−0.016 to 0.003)	50787	73%	17%	5%	5%
SA2—complete-case analysis—healthcare perspective							
Spotting days	−9 (−251 to 174)	0.186 (−0.486 to 0.103)	−46	54%	37%	4%	5%
QALY	1 (−256 to 172)	0.007 (−0.016 to 0.002)	80	59%	34%	4%	3%
SA3—per-protocol analysis—societal perspective							
Spotting days	43 (−820 to 903)	0.043 (−0.274 to 0.361)	1008	32%	29%	17%	22%
QALY	43 (−820 to 903)	0.004 (−0.006 to 0.013)	11909	47%	31%	15%	7%
SA3—per-protocol analysis—healthcare perspective							
Spotting days	−39 (−301 to 126)	0.043 (−0.2748 to 0.361)	−909	23%	38%	23%	16%
QALY	−39 (−301 to 126)	0.004 (−0.006 to 0.013)	−10745	32%	45%	16%	7%
SA4—main analysis adjusted—societal perspective							
Spotting days	226 (−633 to 1092)	0.046 (−0.277 to 0.369)	4961	41%	19%	12%	28%
QALY	226 (−633 to 1092)	−0.004 (−0.014 to 0.006)	−58497	10%	11%	20%	59%
SA4—main analysis adjusted—healthcare perspective							
Spotting days	−11 (−267 to 154)	0.046 (−0.277 to 0.369)	−248	29%	31%	19%	21%
QALY	−11 (−267 to 154)	−0.004 (−0.014 to 0.006)	2925	9%	13%	37%	41%

Data are mean (95% CI).
Main analysis: CEA from a societal and a healthcare perspective for spotting days and QALY including only women without amenorrhoea (total=1620, control n=813, intervention n=807).
SA1: CEA from a societal and a healthcare perspective for QALY, including all women randomised in the study after multiple imputation (ie, without excluding amenorrhoeic women, n=2292) (online supplemental table S3)).
SA2: CEA from a societal perspective using complete cases for spotting days and total societal costs (total=1065, control n=544, intervention n=521) including only women without amenorrhoea (n=1620).
SA2: CEA from a societal perspective using complete cases for QALY and total societal costs (total=1057, control n=541, intervention n=516) including only women without amenorrhoea (n=1620).
SA2: CEA from a healthcare perspective using complete cases for spotting days and total healthcare costs (total=1315, control n=662, intervention n=653) including only women without amenorrhoea (n=1620).
SA2: CEA from a healthcare perspective using complete cases for QALY and total healthcare costs (total=1310, control n=657, intervention n=653) including only women without amenorrhoea (n=1620).
SA3: per-protocol analysis for spotting days and QALY from a societal perspective (total=1620, control n=828, intervention n=792) including only women without amenorrhoea (n=1620).
SA3: per-protocol analysis for spotting days and QALY from a healthcare perspective (total=1620, control n=828, intervention n=792) including only women without amenorrhoea (n=1620).
SA4: main analysis adjusted for the use of contraception and breastfeeding during follow-up from a societal and a healthcare perspective (total=1620, control n=813, intervention n=807).
*The effect outcome 'spotting days' was multiplied by −1 in the cost-effectiveness analysis to keep the CE-plane interpretable.
CE, cost-effectiveness; CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SA, sensitivity analysis.
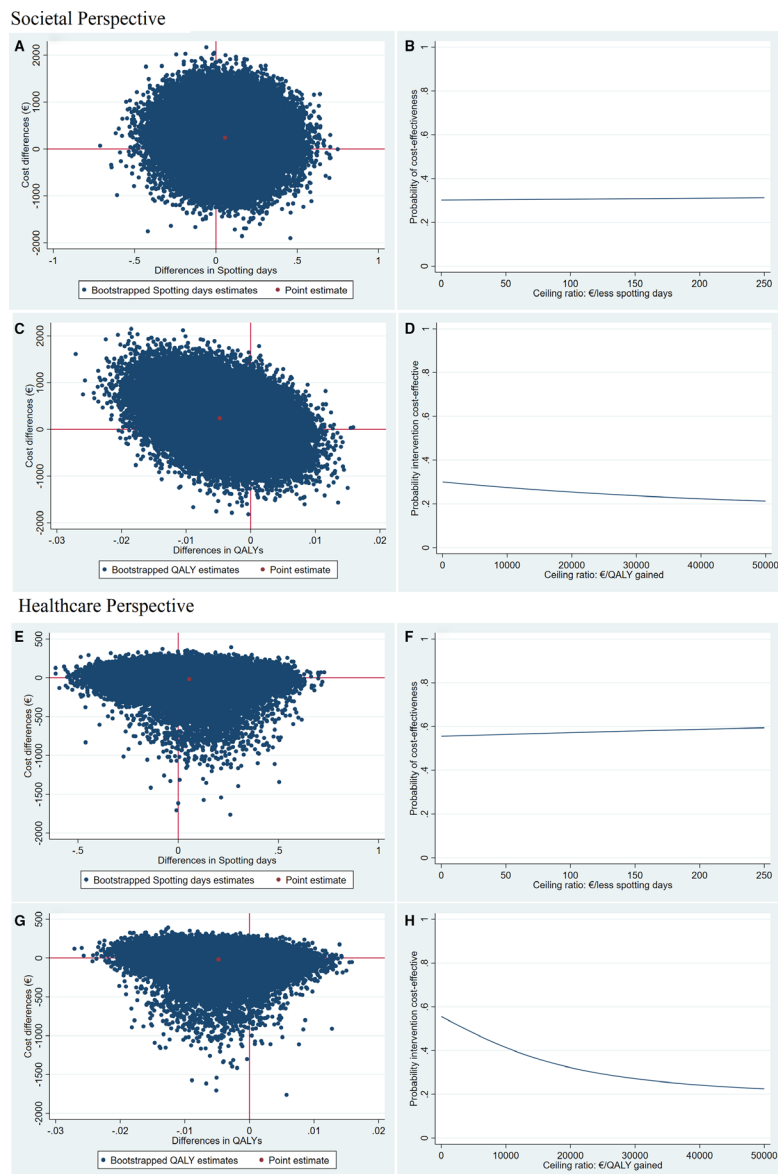
Figure 2 Cost-effectiveness planes and cost acceptability curves from a societal and healthcare perspective comparing double-layer to single-layer uterine closure. (1) Cost-effectiveness plane (CE plane) showing the incremental cost-effectiveness ratio point estimate (ICER, red dot) and the distribution of the 5000 replications of the bootstrapped cost-effective pairs (blue dots). (2) Cost-effectiveness acceptability curve (CEAC) indicating the probability of double-layer uterine closure being cost-effective compared with single-layer closure (y-axis) for different willingness-to-pay (WTP) thresholds per unit of effect gained (x-axis). (A) CE plane for spotting days from a societal perspective showing that most of bootstrapped cost-effect pairs were equally distributed across CE plane quadrants representing high uncertainty around ICER. (B) CEAC for spotting days from a societal perspective indicating a steady 0.2 probability of double-layer uterine closure being cost-effective compared with single-layer closure for different WTP thresholds per fewer spotting days. (C) CE plane for QALYs from a societal perspective showing that most of the bootstrapped cost-effect pairs were in the Northern quadrants (ie, higher costs) and Western quadrants where double-layer uterine closure was less effective compared with single-layer closure. (D) CEAC for QALYs from a societal perspective indicating a probability of double-layer uterine closure being cost-effective around 0.2 for different WTP thresholds per QALY gained. (E) CE plane for spotting days from a healthcare perspective showing that most of the bootstrapped cost-effect pairs were in Southern quadrants, where double-layer uterine closure was less costly compared with single-layer closure, but they are equally distributed across the Eastern and Western quadrants representing high uncertainty around the effectiveness of double-layer uterine closure compared with single-layer closure. (F) CEAC for spotting days from a healthcare perspective indicating a steady 0.6 probability of double-layer uterine closure being cost-effective compared with single-layer closure for different WTP thresholds per fewer spotting days. (G) CE-plane for QALYs from a healthcare perspective showing that most of the bootstrapped cost-effect pairs were in the Southern quadrants (ie, lower costs) and Western quadrants where double-layer uterine closure was less effective compared with single-layer closure. (H) CEAC for QALYs from a healthcare perspective indicating that the probability of double-layer uterine closure being cost-effective compared with single-layer closure decreased with an increasing of the different WTP thresholds per QALY gained because healthcare costs were on average lower in the intervention group while it is less effective compared with the usual practice.

a healthcare perspective, most of bootstrapped cost-effect pairs were in the North West Quadrants of the CE-plane (table 3, figure 2G). The probability of double-layer closure being cost-effective compared with single-layer closure at the Dutch and UK WTP threshold (€20 000 and €23 420/QALY gained, respectively) was 0.41 from a healthcare perspective (table 3, figure 2G2H).

The results of the SA were similar to those of the main analysis (table 3).

DISCUSSION

The results of this trial-based economic evaluation showed that double-layer uterine closure after a first CS did not significantly decrease spotting days nor improve QALYs compared with single-layer closure at nine months follow-up. In addition, total healthcare costs and societal costs related to double-layer closure did not significantly differ from single-layer closure. Low probabilities of double-layer closure being cost-effective in comparison with single-layer closure were found for all relevant WTP thresholds. Therefore, double-layer closure was not considered cost-effective compared with single-layer closure after a first CS from a societal and a healthcare perspective.

Comparison with previous studies

The results of this economic evaluation are not in line with our hypothesis, which was based on previously conducted observational studies[5 6 40] and meta-analyses.[14] These showed that single-layer closure resulted in thinner residual myometrium and a higher proportion of large niches than double-layer closure. These sonographical findings, or surrogates, were suggested to lead to more postmenstrual spotting and, therefore, higher related costs. Although double-layer closure resulted in increased CS costs, these costs were neutralised by higher secondary care and presenteeism costs in the single-layer closure group, resulting in no overall difference in total healthcare costs or total societal costs.

To the best of our knowledge, this is the first study evaluating the CE of double-layer closure in comparison with single-layer closure after a CS. The largest study (n=15 935) on this topic mentioned possible cost savings but no CE analysis was performed.[41] The second largest study (n=3033) comparing single-layer versus double-layer closure in a factorial randomised controlled trial hypothesised on a possible reduction in costs in their study protocol, since a CS is conducted so frequently that 'any difference in morbidity is likely to have significant cost and community effects'. The authors found a difference in operative time, though they did not discuss costs in the 2010 publication, and it is unlikely that a CE analysis is going to be performed.[42]

Based on the current and previous studies,[43 44] we recommend to leave the choice of uterine closure technique with the preference of the surgeon. Previous studies reported only short-term maternal outcomes in the first few weeks after CS.[42–44] We confirmed these findings using a follow-up of nine months after CS. In addition, we showed that there is no difference in costs between the two types of closure. Our three years follow-up results will show whether double-layer is superior compared with single-layer closure with regard to long-term outcomes. These outcomes include fertility outcomes, pregnancy complications and mode of delivery, as well as safety outcomes such as uterine dehiscence or rupture and related neonatal and maternal morbidity. In addition, a CE analysis for long-term outcomes will be performed as well. When superiority cannot be shown on the long-term either, guidelines should recommend to leave the uterine closure technique regarding single-layer versus double-layer up to the preference of the performing surgeon.

Strengths and limitations

This study was performed alongside a large multicentre randomised controlled superiority trial, which is considered the best vehicle for economic evaluations because it allows the prospective collection of cost and effect data and the use of patient level information for drawing inferences about additional costs and benefits of interventions.[16] Additionally, the CEA was conducted from a societal perspective meaning that all relevant costs for decision making (ie, intervention, healthcare utilisation, informal care and lost productivity costs) were included in the analysis.[22] Several SAs were performed, to assess the robustness of our results, which resulted in similar results as compared with the main analyses.

However, one of the limitations of this study was that the cost questionnaires included retrospective self-reported questions over a 3-month and 6-month period, which may have caused recall bias. Nevertheless, we assume that this bias is equally distributed across the two groups and does, therefore, does not impact the difference between groups. Although there is no gold standard for measuring lost productivity costs, we used a standardised instrument,[29] which is considered best practice currently.[45] Another limitation is that generalisability of the results to healthcare systems in other countries may be limited, as they may adopt different usual practices and have different payment systems.[46] Additionally, generalisability may be impaired since in our study sample relatively many planned CS were performed compared with the Dutch average,[47] probably resulting in an overall underestimation of niche related postmenstrual spotting.

Future research

It is important to realise that we have only evaluated the aspect of single-layer versus double-layer closure of the uterine incision in our trial. A CS consists of multiple steps and other aspects of the surgical technique used to perform a CS may also affect clinical outcomes and costs, and should therefore be subject to future research. Examples of uterine incision and repair are the level of hysterotomy (above or below the plica vesicouterina)[48]

and inclusion or exclusion of the endometrium in the uterine suture.

Conclusions and policy implications

In conclusion, double-layer uterine closure is not cost-effective compared with single-layer uterine closure from both a societal and healthcare perspective. Thus, from a CE point of view, there is no reason to advocate double-layer over single-layer uterine closure. Long-term follow-up will show whether guidelines should be adapted based on obstetric and reproductive outcomes of double-layer closure compared with single-layer closure.

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Supplementary appendix

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Tergooi hospital, Blaricum	Harry Visser
Zuyderland Medical Centre, Heerlen	Josje Langenveld

Supplementary tables

Table S1: Costs of the intervention per participant

Resources	Units	Unit price, €	Costs, €
Additional suture material	One piece	6.14	6.14
Additional operation time, academic hospital (3.9 minutes)	Hour	1379.27	89.65
Total costs per participant in academic hospital			95.79
Additional operation time, non-academic hospital (3.9 minutes)	Hour	1000	65.00
Total costs per participant in non-academic hospital			71.14

Table S2: Probability of the intervention being cost-effective at different willingness-to-pay thresholds for spotting days

	Main analyses – spotting days	
WTP €/ unit of effect gained	*Societal Perspective*	*Healthcare perspective*
0	0.30	0.55
31.6 (1 working hour)	0.30	0.56
126.4 (4 working hours)	0.31	0.58
252.8 (8 working hours)	0.31	0.59
	Main analyses - QALYs	
0	0.30	0.55
10000	0.27	0.41
20000	0.25	0.32
30000	0.24	0.27
40000	0.22	0.24
50000	0.21	0.22

WTP=willingness-to-pay; QALY=quality-adjusted life-years

Table S3: Description of follow-up complete cases and missing cases by effect and cost outcomes without excluding cases of amenorrhoea

	Complete cases			Missing cases (%)		
	Intervention	*Control*	*Total*	*Intervention*	*Control*	*Total*
Spotting days	936	940	1876	212 (23)	204 (22)	416 (22)
QALY	845	851	1696	303 (36)	293 (34)	596 (35)
Primary care costs	913	924	1837	235 (26)	220 (24)	455 (25)
Secondary care costs	838	833	1671	310 (37)	311 (37)	621 (37)
Medication costs	834	825	1659	314 (38)	319 (39)	633 (38)
Total healthcare costs	830	823	1653	318 (38)	321 (39)	639 (39)
Informal care costs	913	924	1837	235 (26)	220 (24)	455 (25)
Absenteeism costs at work	852	849	1701	296 (35)	295 (35)	591 (35)
Absenteeism costs at unpaid work	905	921	1826	243 (27)	223 (24)	466 (25)
Presenteeism costs	680	690	1370	468 (69)	454 (66)	922 (67)
Total lost productivity costs	677	689	1366	471 (69)	455 (66)	926 (68)
Total societal costs	664	671	1335	484 (73)	473 (70)	957 (72)

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STUDY PROTOCOL   **Open Access**

Single- versus double-layer closure of the caesarean (uterine) scar in the prevention of gynaecological symptoms in relation to niche development – the 2Close study: a multicentre randomised controlled trial

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Abstract

Background: Double-layer compared to single-layer closure of the uterus after a caesarean section (CS) leads to a thicker myometrial layer at the site of the CS scar, also called residual myometrium thickness (RMT). It possibly decreases the development of a niche, which is an interruption of the myometrium at the site of the uterine scar. Thin RMT and a niche are associated with gynaecological symptoms, obstetric complications in a subsequent pregnancy and delivery and possibly with subfertility.

(Continued on next page)

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(Continued from previous page)

Methods: Women undergoing a first CS regardless of the gestational age will be asked to participate in this multicentre, double blinded randomised controlled trial (RCT). They will be randomised to single-layer closure or double-layer closure of the uterine incision. Single-layer closure (control group) is performed with a continuous running, unlocked suture, with or without endometrial saving technique. Double-layer closure (intervention group) is performed with the first layer in a continuous unlocked suture including the endometrial layer and the second layer is also continuous unlocked and imbricates the first. The primary outcome is the reported number of days with postmenstrual spotting during one menstrual cycle nine months after CS. Secondary outcomes include surgical data, ultrasound evaluation at three months, menstrual pattern, dysmenorrhea, quality of life, and sexual function at nine months. Structured transvaginal ultrasound (TVUS) evaluation is performed to assess the uterine scar and if necessary saline infusion sonohysterography (SIS) or gel instillation sonohysterography (GIS) will be added to the examination. Women and ultrasound examiners will be blinded for allocation. Reproductive outcomes at three years follow-up including fertility, mode of delivery and complications in subsequent deliveries will be studied as well. Analyses will be performed by intention to treat. 2290 women have to be randomised to show a reduction of 15% in the mean number of spotting days. Additionally, a cost-effectiveness analysis will be performed from a societal perspective.

Discussion: This RCT will provide insight in the outcomes of single- compared to double-layer closure technique after CS, including postmenstrual spotting and subfertility in relation to niche development measured by ultrasound.

Trial registration: Dutch Trial Register (NTR5480). Registered 29 October 2015.

Keywords: Caesarean section, Closure techniques, Long-term outcomes, Postmenstrual spotting, Niche, Quality of life, Fertility, Reproductive outcomes,

Background

Caesarean section (CS) rates have increased from 14.5 to 27.2% in the last two decades in the Western world. [1] In 2016, 26.664 CSs were performed in the Netherlands, being 16.0% of the total number of deliveries. [2] The increasing CS rate has stimulated an interest in the potential long-term morbidity of a CS scar, such as uterine rupture or malplacentation. [3–7] Other less severe, but more prevalent long-term symptoms are gynaecological symptoms and subfertility.

Only recently, gynaecological symptoms such as painful menstruations and postmenstrual spotting have been associated with CSs. [8–10] These symptoms are considered to be related to a niche, defined as *"an indentation at the site of the caesarean scar with a depth of at least 2 mm"*, visible on transvaginal ultrasound (TVUS). [11] Two cohort studies reported a strong association between postmenstrual spotting and a niche: odds ratio (OR) 3.1; 95% confidence interval (CI) 1.5–6.3 [8] and OR 5.5; 95% CI 1.1–26.5. [10] In these studies, a niche was observed in 50 to 60% of the women after a CS, using transvaginal ultrasound. [8, 10] Spotting was correlated to niche volume and inversely correlated to the residual myometrium thickness (RMT). [8, 10]

In addition to the gynaecological symptoms, a niche may influence fertility. A recent meta-analysis reported that a CS on average reduced the probability of subsequent pregnancy with 9% (relative risk (RR) 0.91; 95% CI 0.87–0.95) in comparison to a vaginal delivery. [12]

None of the included studies in this meta-analysis evaluated the relation between subsequent fertility and the presence of a niche. One of the hypotheses is that intra-uterine fluid or cervical mucus or blood accumulation in the niche are expected to hamper the penetration of sperm cells or impair embryo implantation. [13] Long-term follow-up will facilitate the evaluation of the association between uterine closure, niche development, accumulation of intra-uterine fluid and subfertility.

In the last years, various therapies have been developed and implemented to treat niche related symptoms such as menstrual disorders. [14–18] Effectiveness of both hysteroscopic [19] and laparoscopic niche resection [15] have recently been published. Because both niche related symptoms and applied therapies lead to increases in medical consultations and costs, it seems to be more efficient to prevent niche development in the first place. Uterine closure technique of the CS scar has been proposed as an independent factor for niche development. [9] However, large randomised trials evaluating the effect of uterine closing techniques on postmenstrual spotting or other gynaecological or reproductive outcomes in relation to niche development and thin residual myometrium are lacking, as well as cost-effectiveness evaluations.

In order to shorten surgery time and in the absence of significant differences in short-term outcomes [20, 21], most Dutch gynaecologists (92%) have replaced double-layer by single-layer closure after a CS, using

Supplemental material

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multifilament continuous unlocked sutures. Given the higher risk on myometrium loss and thus development of a thinner residual myometrium after single-layer closure [5, 22], we hypothesise that this method introduces a higher risk on postmenstrual spotting and possibly subfertility after a CS and that it can be prevented by applying double-layer unlocked closure.

Double-layer unlocked closure is considered safe, without a clinically relevant higher risk on short-term outcomes. [5, 23, 24]. Moreover, it results in a thicker residual myometrium, especially when unlocked sutures are applied. [5, 22, 24] Dysmenorrhea was reported more frequently after single-layer closure, but this was only studied in two RCTs and not always related to ultrasound findings such as myometrial thickness or niche presence. [24] Prevalence of uterine rupture seems to be similar after single- versus double-layer closure [5, 22, 24], but has neither been related to ultrasound findings and since it has a very low incidence, statistically significant differences are difficult to find. Since long-term outcomes such as gynaecological symptoms, fertility outcomes and results of subsequent pregnancies are studied infrequently, additional evidence is needed before a preference for either technique can be indicated.

Objective

Our primary objective is to determine the effectiveness of unlocked double-layer uterine closure compared to unlocked single-layer uterine closure in the prevention of niche related gynaecological symptoms nine months after a first CS. Secondary objectives are to assess niche prevalence measured by ultrasound at three months follow-up and to study both reproductive outcomes related to a subsequent pregnancy and gynaecological symptoms at three years follow-up. Additionally we aim to study the cost-effectiveness alongside the trial.

Methods/design
Design

This multicentre randomised controlled superiority trial will be performed in the Netherlands, in hospitals that collaborate within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (NVOG Consortium 2.0, www.zorgevaluatieneder-land.nl). Centres that participate are district, teaching or university hospitals in the Netherlands. A list of study sites is available in Additional file 1.

Participants and eligibility criteria

All women who undergo a first CS, planned or unplanned, will be asked to participate in the study. Other inclusion criteria are: sufficient command of the Dutch or English language, age ≥ 18 years and written informed

consent. To prevent confounding effects on niche development during the study, we will exclude women with a previous CS. Other exclusion criteria are: inadequate possibility for counselling (e.g. indication for emergency CS without being informed about the study previously, women in severe pain without adequate therapy), previous major uterine surgery (e.g. laparoscopic or laparotomic fibroid resection, septum resection), women with known causes of menstrual disorders (e.g. cervical dysplasia, communicating hydrosalpinx, uterine anomaly or endocrine disorders disturbing ovulation), placenta inor percreta during the current pregnancy or ≥ three foetuses during the current pregnancy.

Recruitment and randomisation

Eligible women will be asked by a gynaecologist, resident, clinical midwife or research nurse to participate in the trial when they undergo a planned CS. Eligible women who are planned to undergo a vaginal delivery will also be informed about this study during pregnancy in case they need an unplanned CS. Furthermore, women during induced labour and women receiving adequate therapy for pain during labour, will be asked to participate in case a CS is needed during labour for any indication.

When the decision of a CS is made and all selection criteria are met, women will be randomly allocated to single-layer (control group) or double-layer (intervention group) closure (1:1) (see Fig. 1). Randomisation will be performed using a web-based application ALEA 2.2 which displays a computer-generated random number, managed by the Clinical Research Unit of the Amsterdam UMC - location AMC. We will use a permuted block-design, stratified for recruiting centres and for planned or unplanned CS. All women that decline to participate will be registered anonymously in order to record the number and reason for refusal. Subjects who withdraw from this study will not be replaced.

Gynaecologists, residents, clinical midwives or research nurses enrol participants and assign them to the intervention. The CS will be performed by either a gynaecologist, a resident supervised by a gynaecologist or by a resident that is authorised to perform CSs without supervision. Participants and sonographers will be blinded for the closure technique. If operative reintervention after CS is needed and the gynaecologist that performs the reintervention needs to know the closure technique that the participant was assigned to, unblinding is possible through the logistic trial coordinator. We expect this situation to occur very infrequently.

Intervention (double-layer closure)

In both study arms, women will undergo a CS following a standard way with respect to mode of uterotomy,

correct approximations of the cutting edges and non-closure of the peritoneum. In the intervention arm, double-layer closure of the uterus will be performed using unlocked multifilament continuous running sutures for both layers and the endometrial layer will be included in the first layer (see Fig. 2). The second layer is a continuous running suture that imbricates the first layer. Since this is not the standard method for uterine closure in the Netherlands, a short online instruction film will be shown to all participating centres and surgeons prior to participation (see Additional file 2).

Surgical outcomes will be registered after the procedure in the electronic case report form (eCRF).

Control group (single-layer closure)

The control group will receive usual closure technique of the uterus: a single-layer closure using unlocked continuous running multifilament sutures. The currently available evidence is inconclusive with respect to endometrial saving technique or not. Therefore, we decided that in our study surgeons are free to choose to close either full thickness (including the endometrium) or split

Fig. 1 Flowchart of the 2Close study. * = baseline questions, EQ-5D-5L. ** = symptom questionnaire, EQ-5D-5L, SF36, PROMIS SF8a, iMCQ, iPCQ. *** = symptom questionnaire, FSFI, EQ-5D-5L, SF36, iMCQ, iPCQ. **** = symptom questionnaire, fertility questionnaire, FSFI, EQ-5D-5L, SF36, PROMIS SF8a.

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thickness (excluding the endometrium) in the control group. The applied method, including endometrial saving technique or not, will be registered.

Niche evaluation

The care after CS will be according to the normal local protocol with the regular outpatient visit that is normally executed six weeks after the CS. This routine visit may be postponed to three months after the CS to enable an ultrasound evaluation to identify the existence of a niche, but participating centres may decide whether they want visits at six weeks (routine follow-up) and at three months (ultrasound follow-up) or only one visit after three months combining the regular control and the ultrasound follow-up. The ultrasound evaluation is standardised as proposed by Jordans et al. [11] (see Fig. 3). Based on this standardisation, we created an obligatory e-learning for all ultrasound performers to let all ultrasounds be performed in a uniform manner. To increase consistency and to improve the learning curve, we will evaluate a sample of ultrasounds in each centre based on recorded pictures and provide feedback to the examiners. Since it is known that a niche can be missed during TVUS only [8, 10, 25] we will additionally perform a saline infusion sonohysterography (SIS) or gel installation sonography (GIS) in case no niche is observed during the normal TVUS or if the ultrasound is inconclusive. It would be optimal to have a contrast enhanced ultrasound in all women when the uterine cavity or niche are not naturally filled with fluid, but we have chosen for this approach to prevent unnecessary burden for the participants and to reduce costs.

Outcome measures
Primary outcome measure

The primary outcome is the number of days of postmenstrual spotting during one cycle at nine months after CS. We defined postmenstrual spotting as brownish discharge for more than two days at the end of the menstruation, with a total duration (menstruation and spotting) of more than seven days, or intermenstrual blood loss that starts after the end of the menstruation. [8] The number of days of postmenstrual spotting will be counted as follows: days with brownish discharge (> two days) when the total duration of menstruation and spotting exceeds seven days + number of days with
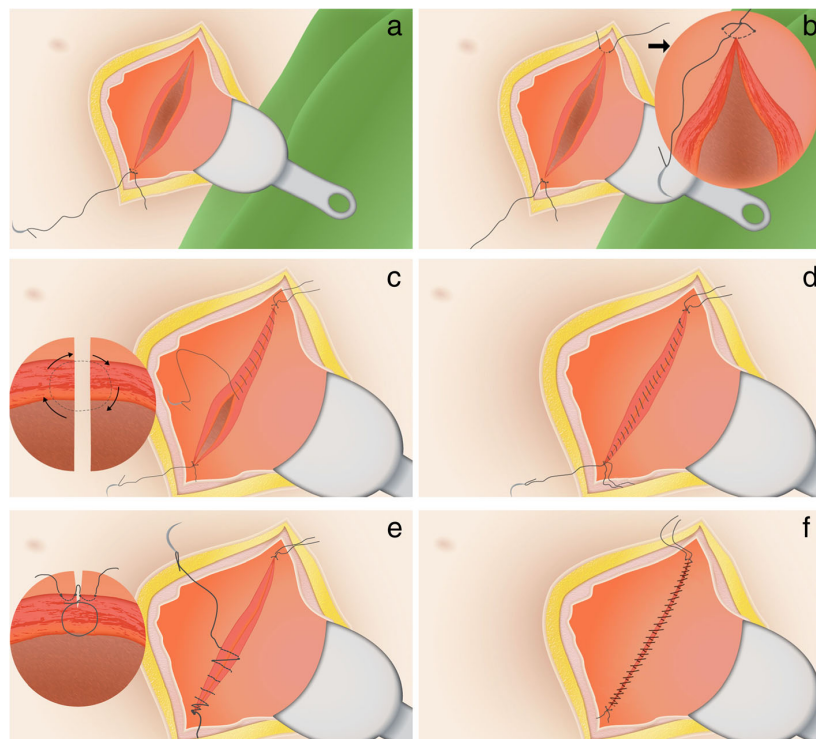
Fig. 2 Double-layer uterine closure technique. **a**. Step 1: lateral suture; **b**. Step 2: lateral suture on the other side; **c**. Step 3: First layer: full thickness, continuous, including large part of myometrium, including the endometrial layer; **d**. Step 4: End of this first layer; **e**. Step 5: Second layer: superficial continuous layer of serosal tissue, imbricating the first layer; **f**. Step 6: First and second layer should be closely connected

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intermenstrual blood loss. Amenorrhoeic women, due to lactation, medication or other diseases, will not be evaluable for the primary outcome and will be left out of this analysis.

Secondary outcome measures at short-term

– Perioperative outcomes including blood loss, operative time, additional haemostatic sutures and complications.
– Menstruation characteristics, dysmenorrhea (visual analogue scale (VAS)), Quality of Life (QOL) using Short-Form-36 [26] and EQ-5D-5L [27, 28], societal reintegration (PROMIS Short-Form-8a [29]), sexual function using the Female Sexual Function Index (FSFI [30]), applied medical and/or surgical therapy because of gynaecological symptoms, all obtained through digital questionnaires, will be assessed at three and nine months follow-up.
– Ultrasound evaluation will be performed at three months follow-up using TVUS, in which RMT, adjacent myometrium thickness (AMT), presence of a niche (depth of ≥2mm), length, depth and width of the niche, presence of large niches (RMT < 50% of AMT, RMT <3mm) and niche volume will be measured.

Cost-effectiveness outcomes

Costs will be measured using adapted versions of the iMTA Productivity Cost Questionnaire (iPCQ [31]) and iMTA Medical Consumption Questionnaire (iMCQ [32]) from a health care and societal perspective at nine months of follow-up.

Secondary outcome measures at long-term

– Menstruation characteristics, pain, sexual functioning, QOL and social reintegration will be evaluated at three years follow-up.
– Reproductive outcomes at three years follow-up: % of women desiring to conceive, % of women that conceived including time to conceive, % of women with an ongoing pregnancy, the need for fertility treatment and pregnancy outcomes such as mode of delivery or complications will be determined.

Long-term outcomes will be presented in a separate article.

Data collection and data management
Intraoperative data
Immediately after the CS we will register relevant items regarding the delivery and CS in an eCRF, in which confidentiality and anonymity are ensured and audit trails are accessible. These items include: reason for planned or unplanned CS, emergency CS or not, whether women experienced contractions, dilatation, performed method for uterine closure, endometrial saving technique applied, used suturing material, extra haemostatic sutures, operative time, blood loss and complications.

Collection of baseline characteristics and patient reported outcomes
Baseline characteristics will be collected through a digital questionnaire at 2–4 weeks after caesarean section, sent to the e-mail address of participants. Since we will also include unplanned CSs, we decided that it is not possible for all participants to answer questions regarding baseline characteristics before the operation. Baseline parameters include maternal age, body mass index, social economic status, smoking habit, medical and obstetric history, gestational age and previous vaginal deliveries, all reported by the participant. We expect that the impact of niche related symptoms such as postmenstrual spotting on daily activities and sexual behaviour may be influenced by ethnic background and religion, therefore we will also register these characteristics. At three months, nine months and three years follow-up, again digital questionnaires will be sent to participants to assess the primary and secondary outcomes (see Fig. 1). At nine months, we ask participants record their exact menstrual and spotting pattern, if any, in an adjusted menstruation score chart. [33] Reminders for all questionnaires will be sent every two weeks, with a maximum of three times. When no response is given after the reminders, research nurses from participating centres will be asked to call the participant.

Data niche evaluation
Results of the TVUS and GIS or SIS, performed three months after CS, will be registered. Women will not receive information regarding the presence of a niche, since it has no clinical consequences so shortly after CS and this may influence the answers given in the questionnaires. Other important abnormalities visualised by ultrasound will be reported as usual.

Statistical issues
Sample size calculation
We use a superiority design since we expect double-layer closure to be favourable. Literature for making reliable estimations on postmenstrual spotting in relation to niches is scarce. We have used baseline data from the HysNiche [19] and LapNiche [15] study. We

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Fig. 3 Standardised transvaginal ultrasound evaluation of a niche in the non-pregnant uterus. **a**. Measured in the transversal plane: niche width (1); **b**. Measured in the sagittal plane: niche length (2), niche depth (from cervical canal until apex of the niche) (3), residual myometrium thickness (from deepest part of the niche until the serosa) (4), adjacent myometrium thickness (myometrium thickness close to base of the niche) (5), distance from apex of the niche to vesico-vaginal fold (see **c**) (6); **c**. Measuring the niche relatively to the vesico-vaginal fold in the sagittal plane: positive value (green arrow, in mm) or negative value (red arrow, in mm)

estimate the mean number of spotting days to be 3.5 days/month in the total group. We consider a 15% reduction in the mean number of spotting days clinically relevant, which is 0.5 day/month reduction. Assuming a standard deviation (SD) of 3.4 and a two-sided significance level of 5%, a total of 1488 women need to be included to achieve a power of 80%. Increasing the sample size to take into account 35% of women unevaluable (due to drop-out, non-response or amenorrhoea) for the primary outcome, 2290 women need to be included.

Data-analysis

Data-analysis will be performed according to the intention to treat principle and additional per protocol analyses will be performed. A test will be considered statistically significant when the two-sided test shows a p-value < 0.05. Baseline characteristics will be presented using percentages, means with SD and 95% CI or medians with interquartile ranges (IQR), where appropriate.

The primary outcome, number of days of postmenstrual spotting, will be presented for both groups as mean with SD or median with IQR, and presented in a Box-Whisker graph to show the distribution. Differences in primary outcome between the groups will be tested

using the independent t-test in case of normal distribution (possible after transformation of the outcome) or Mann-Whitney U test. An adjusted analysis will be performed using linear regression analysis in which we adjust for factors on which randomisation was stratified and for baseline factors on which relevant differences are observed despite randomisation.

Dichotomous secondary outcomes will be presented as percentages and RR with corresponding 95% CI. P-values will be calculated using the chi-square test or, if the expected count for at least one cell is below 5, using the Fisher exact test. Normally distributed continuous variables will be presented as means with SD, and differences between the groups will be calculated with an independent t-test. Non-normally distributed continuous variables will be presented as medians with IQR and differences between the groups will be calculated with Mann-Whitney U test. The questionnaires will be analysed using the appropriate algorithms and usual presentation methods (FSFI, EQ-5D-5L, SF36, PROMIS SF8a, iMCQ, iPCQ).

Comparison of primary outcome between women receiving single- and double-layer closure will be done as secondary analyses within each of the following subgroups separately:

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1. Planned (without labour) or unplanned (in labour) CS
2. Emergency CS or not
3. Preterm (< 37 weeks gestational age) or term (≥ 37 week gestational age) CS
4. Presence (> 3cm) or absence (≤ 3cm) of dilatation
5. Placenta praevia or not
6. Presence or absence of specific maternal morbidity (e.g. diabetes, pre-eclampsia, haemolysis/elevated liver enzymes/low platelet count (HELLP) syndrome, immunodeficient women)
7. Singleton versus twin pregnancy
8. Natural cycle or hormonally induced withdrawal bleeding

Within the single-layer group (control group) we will compare the primary outcome between women in whom endometrial saving technique (split thickness) was applied and women in whom an endometrial saving technique was not applied (full thickness).

Economic evaluation

The economic evaluation will be performed alongside the RCT from a societal perspective. Both a cost-effectiveness and cost-utility analysis will be performed with a time horizon of nine months to relate the difference in societal and healthcare costs between double-layer and single-layer unlocked uterine closure during a CS to the difference in clinical effects. Healthcare costs include costs of primary and secondary care, complementary care and home care. Costs in other sectors include presence and absence from paid and unpaid work. The friction cost approach will be used to estimate indirect costs. For the valuation of health care utilization standard prices published in the Dutch Costing guidelines will be used. [34] Medication use will be valued using prices of the Royal Dutch Society for Pharmacy.

Societal costs will be related to the following effect measures in the economic evaluation: days with postmenstrual spotting and quality-adjusted life-years (QALYs) based on the Dutch tariff for the EuroQol (EQ-5D-5L). [27, 28, 35]

We hypothesise that double-layer uterine closure will reduce postmenstrual spotting and related consultations for gynaecological or fertility related problems and applied therapies, and as a consequence that it will be cost-effective in comparison with single-layer uterine closure.

The analysis will be done according to the intention to treat principle. Missing costs and effect data will be imputed using multiple imputation. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the treatment groups by the difference in mean effects.

Bootstrapping with 5000 replications will be used to estimate 95% CI around cost differences and the uncertainty surrounding the ICERs. Uncertainty surrounding the ICERs will be graphically presented on cost-effectiveness planes. Cost-effectiveness acceptability curves showing the probability that double-layer uterine closure is cost-effective in comparison with single-layer uterine closure for a range of different ceiling ratios will also be estimated. Adjustment for confounders and effect modifiers will be done if necessary. [36]

Interim analysis and safety monitoring

Because of the type of intervention, the Medical Ethics Committee (MEC) determined that the risk for participation is negligible. Therefore, we do not have a Data Safety Monitoring Committee. No interim analysis is planned.

All serious adverse events (SAEs) will be reported to the MEC by line listing yearly. Life threatening SAEs or an event that leads to death will be reported to the MEC immediately. All SAEs will be followed until they have abated, until a stable situation has been reached or the patient was discharged. We do not expect to terminate the study prematurely given the low risk of adverse events.

Confidentiality and data security

All participating centres receive a login name and password to gain access to ALEA 2.2, the web-secured randomisation database. Randomisation is performed pseudo-anonymously with only the initials and year of birth of the participants. Linking personal data to the study number can only be performed in the local participating centres or by the trial coordinator (SS). Written informed consent forms are stored in every centre in a lockable room. All forms and data will be archived for 15 years in the participating centres.

Discussion

In the last years, studies examining complications of CSs are increasing, including the development of niches or thin residual myometrium at the site of the previous CS and related symptoms. Both RMT and the presence of a niche have been associated with postmenstrual spotting. [8, 10] Double-layer unlocked closure has been shown to result in a thicker residual myometrium and as a consequence can possibly lead to a decrease of niche development after a CS compared to single-layer closure. [5, 22, 24, 37] However, the long-term clinical outcomes in terms of postmenstrual spotting or subfertility have not been studied previously or have not been related to ultrasound findings. We hypothesise that niche related postmenstrual spotting and fertility problems will reduce together with decrease in niche prevalence, in which

identification of the best uterine closure technique regarding RMT and niche development will be of great significance.

Strengths and limitations

The design of this study is one of the strengths; this is the first large RCT that will evaluate the effectiveness of double-layer uterine closure compared to single-layer uterine closure after CS regarding niche related gynaecological symptoms and reproductive outcomes with a long-term follow-up. The study is adequately powered. Randomisation is performed by using a web based randomisation program. Furthermore, all participants and examiners are blinded which reduces the chance for bias regarding reported symptoms and ultrasound findings. An additional strength is the uniform manner in which we try to perform double-layer closure and ultrasound evaluation, instructed by mandatory online instruction film and e-learning, respectively. Moreover, the 2Close study will compare the cost-effectiveness of both techniques which has never been done before. As we expect that double-layer closure will reduce the incidence of niche development and as a consequence that it could possibly reduce the gynaecological symptoms including postmenstrual spotting after CS, we assume double-layer closure to be more cost-effective. Also, we expect that double-layer closure will improve the chances of conceiving after CS and lower costs in fertility treatment.

We also expect some limitations. Baseline characteristics will be collected through questionnaires that are filled in by women in the first month after CS, which might lead to recall bias regarding medical history, complications during pregnancy and labour, and other baseline measurements. We decided to lower the administrative load for participating hospitals by obtaining these characteristics through the participants. Furthermore, there is no validated questionnaire available yet for postmenstrual spotting; therefore, the questionnaires that are used in the 2Close study are not adjusted or validated for these symptoms. Moreover, the surgical techniques performed during the CS in this study are standardised in both study arms except for saving the endometrium in the control group. There is no conclusive evidence whether or not to save the endometrium in the suture according to its influence on niche development. Therefore, we chose to leave this decision with the surgeons. There may possibly be a difference in the incidence of niche development between the participants receiving single-layer split thickness or full thickness closure, also when compared to the incidence of niche development in the double-layer group. This will be further examined in a subgroup analysis.

To prevent bias regarding niche evaluation three months after CS, all ultrasonographic examiners are trained by an online learning program and a sample of ultrasounds will be evaluated. The learning module is based on the results of a Delphi procedure among international niche experts. [11] Although the niche examiners in the 2Close are trained by a standardised method, experience in measuring niches and as a consequence differences in niche measurement may occur among examiners.

Potential impact and implications

This study will gain insight in the most optimal uterine closure technique after CS which is relevant for women and gynaecologists, since we will focus on long-term gynaecological symptoms and reproductive outcomes in relation to changes of the lower uterine segment after CS and in particular niche development. Since many studies have already shown that RMT and niches are related to several symptoms and therapies for niche resection are being developed, we think it is necessary to provide evidence for the development of preventive strategies regarding niche related symptoms. It is important to realise that the best way to prevent a niche and its related symptoms, is to not perform a CS. But since it is often inevitable to perform a CS, care takers should perform it in the most optimal way.

After the results of this study become available, the most optimal and cost-effective technique can be implemented in order to reduce symptoms and problems in a subsequent pregnancy. This will not be difficult, since the technique is easy to learn and many gynaecologists and residents are familiar with it after the trial. Especially for a scheduled CS, women should be informed about the risk to develop a niche and the risk that it might cause symptoms or complications later in life.

Additional files

Additional file 1: Affiliations of all 32 participating hospitals in the Netherlands that granted approval. The board of the hospitals granted approval to participate and to start recruiting patients. (DOCX 15 kb)

Additional file 2: Text of the online standardised instruction film for double-layer closure of the uterotomy. The spoken text in the online instruction film, which shows a standardised way to perform double-layer closure of the uterotomy, has been translated into English. (DOCX 15 kb)

Abbreviations

AMT: Adjacent myometrium thickness; BROK: Basic course Regulations and Organisation for Clinical researchers; CI: Confidence interval; eCRF: electronic case report form; CS: Caesarean section; GCP: Good clinical practice; GIS: Gel instillation sonohysterography; ICER: Incremental cost-effectiveness ratio; iMCQ: iMTA Medical Consumption Questionnaire; iMTA: Institute for Medical Technology Assessment; iPCQ: iMTA Productivity Cost Questionnaire; IQR: Interquartile range; MEC: Medical ethics committee; OR: Odds ratio; QALY: Quality adjusted life years; QOL: Quality of life; RCT: Randomised controlled trial; RMT: Residual myometrium thickness; RR: Relative risk; SAE: Serious adverse event; SD: Standard deviation; SIS: Saline infusion sonohysterography; TVUS: Transvaginal ultrasound; VAS: Visual analogue scale

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Availability of data and materials
Data entry and secure storage is performed with data management system OpenClinica (OpenClinica LLC and collaborators, facilitated by TraIT (Translational Research IT infrastructure) and hosted by Vancis, which meets the ISO 27001 standard for information security management, version: 3.6). Data control during the trial is possible. The trial will be monitored on-site by a quality advisor of the Dutch Consortium for Studies in Women's Health and Reproduction. The quality advisor will also perform data verification at the end of the trial. The NVOG Consortium stores all data from clinical trials centrally so data will not become publicly available but will be available upon reasonable request to the corresponding author and with permission of the NVOG Consortium. Trial data will be accessible for verification or other research purposes, after an embargo period of 12 months in order to enable publication of the results by the project group.

Authors' contributions
JH, IJ, LvdV, MB, CdG, CL, RdL and WH made substantial contributions to the conception and design of the study. SS is responsible for the overall logistical aspects of the trial and general acquisition of data. SS and IJ drafted the manuscript. PV and JB provided statistical support regarding future analyses. EP, EB1, CR, MH, WvB, HV, JvL, HvV, RR, MS, CJ, WH, AF, KK, HS, JL, KdB, SC, DS, AO, MK, DP, LdV, EvB, MB, AH, WM, KD, EB2 and HvE made substantial contributions to acquisition of data. All authors critically revised the manuscript, approved the final version of the manuscript and agreed to be accountable for all aspects of the manuscript ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

Ethics approval and consent to participate
This study is approved by the ethics committee of Amsterdam UMC - location VUmc (reference number: 2015.462) and by the boards of all participating hospitals (Additional file 1). Protocol amendments will be communicated to participating hospitals, after approval of the central MEC of Amsterdam UMC – location VUmc. This trial is registered in the Dutch Trial Register (NTR5480, www.trialregister.nl). Counselling of eligible women will be done according to the 'good clinical practice' (GCP) guidelines or doctors certified according to Basic course Regulations and Organisation for Clinical researchers (BROK). After reading the patient information form and counselling by GCP- or BROK-certified personnel, women will be asked for written consent. This informed consent form will be obtained before participation in the clinical trial.
The research team declares that the SPIRIT guidelines were followed. All recommended items of the SPIRIT 2013 checklist were addressed in this clinical trial protocol.
The trial results will be communicated after the final inclusion and follow-up through publication in a peer-reviewed international journal and in an international congress. Participants will be informed through e-mail and the study website.

Consent for publication
Not applicable.

Competing interests
All authors declare that they have no competing interests.

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