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ORIGINAL ARTICLE *Infertility*

Endometrial scratching in women with one failed IVF/ICSI cycle—outcomes of a randomised controlled trial (SCRaTCH)

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STUDY QUESTION: Does endometrial scratching in women with one failed IVF/ICSI treatment affect the chance of a live birth of the subsequent fresh IVF/ICSI cycle?

SUMMARY ANSWER: In this study, 4.6% more live births were observed in the scratch group, with a likely certainty range between −0.7% and +9.9%.

WHAT IS KNOWN ALREADY: Since the first suggestion that endometrial scratching might improve embryo implantation during IVF/ICSI, many clinical trials have been conducted. However, due to limitations in sample size and study quality, it remains unclear whether endometrial scratching improves IVF/ICSI outcomes.

STUDY DESIGN, SIZE, DURATION: The SCRaTCH trial was a non-blinded randomised controlled trial in women with one unsuccessful IVF/ICSI cycle and assessed whether a single endometrial scratch using an endometrial biopsy catheter would lead to a higher live birth rate after the subsequent IVF/ICSI treatment compared to no scratch. The study took place in 8 academic and 24 general hospitals. Participants were randomised between January 2016 and July 2018 by a web-based randomisation programme. Secondary outcomes included cumulative 12-month ongoing pregnancy leading to live birth rate.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with one previous failed IVF/ICSI treatment and planning a second fresh IVF/ICSI treatment were eligible. In total, 933 participants out of 1065 eligibles were included (participation rate 88%).

MAIN RESULTS AND THE ROLE OF CHANCE: After the fresh transfer, 4.6% more live births were observed in the scratch compared to control group (110/465 versus 88/461, respectively, risk ratio (RR) 1.24 [95% CI 0.96–1.59]). These data are consistent with a true difference of between −0.7% and +9.9% (95% CI), indicating that while the largest proportion of the 95% CI is positive, scratching could have no or even a small negative effect. Biochemical pregnancy loss and miscarriage rate did not differ between the two groups: in the scratch group 27/153 biochemical pregnancy losses and 14/126 miscarriages occurred, while this was 19/130 and 17/111 for the control group (RR 1.21 (95% CI 0.71–2.07) and RR 0.73 (95% CI 0.38–1.40), respectively). After 12 months of follow-up, 5.1% more live births were observed in the scratch group (202/467 versus 178/466), of which the true difference most likely lies between −1.2% and +11.4% (95% CI).

LIMITATIONS, REASONS FOR CAUTION: This study was not blinded. Knowledge of allocation may have been an incentive for participants allocated to the scratch group to continue treatment in situations where they may otherwise have cancelled or stopped. In addition, this study was powered to detect a difference in live birth rate of 9%.

WIDER IMPLICATIONS OF THE FINDINGS: The results of this study are an incentive for further assessment of the efficacy and clinical implications of endometrial scratching. If a true effect exists, it may be smaller than previously anticipated or may be limited to specific groups of women undergoing IVF/ICSI. Studying this will require larger sample sizes, which will be provided by the ongoing international individual participant data-analysis (PROSPERO CRD42017079120). At present, endometrial scratching should not be performed outside of clinical trials.

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TRIAL REGISTRATION DATE: 31 July 2015.

DATE OF FIRST PATIENT'S ENROLMENT: 26 January 2016.

Key words: endometrium / endometrial scratch / endometrial injury / embryo implantation / IVF / ICSI / pregnancy / live birth / cumulative live birth / endometrial biopsy catheter

Introduction

Each year ∼2.4 million IVF/ICSI cycles are carried out globally (De Geyter *et al.*, 2018; Fauser, 2019). Despite advances in techniques, pregnancy rates still remain maximally 35% per embryo transfer and embryo implantation seems to be the rate-limiting step in the success of IVF/ICSI treatment (De Geyter *et al.*, 2018). Endometrial scratching has been suggested as a promising add-on treatment to improve IVF/ICSI pregnancy rates (Barash *et al.*, 2003; Nastri *et al.*, 2015), even though its effectiveness (Panagiotopoulou *et al.*, 2015; Santamaria

et al., 2016), and the potential underlying biological mechanisms (Li and Hao, 2009; Gnainsky et al., 2015) have not been proven. Nevertheless, since the publication of the first randomised controlled trials (RCTs) in 2010, endometrial scratching has been widely implemented in daily practice (Lensen et al., 2016, 2019b; Farquhar, 2019; Mol and Barnhart, 2019).

At present, it is still unclear if endometrial scratching improves the chance of a live birth and, if so, which population benefits most (Yeung et al., 2014; Nastri et al., 2015; Vitagliano et al., 2018; Lensen et al., 2019a; van Hoogenhuijze et al., 2019). Most studies that reported a positive effect on pregnancy chances were associated with a high risk of bias (Nastri et al., 2015; Vitagliano et al., 2018; van Hoogenhuijze et al., 2019) and often only outcomes such as clinical- or ongoing pregnancy were reported, while a live birth is considered as the most important outcome (Legro and Wu, 2014). The only large RCT to date did not standardise the method of endometrial scratching and had a follow-up duration of one embryo transfer (Lensen et al., 2019a). Also, the participation rate was only around 50% of eligible women, which may have impacted the generalisability of the findings.

With the SCRaTCH trial, our aim was to study whether endometrial scratching using an endometrial biopsy catheter improves live birth rates both in the short and long term in a large, relatively homogeneous population, with at least one previous failed embryo transfer. This led to our research question 'does a single mid-luteal endometrial scratch in women with one failed IVF/ICSI treatment affect the chance of a live birth of the subsequent fresh IVF/ICSI cycle?'.

Materials and methods

Study design and participants

This trial was a multicentre, randomised controlled, non-blinded trial executed in 8 academic and 24 general hospitals in the Netherlands. The trial was coordinated by the University Medical Centre Utrecht and was performed within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (NVOG Consortium 2.0). Eligible women were recruited and counselled by staff of the participating hospitals. The study protocol was published previously (van Hoogenhuijze et al., 2017b).

In short, women were eligible if they had undergone one full IVF/ICSI cycle with at least one embryo transfer without achieving a clinical pregnancy and were planning a new fresh IVF/ICSI cycle. Inclusion criteria were regular indication for IVF/ICSI, age 18–44 years, primary or secondary infertility and a normal transvaginal ultrasound. Exclusion criteria were endometriosis grade III/IV, untreated uni- or bilateral hydrosalpinx, previous endometrial scratching, untreated endocrine abnormalities, intermenstrual blood loss, previous Caesarean section with niche-formation and intracavitary fluid visible on ultrasound, increased risk of intra-abdominal infection, oocyte donation cycles or pre-implantation genetic testing.

Ethics approval was obtained from the institutional review board of the University Medical Centre Utrecht (METC 10-272). Approval was obtained from the board of directors of each participating centre. All women gave written informed consent.

Randomisation

Participants were randomised after the last failed embryo transfer and prior to the start of medication for the second fresh IVF/ICSI treatment by a staff member of the participating centre. Participants were randomised 1:1 to the intervention or control group by a centrally located, non-centre-stratified, web-based randomisation programme (ALEA Clinical B.V.) using randomly permuted blocks, with block size varying randomly between two and four.

Study procedure

Participants allocated to the intervention group received a single endometrial scratch in the menstrual cycle prior to the start of stimulation for IVF/ICSI. The scratch was performed either in the mid-luteal phase of a natural cycle or in a cycle with hormonal contraceptives. Timing of the scratch was determined by the LH surge through urine ovulation tests (LH + 5–8 days), the cycle day (5–10 days before the expected next menstruation), or the planned last day of contraceptive use (5–10 days before the expected withdrawal bleeding).

The scratch was performed by a maximum of two or three physicians per participating centre, who followed a strict protocol as described previously (van Hoogenhuijze et al., 2017b). Endometrial scratching was performed by suction, using an endometrial biopsy catheter. Directly afterwards, participants indicated the maximum pain level during the scratch on a visual analogue score (VAS). One week later, participants who had undergone a scratch procedure were asked by phone whether they had experienced abdominal pain, vaginal bleeding other than the menstruation, or fever.

Participants allocated to the control group did not undergo endometrial scratching or a sham intervention.

Follow-up

Follow-up ended at 12 months after randomisation or, if an ongoing pregnancy was achieved within that period, after giving birth. If a participant became pregnant, ultrasonic evaluation was performed at 6–7 and 10–12 weeks' gestational age. Follow-up information was retrieved from the electronic patient file or via a questionnaire sent to the participant. If questionnaires were not returned, information was obtained by telephone contact with the participant, general practitioner or the clinic where the participant continued treatment. If obtaining follow-up information was unsuccessful, participants were marked as lost to follow-up.

Outcomes

The primary outcome was live birth after a fresh transfer from the second IVF/ICSI treatment (i.e. the first cycle after randomisation). Secondary outcomes were implantation rate after the second fresh IVF/ICSI treatment (only calculated for women with an embryo transfer); biochemical pregnancy loss and miscarriage rate after the second fresh IVF/ICSI treatment; cumulative live birth after the full second IVF/ICSI treatment (i.e. including all fresh and frozen embryo transfers); cumulative biochemical-, clinical-, ongoing pregnancy rate, ongoing pregnancy leading to live birth rate and multiple pregnancy rate within 12 months after randomisation; and time to biochemical pregnancy leading to live birth. Clinical pregnancy was defined as an intrauterine gestational sac visible on ultrasound at 6–7 weeks' gestational

age; ongoing pregnancy as a positive heartbeat on ultrasound at 10 weeks' gestational age; live birth as the delivery of at least one live foetus after 24 weeks of gestation; and multiple pregnancy as the birth of multiple live foetuses after 24 weeks of gestation.

As the live birth outcomes were defined as 'ongoing pregnancy *leading to* live birth', this implied that the ongoing pregnancy status should be reached within 12 months after randomisation. In turn, this implies that a biochemical pregnancy (gestational age 4 weeks) should be reached within 323 days (~10 months and 2 weeks) after randomisation. Thus, these criteria were used for all pregnancy outcomes meaning that in case of a biochemical pregnancy loss, the biochemical pregnancy should have occurred within 323 days after randomisation.

Statistical *analysis*

The sample size was calculated based on an estimated increase in the primary outcome from 30% to 39%, an 80% power and a two-tailed alpha of 5%. Taking a drop-out rate of 3% into account, 450 participants were needed per arm.

Pseudo-anonymised data were collected using a web-based registration system. Database cleaning consisted of internal consistency checks and identifying entries outside the expected ranges.

A statistical analysis plan was drafted, signed and dated before start of the analyses. The primary analysis was performed on an intention-to-treat (ITT) basis. Furthermore, an as-treated (AT) analysis and an as-treated analysis only including participants who had a fresh embryo transfer (AT+ET) were performed for the primary outcome only. For the ITT and AT analysis, spontaneous pregnancies occurring within 60 days after randomisation and pregnancies resulting from escape IUI were included in the analysis. All cumulative outcomes were reported *per participant*, meaning that in case of several (unsuccessful) pregnancies, only the last pregnancy was reported. Participants who were lost to follow-up/withdrew consent prior to the start of the second fresh IVF/ICSI treatment were excluded from the analyses for the primary outcome and the secondary outcome of the full second IVF/ICSI cycle, but they were included in the conservative cumulative 12-month analyses (in which they were regarded as no live birth).

All pregnancy outcomes were calculated by 2 × 2 contingency tables and expressed as risk ratios (RR) with 95% CI. In addition, risk differences (RD) with 95% CIs were calculated for the primary outcome and 12-month cumulative live birth. Time to pregnancy leading to live birth was visualised in a Kaplan–Meier curve. Implantation rate was defined as the number of gestational sacs visible on ultrasound divided by the number of transferred embryos and was thus calculated per embryo. In order to account for clustering caused by double embryo transfers, a Generalised Linear Mixed Model was used.

Analyses were performed using SPSS (IBM SPSS Statistics for Windows, version 25.0.0.2, released 2017, IBM corp., Armonk, NY, USA).

Results

Participants and intervention

From January 2016 to July 2018, 1065 eligible women were approached of whom 946 women were randomised. Thirteen women were excluded for various reasons (Fig. 1) resulting in a total of 933 women included in the ITT analysis: 467 in the scratch and 466 in the control group (participation rate 88%). Additional information on the randomisation procedure and stratification per centre can be found in Supplementary Data File S1, Data File S2 and Table SI.

Baseline and treatment history characteristics are shown in Table I. In the scratch group, introduction of the biopsy catheter failed in three participants, and 16 participants did not undergo scratching for other reasons. In the control group, five women did receive a scratch after randomisation and before the subsequent IVF/ICSI (Fig. 1). The median VAS during the scratch procedure was 4.5/10 (interquartile range 3.0–6.0). One week after the scratch procedure, 242/453 women (53.9%) reported having experienced symptoms of blood loss, abdominal pain and/or fever, but only 12 women (2.6%) reported severe symptoms and none needed hospitalisation or antibiotic treatment (Table II).

Follow-up was completed in January 2020 when the last ongoing pregnancy resulted in live birth. The 12-month study flow is depicted in Fig. 2. Both groups were comparable as to their exposure to pregnancy chances in terms of number of started fresh IVF/ICSI cycles and total number of embryo transfers (Supplementary Table SII). Additional treatment characteristics of the second IVF/ICSI cycle are shown in Supplementary Tables SIII and SIV. While the study protocol demanded no additional scratches during follow-up, in the scratch group seven women received a second scratch and one woman a second and third scratch. In the control group, 11 women received a first scratch at some point after the second fresh IVF/ICSI treatment but during follow-up (Supplementary Table SV). Follow-up was completed for 889 participants (445/467 in scratch and 444/466 in control group), and 44 of the participants were lost at any time-point after randomisation.

Outcomes

In women with a previous failed cycle, live birth after the second fresh IVF/ICSI treatment occurred in 110/465 (23.7%) women in the scratch and 88/460 (19.1%) in the control group (RR 1.24 [95% CI 0.96–1.59]) (Table III). This equals an RD of 4.6% [95% CI −0.7% to +9.9%]. Biochemical pregnancy loss occurred in 17.6% versus 14.6% (RR 1.21 [95% CI 0.71–2.07]) of the pregnant women in the scratch and control group, respectively, and miscarriage in 11.1% and 15.3% (RR 0.73 [95% CI 0.38–1.40]), respectively, of the women with a clinical pregnancy (Table III).

After the full second IVF/ICSI treatment, live birth occurred in 149/465 (32.0%) women in the scratch and 132/460 (28.7%) women in the control group (RR 1.12 [95% CI 0.92–1.36]). Taking all treatments and pregnancies into account within the 12 months of time horizon, 202/467 (43.3%) women in the scratch and 178/466 (38.2%) women in the control group had reached a live birth, which corresponds to an RD of 5.1% [95% CI −1.2% to +11.4%] (Table III). The course of the 12-month follow-up period, showing time to biochemical pregnancy leading to live birth, is visualised in Fig. 3.

Results from the AT and AT+ET analysis for live birth, biochemical pregnancy loss and miscarriage were in line with the ITT analysis (Tables IV and V). Implantation rate was only calculated in the AT+ET analysis. In the scratch group, slightly more embryos were transferred in the second fresh IVF/ICSI treatment, and relatively more of these

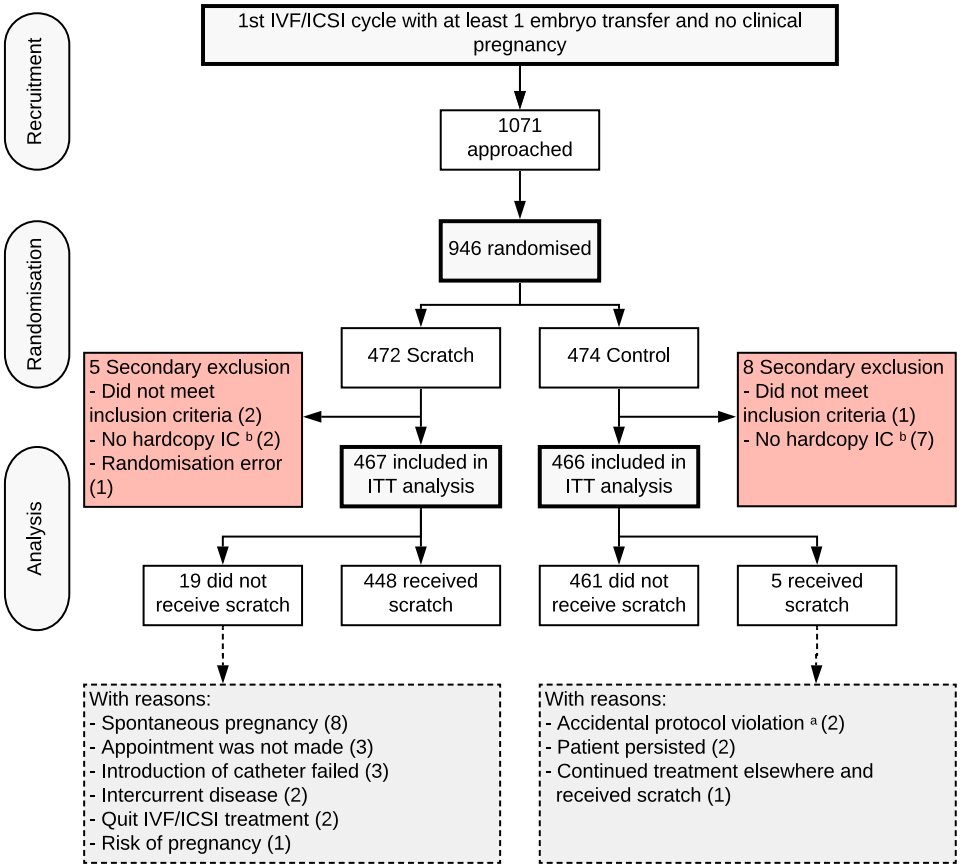

Figure 1. Flow chart of study inclusion. IC, informed consent; ITT, intention to treat. [a]Two participants provided IC but were accidentally registered as refuser due to misinterpretation of one of the items on the randomisation form. After discovering the unintended mistake, the randomisation was still performed. Cases were considered as protocol violations if the outcome was contrary to the misinterpreted allocation, and were analysed according to the ITT and the *as-treated* principle. [b]Hardcopy IC was mandatory by the Institutional Review Board. Participants who were randomised based on a digital copy of the IC and failed to hand over the hardcopy IC (despite repeated attempts to retrieve this) had to be excluded from analysis.

embryos implanted: 121/435 (27.8%) embryos in the scratch group and 99/413 (24.0%) in the control group (RR 1.09 [95% CI 0.96–1.25]) (Table V).

Discussion

The SCRaTCH multicentre trial included women with one failed IVF/ICSI treatment. After the fresh IVF/ICSI treatment directly after randomisation, 4.6% more live births were observed in the endometrial scratch group compared to controls, consistent with a true difference of between −0.7% and +9.9%. After 12 months of follow-up, the cumulative live birth rate was 5.1% higher in the scratch group compared to controls, compatible with a true difference of between −1.2% and +11.4% with 95% confidence.

Several reviews on endometrial scratching have been published, with some stating a cautious association between endometrial injury and increased pregnancy rates whilst others stated that no firm conclusions can be drawn. The overall message was that the studies performed up to that date included small sample sizes, heterogeneous study populations and had a high risk of bias (Nastri *et al.*, 2015; Santamaria *et al.*, 2016; Zygula *et al.*, 2016; Vitagliano *et al.*, 2018; van Hoogenhuijze *et al.*, 2019). The high risk of bias was also confirmed by a recent study that assessed methodological issues in RCTs on endometrial scratching in IVF/ICSI treatments (Li *et al.*, 2019): they concluded that almost all of the RCTs (23/25) suffered from at least one issue regarding trial registration, statistical methods or reproducibility of baseline/intermediate outcomes, and that many (19/25) had multiple issues. Fully published studies that had adequate trial registration and were evaluated as having no or few issues regarding statistical method or outcome inconsistencies include the PIP trial (Lensen *et al.*, 2019a), a study by Nastri *et al.* (2013) and a trial by Mak *et al.* (2017). In addition, two RCTs have been published even more recently: an RCT performed in Denmark (Olesen *et al.*, 2019) and the REFRESH trial (Mackens *et al.*, 2020).

Nastri *et al.* (2013) evaluated endometrial scratching by Pipelle compared to a sham procedure (drying the cervix with a gauze) 7–14 days

Table I Baseline characteristics of the participants.

	Scratch (n = 467)		Control (n = 466)	
Female age, years	35.5	(31.8–39.0)	35.4	(31.4–38.7)
Female BMI, kg/m^2[a]	23.5	(21.1–26.1)	24.1	(21.5–27.3)
Duration of infertility, months	29.0	(20.0–43.0)	32.0	(20.0–45.0)
Female smokers[b]	57	(12.6%)	62	(13.6%)
Type of infertility of the female[c]				
Primary	263	(56.3%)	257	(55.2%)
Secondary	204	(43.7%)	209	(44.9%)
Cause of infertility				
Idiopathic	138	(29.6%)	137	(29.4%)
Male factor	225	(48.2%)	213	(45.7%)
Tubal factor	21	(4.5%)	23	(4.9%)
Ovulatory disorder	18	(3.9%)	16	(3.4%)
Endometriosis grade I/II	5	(1.1%)	3	(0.6%)
Other	18	(3.9%)	25	(5.4%)
Mixed diagnosis	42	(9.0%)	49	(10.5%)
No. of previous embryo transfers—per participant	2.3	(±1.6)	2.2	(±1.5)

Data are presented as median (interquartile range), number (%) or mean (±SD).
[a]Data were missing for two participants in the scratch group and eight participants in the control group.
[b]Data were missing for 13 participants in the scratch group and 10 participants in the control group.
[c]Primary: female has never conceived before. Secondary: female has conceived before.

Table II Symptoms within the first week after the scratch.

		Scratch (n = 453)	
No. of patients that reported symptoms		242	(53.9%)
Blood loss		201	
	Minimal		168
	Moderate		30
	Severe		3
	Hospitalisation		0
Abdominal pain		150	
	Minimal		109
	Moderate		32
	Severe		9
	Hospitalisation		0
Fever		3	
	Telephone consultation with hospital		2
	Hospital visit and/or antibiotic Trt.		0
	Hospitalisation		0
	Unknown severity		1

Data were missing for four participants. In total, 112 participants reported experiencing more than one symptom: blood loss and abdominal pain (n = 111), blood loss and fever (n = 1). Women in the control group were not contacted to ask for any symptoms.
Trt, treatment.

prior to ovarian stimulation in 158 women using oral contraceptives and undergoing a fresh IVF/ICSI treatment. They found a statistically significant difference in live birth, with 41.77% live birth in the scratch group compared to 22.78% in the control group (RR1.83 [95% CI 1.13–2.97]).

Likewise, the Danish multicentre trial observed 6.9% more live births after mid-luteal phase scratching prior to ovarian stimulation in 304 women with at least one previous failed IVF/ICSI treatment (non-significant difference) (Olesen *et al.*, 2019). *Post-hoc* subgroup analyses did not yield significant results, but non-significant differences in live birth were observed with increased live birth rates after scratching in women with one failed transfer (RD 8.9%) and three or more failed transfers (RD 15.9%), and decreased live birth rate for women with two failed transfers (RD −11.0%). Mak *et al.* (2017) also performed an RCT that evaluated mid-luteal phase Pipelle scratching prior to the embryo transfer cycle, but they studied this in an unselected population undergoing a natural-cycle frozen-thaw embryo transfer, and they compared it to a control group undergoing an 'endocervical manipulation' sham procedure. No significant difference in combined outcome ongoing pregnancy/live birth rate was found (34.4% in the scratch group compared to 31.2% in the control group, RR 1.16 [95% CI 0.63–2.14]) (Mak *et al.*, 2017).

The PIP trial was a multicentre RCT including 1364 unselected participants undergoing fresh or frozen embryo transfers. Lensen *et al.* (2019a) compared a scratch, performed with an endometrial biopsy catheter anytime between cycle day 3 of the pre-transfer and cycle day 3 of the transfer cycle, to no scratch or sham, and found exactly no difference with 26.1% live births in both the scratch and control group.

The REFRESH RCT studied endometrial scratching in the follicular phase of the transfer cycle of 200 women, but stopped prematurely due to safety concerns. In interim analysis—the trial aimed to include 400 women—a higher miscarriage rate was observed in the scratch group (25% versus 8% in controls), while the live birth rate was

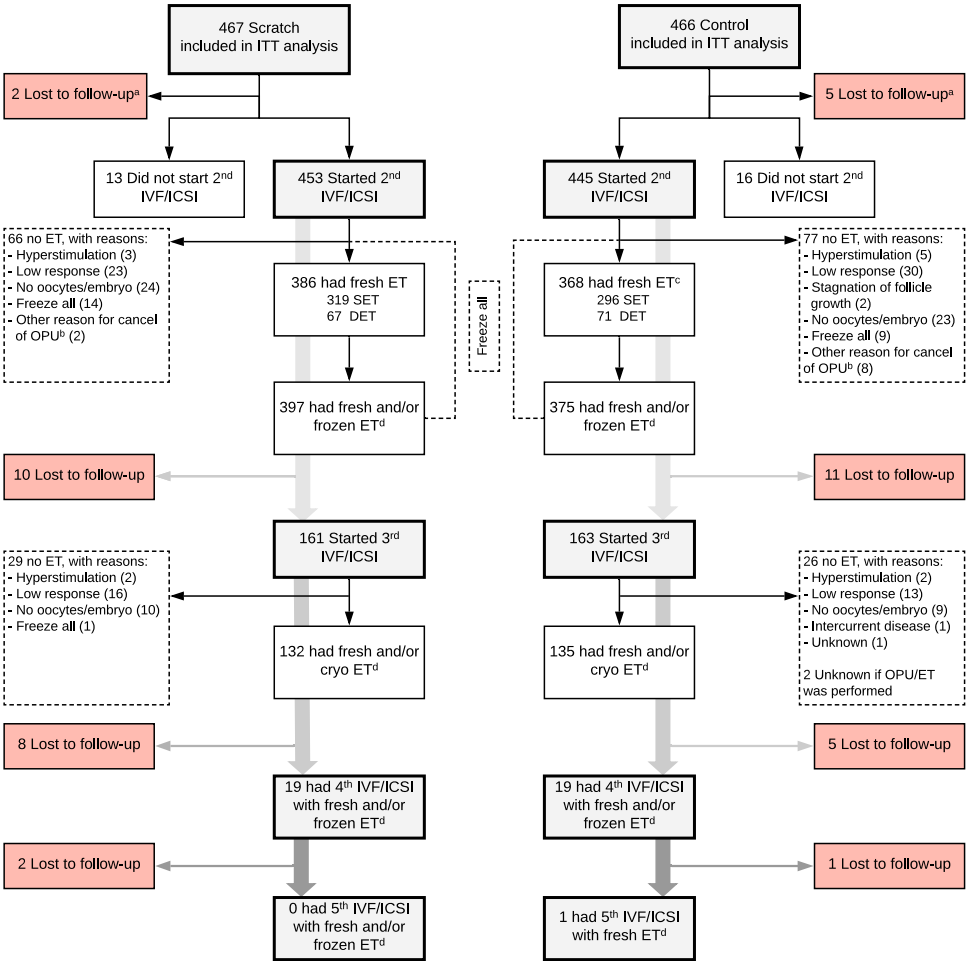

Figure 2. Flow chart of follow-up period. SET, single embryo transfer; DET, double embryo transfer; OPU, ovum pick-up; ET, embryo transfer. Only treatments are included of which the transfer could have resulted in an ongoing pregnancy (gestational age 10 weeks) at 12 months after randomisation. [a]Scratch group: one participant was withdrawn by the local investigator because of serious intercurrent disease. Control group: four participants withdrew consent immediately after randomisation. The other participants were true lost to follow-up. [b]Other reasons for cancel OPU: Scratch group: one used wrong stimulation dose, one personal circumstances. Control group: one ovarian cyst, one intercurrent disease, one premature ovulation, two no spermatozoa, one intracavitary remnants of previous miscarriage, two patient preference. [c]Data on SET or DET are missing for one participant, but it is known that she had an embryo transfer. [d]Supplementary Table SII provides cumulative information about the subsequent IVF/ICSI treatments.

comparable between scratch and controls (32% versus 36%, respectively) (Mackens *et al.*, 2020).

Like the current trial, all five RCTs mentioned above performed the scratch using an endometrial biopsy catheter (suction), but all have significant differences in their study population, scratching method and subsequent ART treatment. While the trials by Nastri *et al.* (2013) (unselected population), Olesen *et al.* (2019) (at least one failed IVF/ICSI cycle), and the SCRaTCH trial (just one failed IVF/ICSI cycle) studied the effect of *mid-luteal scratching* before a *fresh treatment with ovarian stimulation*, the trial by Mak *et al.* (2017) did this in a population undergoing *natural-cycle frozen-thaw* embryo transfer (Nastri *et al.*, 2013; Mak *et al.*, 2017; Olesen *et al.*, 2019). The REFRESH trial also included only women undergoing a fresh ovarian stimulation treatment, but they performed the scratch in the *same-cycle follicular phase* (Mackens *et al.*, 2020). The PIP trial included an unselected population undergoing either fresh or frozen transfer cycles, but performed the scratch at *any time between the cycle days three of the pre-transfer and same cycle* (Lensen *et al.*, 2019a). The three trials that studied mid-luteal scratching prior to ovarian stimulation observed increased live birth rates in the scratch group, while the trials evaluating scratching prior to frozen-thaw cycles or other-timed scratching found no difference in pregnancy rates, or even a possible harmful effect. These findings together suggest that the timing of the scratch and/or the specific patient population may play a role in the outcome.

Table III Pregnancy outcomes—intention-to-treat analysis.

	Scratch (n = 467)		Control (n = 466)		RR	95% CI
2nd *fresh* IVF/ICSI treatment (i.e. 1st after randomisation)[a]						
Biochemical pregnancy	153	(32.9%)	130	(28.2%)	1.17	0.96–1.42
Clinical pregnancy	126	(27.1%)	111	(24.1%)	1.13	0.90–1.40
Ongoing pregnancy	112	(24.1%)	94	(20.4%)	1.18	0.93–1.51
Live birth[b,c]	110	(23.7%)	88	(19.1%)	1.24	0.96–1.59
			Live birth Risk Difference		*4.6%*	*−0.7% to +9.9%*
Biochemical pregnancy loss[d]	27	(17.6%)	19	(14.6%)	1.21	0.71–2.07
Miscarriage[e]	14	(11.1%)	17	(15.3%)	0.73	0.38–1.40
2nd *full* IVF/ICSI treatment (i.e. 1st after randomisation)[a]						
Biochemical pregnancy	207	(44.5%)	187	(40.6%)	1.10	0.95–1.28
Clinical pregnancy	175	(37.6%)	161	(34.9%)	1.08	0.91–1.28
Ongoing pregnancy	152	(32.7%)	139	(30.2%)	1.08	0.90–1.31
Live birth[b]	149	(32.0%)	132	(28.7%)	1.12	0.92–1.36
Cumulative 12 months follow-up[f]						
Biochemical pregnancy	271	(58.0%)	240	(51.5%)	1.13	1.00–1.27
Clinical pregnancy	234	(50.1%)	211	(45.3%)	1.11	0.97–1.27
Ongoing pregnancy	208	(44.5%)	186	(39.9%)	1.12	0.96–1.30
Live birth[b]	202	(43.3%)	178	(38.2%)	1.13	0.97–1.32
			Live birth Risk Difference		*5.1%*	*−1.2% to +11.4%*
Singleton	191	(94.6%)	170	(95.5%)		
Twin	11	(5.4%)	8	(4.5%)		

Data are presented as number (%).
[a]Data were missing for two in scratch group and five in control group because of loss to follow-up, and one in control group was lost after reaching ongoing pregnancy.
[b]Loss of ongoing pregnancy occurred in 12 women during 12-month follow-up. Six in scratch: termination of pregnancy (4), intra-uterine foetal death (2). Six in control: termination of pregnancy (3), intra-uterine foetal death (2), extreme premature birth (1).
[c]Modes of conception: natural conception leading to live birth occurred in six women (three in scratch and three in control). In addition, one participant in the control group had a natural conception but became lost to follow-up after reaching ongoing pregnancy. Escape IUI leading to live birth occurred in one woman in the control group.
[d]Calculated using the number of biochemical pregnancies as denominator.
[e]Calculated using the number of clinical pregnancies as denominator.
[f]Conservative analysis, i.e. data are based on all participants (n = 933) and participants who were lost to follow-up (n = 44) were regarded as not pregnant/no live birth.
RR, risk ratio.

The SCRaTCH trial is the only RCT on scratching in the pre-transfer cycle with a follow-up period that extends beyond one embryo transfer. This enables looking into a possible carry-over effect of the scratch over multiple transfer cycles. In our results, the difference in live births was observed directly after the fresh transfer—after that, the control group did not seem to 'catch up' despite having had similar numbers of embryo transfers during the full study period. It remains difficult how to interpret these results as there are no RCTs for comparison and the putative biological effect of scratching has not been clarified. If, in the future, endometrial scratching appears to positively affect live birth chances, the biological and clinical effects in the long term should be evaluated further.

Important strengths of the SCRaTCH trial are the high participation rate, which reduces the risk of participation bias and improves generalisability, and that the study was powered on the outcome 'live birth', which is clinically the most important. The high participation rate most likely stems from the fact that in the Netherlands, scratching is not performed outside of clinical trials. Furthermore, the longer follow-up period allows us to study if a possible carry-over effect of scratching exists and if a single endometrial scratch leads to a reduced number of IVF/ICSI treatments needed to achieve a live birth over 12 months of time. This would be beneficial both in terms of patient burden and healthcare costs. A high rate of completion of follow-up was achieved in both arms, making the cumulative 12-month outcome more robust. Another strength is that the scratch was performed according to a strict protocol and using standardised timing, thereby limiting factors that could affect the possible effect of scratching. Lastly, the relative homogeneity of the study population—all participating women had undergone one previous IVF/ICSI treatment with at least one embryo transfer—could be interpreted as both a strength and a limitation: a strength because it reduces the possible confounders for an effect of scratching, and a limitation in terms of generalisability to participants with different numbers of failed IVF/ICSI transfers.

An important limitation is the lack of blinding. As endometrial scratching is not offered in daily practice in the Netherlands, allocation to the scratch group could have been an incentive to continue treatment despite, for instance, doubts or a suboptimal response.

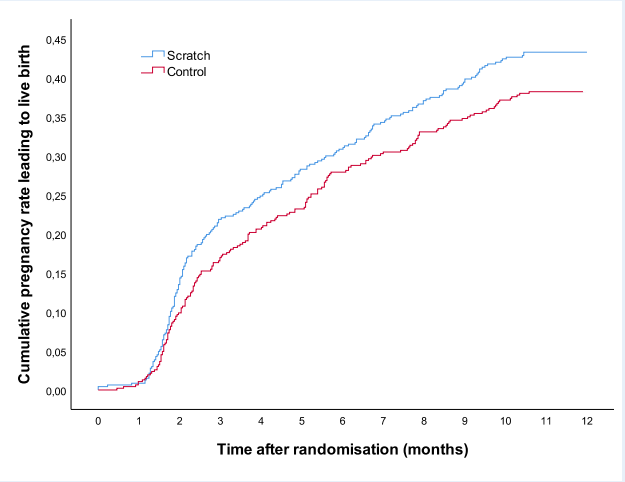

Figure 3. Time to biochemical pregnancy leading to live birth. Intention-to-treat analysis. Kaplan–Meier curve showing the time to biochemical pregnancy for the scratch (n = 467) and control (n = 466) groups. Participants who were lost to follow-up (scratch group n = 22; control group n = 22) were regarded as 'not pregnant/no live birth'.

Table IV Pregnancy outcomes—as-treated analysis.

	Scratch (n = 452)	Control (n = 471)	RR	95% CI
Second *fresh* IVF/ICSI treatment (i.e. first after randomisation)[a]				
Biochemical pregnancy	148 (32.7%)	135 (28.7%)	1.14	0.94–1.39
Clinical pregnancy	123 (27.2%)	114 (24.2%)	1.12	0.90–1.40
Ongoing pregnancy	109 (24.1%)	97 (20.6%)	1.17	0.92–1.49
Live birth	107 (23.7%)	91 (19.4%)	1.22	0.95–1.57
	Live birth risk difference		*4.3%*	*−1.0% to +9.6%*
Biochemical pregnancy loss[b]	25 (16.9%)	21 (15.6%)	1.09	0.64–1.85
Miscarriage[c]	14 (11.4%)	17 (14.9%)	0.76	0.40–1.48

Data are presented as number (%).
[a]Participants who were lost before the start of the subsequent treatment (n = 7) or whose scratch was attempted but failed (n = 3) were excluded. For live birth, data of one participant was missing.
[b]Calculated using the number of biochemical pregnancies as denominator.
[c]Calculated using the number of clinical pregnancies as denominator.

Continuation of the second IVF/ICSI treatment was slightly imbalanced: while 453 (96.8%) and 445 (96.5%) women in the scratch and control group, respectively, started this cycle, 386 (82.7%) had a fresh embryo transfer in the scratch group compared to 368 (79.0%) in the control group (Fig. 2). Baseline characteristics or 'subjective' reasons for not reaching embryo transfer did not explain this difference, but it cannot be excluded that participants with a 'low response' in the scratch group were less inclined to cancel their treatment than participants in the control group. In this instance, performance bias caused by resentful demoralisation is imaginable, but a sham procedure may also cause endometrial disruption, making blinding in scratch research a difficult choice (Lensen, 2018). In a study by Lensen (2018) on the use of a sham procedure in scratch research, knowledge of allocation was not proven to affect participant behaviour. In the current trial, the as-treated analysis on the population that received an embryo transfer (AT+ET) was performed in order to eliminate the effect of cycle cancellation. Importantly, this analysis showed similar results to the ITT analysis: a higher incidence of live births in the scratch group (Table V). This suggests that the observed difference in live birth is not merely a result of less embryo transfers being performed in the control group. Also, the slight imbalance in embryo transfers was only seen in the second IVF/ICSI treatment and not for subsequent IVF/ICSI treatments (Fig. 2). In fact, the total number of started cycles and embryo transfers during the study period of 12 months did not differ between the groups (Supplementary Table SII). Lastly, our literature-based power calculations were based on an expected 9% increase—from 30% to 39%—in live birth after the second fresh IVF/ICSI treatment. This increase may have been overly optimistic, which now leaves us with the difficult interpretation of an observed difference in live birth that to many clinicians and patients may come across as clinically relevant, but that has an uncertainty range also including a small negative effect. On the other hand, our live birth rates were lower than the estimated 30% chance of live birth for the control group. As no Dutch ART statistics were available for our specified population, we based our estimations on previously published literature on endometrial scratching and on the pregnancy rates of the general population undergoing ART in the Netherlands. In hindsight, we think that the 30% live birth rate was an overestimation of live birth chances and believe that our observations of 19.1% live birth rate in the control group reflect the average chance of live birth for our population in the Netherlands. While this may come across as a limitation, the lower 'basal' live birth rates actually *increase* the power of the outcome statistics—therefore, we do not consider this as a limitation of the trial.

Implications for future research

The first scratching RCTs focused on patients with recurrent implantation failure (Raziel *et al.*, 2007; Karimzadeh *et al.*, 2009; Shohayeb and El-Khayat, 2012), but over time scratching studies have shifted towards patients without a history of (repeated) implantation failure (Liu *et al.*, 2017; Hilton *et al.*, 2019). Nevertheless, general belief still is that if scratching works, it would do so for patients that had suffered from multiple implantation failures (Lensen *et al.*, 2016). The results of the smaller Danish trial support this theory (Olesen *et al.*, 2019), but this trend was not observed in the REFRESH or the large PIP trial (Lensen *et al.*, 2019a; Mackens *et al.*, 2020). Although the possibility exists that scratching has no or even a slight negative effect, the observed 4.6% difference in live birth is still an incentive to further assess whether a true effect exists. For this reason, a marker analysis that evaluates whether patient characteristics modify the effect of scratching will be performed on the SCRaTCH dataset to test whether certain subgroups of patients might benefit from scratching. Furthermore, the SCRaTCH, PIP, REFRESH and Danish trials are all part of an individual

Table V Pregnancy outcomes—as-treated analysis of the population with a fresh transfer.

	Scratch (n = 371)	Control (n = 343)	RR	95% CI
Second *fresh* IVF/ICSI treatment (i.e. first after randomisation)				
Biochemical pregnancy	143 (38.5%)	112 (32.7%)	1.18	0.97–1.44
Clinical pregnancy	119 (32.1%)	96 (28.0%)	1.15	0.92–1.44
Ongoing pregnancy	106 (28.6%)	81 (23.6%)	1.21	0.94–1.55
Live birth	104 (28.0%)	76 (22.2%)	1.27	0.98–1.64
	Live birth risk difference		*5.8%*	*−0.5% to +12.1%*
Biochemical pregnancy loss[a]	24 (16.8%)	16 (14.3%)	1.18	0.66–2.10
Miscarriage[b]	13 (10.9%)	15 (15.6%)	0.70	0.35–1.40
Total no. of embryos transferred	n = 435	n = 413		
Implantation rate[c]	121 (27.8%)	99 (24.0%)	1.09	0.96–1.25

Data are presented as number (%).
[a]Calculated using the number of biochemical pregnancies as denominator.
[b]Calculated using the number of clinical pregnancies as denominator.
[c]Calculated as the number of gestational sacs divided by the number of embryos transferred.

participant data-analysis (IPD) (van Hoogenhuijze *et al.*, 2017a) that will provide more power to detect a possible effect of scratching in different subgroups.

Implications for clinical practice

Studies conducted thus far have been too small to test whether a difference of 4–5% is statistically significant, while many clinicians and patients might find it clinically relevant. One could argue that scratching is simple, carrying a low risk of serious complications and could potentially increase live birth rates, which justifies implementation in daily practice. On the other hand, despite the fact that the largest proportion of the 95% CI is positive, we should keep in mind that the possibility exists that endometrial scratching has no, or even a small negative, effect on live birth rate. Participants experienced the procedure as mildly painful and a little over half of the participants reported any kind of complaints during the week after scratching, although it has to be noted that participants of the control group were not contacted to ask for symptoms. Thus, we cannot confirm whether the symptoms reported are related to the scratch or perhaps are caused by other medication used by the participants, such as pituitary down-regulation. Furthermore, patients undergoing fertility treatment are vulnerable (Nap and Evers, 2007) and clinicians should therefore carefully weigh the risk of withholding possibly effective treatment versus inappropriately offering interventions that increase both patients' hopes and expenses. Therefore, implementation of scratching into daily practice is premature. The IPD will be of major importance in the decision of whether or not endometrial scratching could become part of standard care.

Conclusion

In conclusion, in couples with one failed IVF/ICSI treatment, a 4.6% higher live birth rate after the second fresh IVF/ICSI treatment was observed after endometrial scratching, with an estimated true effect between −0.7% and +9.9%. A difference of 5.1% (95% CI −1.2% to +11.4%) was still seen after 12 months, taking all treatments and pregnancies within that period into account. These results suggest that a possible effect of scratching may be smaller than anticipated and/or may only apply to specific groups of women: addressing this will require larger sample sizes that will be provided by the currently ongoing IPD. At present scratching should not be applied outside of clinical trials.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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Authors' roles

N.E.v.H.: trial coordinator, statistical analyses, interpretation of results, drafting manuscript. F.J.M.B. and H.L.T.: trial design, obtaining funding, trial coordinator, interpretation of results, revising the manuscript, final approval of the manuscript. M.J.C.E.: supervising statistical analyses, interpretation of results, revising the pre-final manuscript, final approval of the manuscript. M.v.W.: methodological advice, revising the pre-final manuscript, final approval of the manuscript. All other co-authors: principal investigators at participating sites, revising the pre-final manuscript, final approval of the manuscript.

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Conflict of interest

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