ORIGINAL ARTICLE

A Randomized Trial of Endometrial Scratching before In Vitro Fertilization

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ABSTRACT

BACKGROUND

Endometrial scratching (with the use of a pipelle biopsy) is a technique proposed to facilitate embryo implantation and increase the probability of pregnancy in women undergoing in vitro fertilization (IVF).

METHODS

We conducted a pragmatic, multicenter, open-label, randomized, controlled trial. Eligible women were undergoing IVF (fresh-embryo or frozen-embryo transfer), with no recent exposure to disruptive intrauterine instrumentation (e.g., hysteroscopy). Participants were randomly assigned in a 1:1 ratio to either endometrial scratching (by pipelle biopsy between day 3 of the cycle preceding the embryo-transfer cycle and day 3 of the embryo-transfer cycle) or no intervention. The primary outcome was live birth.

RESULTS

A total of 1364 women underwent randomization. The frequency of live birth was 180 of 690 women (26.1%) in the endometrial-scratch group and 176 of 674 women (26.1%) in the control group (adjusted odds ratio, 1.00; 95% confidence interval, 0.78 to 1.27). There were no significant between-group differences in the rates of ongoing pregnancy, clinical pregnancy, multiple pregnancy, ectopic pregnancy, or miscarriage. The median score for pain from endometrial scratching (on a scale of 0 to 10, with higher scores indicating worse pain) was 3.5 (interquartile range, 1.9 to 6.0).

CONCLUSIONS

Endometrial scratching did not result in a higher rate of live birth than no intervention among women undergoing IVF. (Funded by the University of Auckland and others; PIP Australian New Zealand Clinical Trials Registry number, ACTRN12614000626662.)

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N Engl J Med 2019;380:325-34.
DOI: 10.1056/NEJMoa1808737

The success rate of in vitro fertilization (IVF) remains modest; the probability of live birth is approximately 25 to 30% per initiated cycle.[1-3] Endometrial scratching, which involves the obtaining of an endometrial-biopsy sample with a sampler such as the pipelle, has been proposed to increase the success rate of IVF. It has been postulated that the endometrial injury, or "scratch," that results from the biopsy may facilitate embryo implantation by inflammatory and immunologic mechanisms.[4-7]

Pooled results from randomized trials have suggested benefit from this procedure, especially in women in whom implantation had failed previously.[8] However, many trials have had methodologic limitations, including small size, and unclear methods of randomization and concealment of trial-group assignments; some have been published only as conference abstracts.[9-12] One of the larger trials with a robust design showed a lack of benefit from endometrial scratching; a subgroup analysis suggested lower rates of pregnancy with this intervention than with no intervention among women in whom implantation had failed repeatedly.[10,13] Despite conflicting evidence, a recent survey showed that 83% of fertility clinicians in the United Kingdom, Australia, and New Zealand offer or recommend endometrial scratching, which can cost patients as much as £400 (approximately $500 U.S.).[14]

We conducted the Pipelle for Pregnancy (PIP) trial to investigate whether endometrial scratching, delivered by an endometrial pipelle biopsy, increases the probability of live birth in women undergoing IVF.

Methods

Trial Design and Oversight

The trial protocol was published previously[15] and is available with the full text of this article at NEJM.org. Women were eligible if they were planning IVF with their own oocytes (stimulated IVF cycle with planned fresh-embryo transfer, or frozen-embryo transfer with the use of stored embryos); the choice of stimulation protocol and luteal-phase protocol was according to the standard practice at each clinic. Women were excluded if they were not planning an embryo transfer (e.g., fertility preservation or plan to freeze all embryos for storage [freeze-all cycle]), had any contraindication to pipelle biopsy (e.g., vaginismus), or had undergone any disruptive intrauterine procedures within 3 months before the start of IVF (specifically, hysteroscopy, sonohysterography, hysterosalpingography, laparoscopy, surgically managed miscarriage, or endometrial biopsy). Less disruptive procedures, such as embryo transfer and intrauterine insemination, were permitted. All women provided written informed consent.

The trial was approved by Northern A Health and Disability Ethics Committee, Ministry of Health, New Zealand, and subsequently by the relevant ethics committees at all sites internationally. The first two authors, the fourth author, and the fifth author vouch for the completeness and accuracy of the data and the fidelity of the trial to the protocol.

Randomization

An online, third-party data-collection and randomization system was used to confirm participant eligibility and ensure concealment of trial-group assignments before randomization. Randomization was performed in a 1:1 ratio with the use of block randomization of two different sizes between 6 and 16 repeating in random order, with stratification according to recruiting site and according to whether a fresh-embryo transfer or frozen-embryo transfer was planned. Women underwent randomization on or after day 1 of the cycle that preceded the IVF cycle. After randomization, trial personnel and participants were aware of the trial-group assignments (i.e., no blinding).

Intervention

Women who were assigned to endometrial scratching were scheduled for an endometrial scratch between day 3 of the cycle preceding the IVF cycle and day 3 of the IVF cycle. Day 1 of the IVF cycle was defined as the first day of the menstrual period or withdrawal bleeding, or the day before the first day of stimulation in the case of no bleeding. This time interval was based on previous studies showing benefit from this intervention.[16,17]

A clinician performed the endometrial-scratch procedures using a pipelle, a plastic biopsy catheter approximately 3 mm in diameter (e.g., Pipelle de Cornier, Laboratoire CCD, France). Participants were advised to attend with a full bladder and to take pain medication before the

procedure, according to clinic protocols. The procedure was carried out as described previously.[15] If it was not possible to insert the pipelle into the uterus, a tenaculum, local anesthetic, and cervical dilatation were permitted, or a second attempt was scheduled for another day or with a different clinician (or both). The procedure was discontinued at the participant's request (e.g., because of pain or discomfort) or if the clinician was unable to pass the pipelle. Immediately after the procedure, participants were asked to record the pain experienced during the procedure on a visual analogue scale (scores ranged from 0 to 10, with higher scores indicating worse pain). Participants were contacted within 1 week and asked whether they had any vaginal bleeding the day after the procedure. Participants who were assigned to the control group received standard care.

OUTCOMES

The primary outcome was live birth per randomly assigned woman; we included all participants in their randomly assigned groups and adjusted for stratification variables.[18] Secondary outcomes were ongoing pregnancy (viable pregnancy at 12 weeks of gestation), clinical pregnancy (one or more gestational sacs at approximately 6 weeks of gestation), multiple pregnancy (two or more gestational sacs or heartbeats at the stage of clinical pregnancy), ectopic pregnancy, biochemical pregnancy (defined as a serum level of beta human chorionic gonadotropin of >25 mIU per milliliter or a positive home urinary pregnancy test), miscarriage, stillbirth, pregnancy termination, pain during the procedure, bleeding the day after the procedure, and maternal and neonatal outcomes.

Data were also collected on pregnancy outcomes of delayed cycles and (unplanned) freeze-all cycles followed by frozen-embryo transfer if the embryo transfer occurred within 3 calendar months from the expected day 1 of the IVF cycle. Only the result of the first embryo transfer was captured. In addition, any spontaneous pregnancy that occurred before an embryo transfer and within the 3-month window was recorded.

STATISTICAL ANALYSIS

Originally, the sample size was calculated on the basis of the anticipated effect size of a 16-percentage-point difference between the two groups for the outcome of live birth, as reported in a Cochrane review.[19] At 90% power and a two-sided significance level of 5% and with an adjustment (doubling of the sample) to permit detection of subgroup effects, a sample of 840 women was required.[15]

After the publication of an updated Cochrane review that suggested that the anticipated effect of the intervention might differ between women in whom implantation had failed repeatedly and women in whom it had not, the sample-size calculation was updated on the basis of anticipated effects of the intervention in these two subgroups.[8] For the outcome of live birth and at 80% power and a two-sided significance level of 5%, 280 participants with at least two previous unsuccessful transfers were required to detect a between-group difference in live-birth rates of 15 percentage points (31% vs. 16%), and 1002 women with no more than one previous transfer were required to detect a difference of 8 percentage points (33% vs. 25%). Therefore, the trial aimed to recruit a minimum of 1300 women in total (650 per group, at a 1:1 ratio). The primary analyses were planned for the total trial population; post hoc, this would mean that the trial had 80% power to detect a between-group difference in live-birth rates of 7 percentage points. The sample-size amendment was implemented without knowledge of any interim results in the ongoing trial.

Odds ratios were calculated both with and without covariate adjustment for the stratification variables (site and fresh-embryo or frozen-embryo transfer), with 95% confidence intervals and P values. The adjusted analysis was the primary analysis. Prespecified subgroup analyses were conducted according to fresh-embryo or frozen-embryo transfer, implantation failure (≥2 or ≤1 previous unsuccessful transfers), recruiting center, cause of subfertility, duration of subfertility, exposure to nondisruptive instrumentation (yes or no), and use of contraceptive pills for IVF scheduling (yes or no). We performed these analyses by including an interaction term between trial-group assignment and each covariate in a multivariable logistic regression. Logistic regression was used to investigate prespecified predictors of live birth in the endometrial-scratch group: timing of scratch in relation to embryo transfer and pain during the procedure. Linear regression was used to investigate prespecified predictors of pain in the endometrial-

scratch group: previous cervical surgery, use of contraceptive pills for IVF scheduling, and use of a tenaculum. Confidence intervals for secondary outcomes and subgroups were not adjusted for multiple testing, and inferences that are drawn from the intervals may not be reproducible.

The primary analyses were performed with the use of R software[20] and conducted according to the intention-to-treat principle, including all women in their randomly assigned groups. Missing data were not imputed for any variables; however, the four women who withdrew and the one woman lost to follow-up were assumed not to have conceived.

Two post hoc per-protocol (treatment-received) analyses were performed, which attempted to estimate the effect of receiving endometrial scratching, with the use of randomization as an instrumental variable. These analyses were conducted in reaction to nonadherence observed in the trial, including differences in the proportions of women undergoing embryo transfer between the trial groups. In these analyses, the effect of receiving the scratch was estimated in the whole group and in the subgroup of women who underwent embryo transfer. Both analyses were performed by fitting bivariate probit models with robust standard errors in Stata software.[21]

RESULTS

PARTICIPANTS

Participants were recruited during a 3-year period from June 2014 through June 2017 at 13 sites in five countries (Table S1 in the Supplementary Appendix, available at NEJM.org). In total, 3627 women were assessed for eligibility, and 1364 underwent randomization, 690 to the endometrial-scratch group and 674 to the control group (Fig. 1). Baseline characteristics were similar in the two groups (Table 1, and Table S2 in the Supplementary Appendix). Approximately 25% of the participants had undergone two or more previous unsuccessful embryo transfers.

Cycle characteristics were similar in the two groups (Table 2 and Table 3). In total, 1118 participants (82.0%) underwent embryo transfer, 586 (84.9%) in the endometrial-scratch group and 532 (78.9%) in the control group. Of 133 women undergoing an unplanned freeze-all cycle, 67 underwent a frozen-embryo transfer within the 3-month window permitted by the trial protocol (Fig. 1). In addition, there were 2 women in the endometrial-scratch group whose frozen embryo did not survive thawing and who initiated a new IVF cycle with fresh-embryo transfer within the 3-month window. In total, 20 women became pregnant during the trial without IVF (17 women before starting their IVF cycle, 2 women who were discovered to be pregnant after starting their IVF medication but before oocyte retrieval, and 1 woman during a freeze-all cycle) (Fig. 1).

ENDOMETRIAL SCRATCH

Of the 690 women assigned to endometrial scratching, the procedure was performed in 641 (92.9%), either on the first or second attempt (Table S3 in the Supplementary Appendix). The procedure was not attempted in 28 women assigned to this intervention, and it was discontinued in 19 cases owing to difficulty navigating the cervical canal and in 1 case owing to participant request. (Information regarding completion of the procedure was missing for 1 participant.) The median time between endometrial scratch and embryo transfer was 35 days (interquartile range, 22 to 39).

Women who underwent the procedure had a median pain score of 3.5 on a 10-point scale (interquartile range, 1.9 to 6.0); 37 women had a score of 0, and 6 women had a score of 10. There were 14 adverse reactions: 5 women were recorded as having experienced excessive pain, including 1 woman who presented to the emergency

Figure 1 (facing page). Assessment, Randomization, and Analysis.

A total of 67 women (33 in the endometrial-scratch group and 34 in the control group) underwent randomization as planning a fresh in vitro fertilization (IVF) cycle but instead underwent a freeze-all cycle and subsequent frozen-embryo transfer within the 3-month trial period, and a total of 2 women in the endometrial-scratch group underwent randomization as planning a frozen-embryo transfer but instead underwent an IVF cycle with fresh-embryo transfer within the 3-month trial period (all denoted by numerals next to arrows in the lower portion of the figure). Pregnancies occurring without IVF refer to clinical pregnancies, except for one pregnancy that was a biochemical pregnancy only (positive pregnancy test), in a woman in the control group who underwent randomization as planning a fresh IVF cycle. ICSI denotes intracytoplasmic sperm injection, IUI intrauterine insemination, and OHSS ovarian hyperstimulation syndrome.

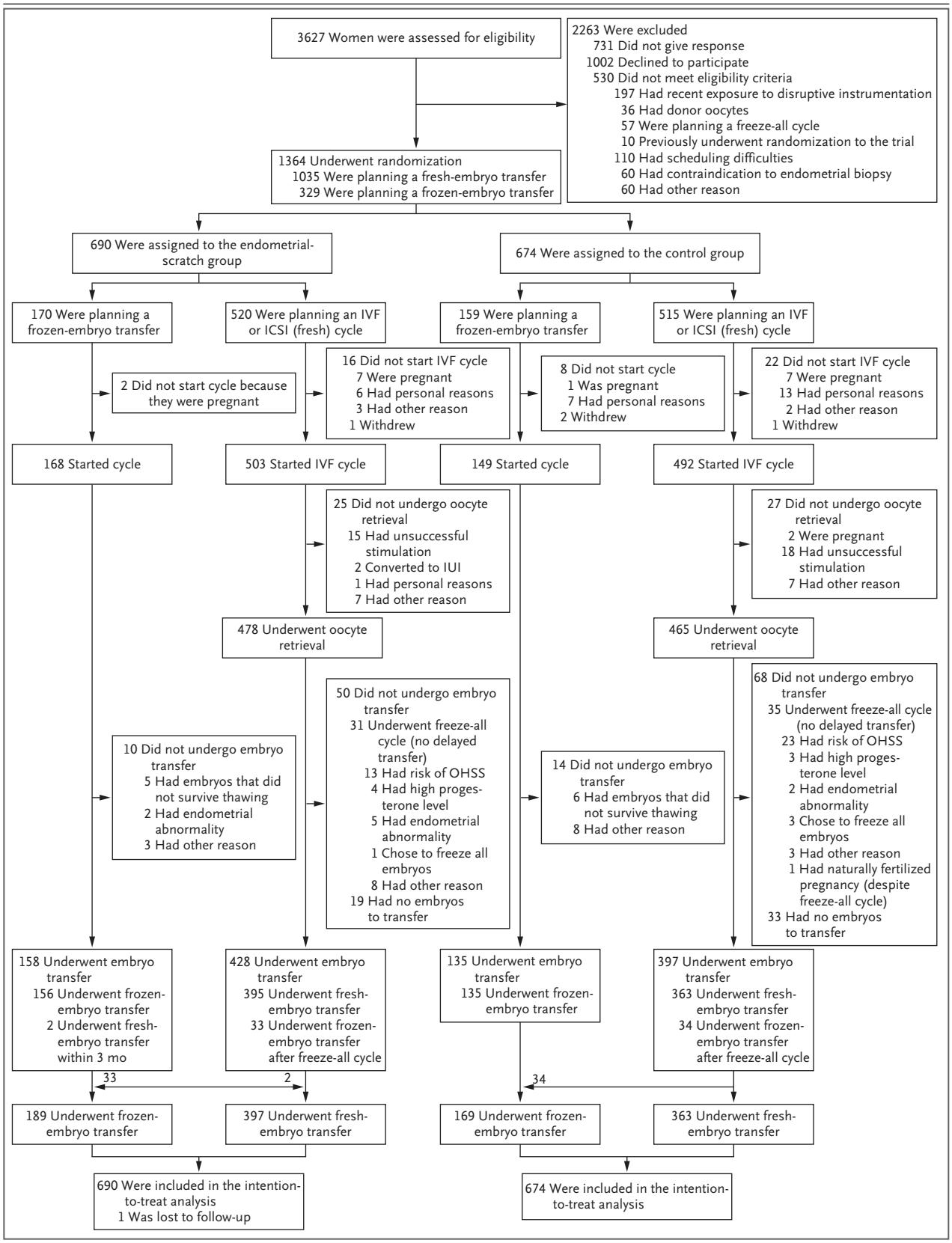

Table 1. Demographic and Clinical Characteristics of the Participants.*

Characteristic	Endometrial Scratch (N=690)	Control (N=674)
Median age (IQR) — yr†	35 (32–38)	35 (32–38)
Body-mass index — median (IQR)‡	23.7 (21.5–27.7)	23.9 (21.5–27.1)
Smoking status — no. (%)		
Current smoker	13 (1.9)	10 (1.5)
Former smoker	145 (21.0)	158 (23.4)
Never smoked	522 (75.7)	495 (73.4)
Missing data	10 (1.4)	11 (1.6)
Median duration of subfertility (IQR) — mo§	43 (30–60)	42 (29–60)
Cause of subfertility — no. (%)		
Ovulation disorder	75 (10.9)	86 (12.8)
Male factor	239 (34.6)	237 (35.2)
Tubal factor	78 (11.3)	80 (11.9)
Endometriosis	55 (8.0)	53 (7.9)
Unexplained	209 (30.3)	193 (28.6)
PGD or PGS	5 (0.7)	3 (0.4)
Same-sex couple	13 (1.9)	13 (1.9)
Other	15 (2.2)	8 (1.2)
Missing data	1 (0.1)	1 (0.1)
Type of subfertility — no. (%)		
Primary	382 (55.4)	352 (52.2)
Secondary	307 (44.5)	321 (47.6)
Missing data	1 (0.1)	1 (0.1)
No. of previous embryo transfers — no. of participants (%)¶		
0	325 (47.1)	301 (44.7)
1	156 (22.6)	173 (25.7)
2	109 (15.8)	90 (13.4)
≥3	100 (14.5)	110 (16.3)
No. of previous unsuccessful embryo transfers — no. of participants (%)¶		
0	350 (50.7)	332 (49.3)
1	174 (25.2)	171 (25.4)
2	85 (12.3)	89 (13.2)
≥3	81 (11.7)	82 (12.2)

* There were no significant between-group differences. Percentages may not total 100 because of rounding. IQR denotes interquartile range, PGD preimplantation genetic diagnosis, and PGS preimplantation genetic screening.
† Data on age were missing for 1 participant in the endometrial-scratch group.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 18 participants in each group.
§ Data on the duration of subfertility were missing for 8 participants in the endometrial-scratch group and 2 participants in the control group.
¶ Double-embryo or triple-embryo transfer was considered to be one embryo transfer.

department owing to intense pain after the endometrial scratch, which had been conducted concurrently with a sonohysterogram procedure; 7 women fainted or felt very dizzy or nauseous after the procedure; and 2 women had excessive bleeding. These outcomes were subjectively assessed by the clinician performing the procedure. There were no reported cases of infection or other adverse events after the procedure. The procedural information was not captured for 8 participants in the control group who underwent endometrial scratching despite their trial-group assignment.

PROTOCOL VIOLATIONS

In addition to the 36 participants whose treatment was inconsistent with their assignment, 5 women underwent a disruptive instrumentation procedure within 3 months before initiating the IVF cycle (four sonohysterogram procedures and one hysterosalpingogram procedure), including 4 in the endometrial-scratch group and 1 in the control group. A total of 4 women withdrew from the trial, all for personal reasons (Fig. 1). Demographic data were recorded for these women, but no further information was collected.

OUTCOMES

The live-birth rate was 180 of 690 (26.1%) in the endometrial-scratch group and 176 of 674 (26.1%) in the control group (adjusted odds ratio, 1.00; 95% confidence interval [CI], 0.78 to 1.27; P=0.97; unadjusted odds ratio, 1.00; 95% CI, 0.78 to 1.27; P=0.99) (Table 4). There were no significant between-group differences in the rates of ongoing pregnancy, clinical pregnancy, biochemical pregnancy, multiple pregnancy, ectopic pregnancy, or miscarriage (Table 4). The results of the per-protocol analyses were similar to those of the primary analysis (Table S4 in the Supplementary Appendix).

There was no evidence of any benefit from endometrial scratching among women in whom implantation had failed at least twice or among women in whom it had failed no more than once (estimated interaction odds ratio, 0.63; 95% CI, 0.35 to 1.15; P=0.14) (Table S5 in the Supplementary Appendix). In addition, there were no significant interactions for any other subgroups for the outcome of live birth (Table S5 in the Supplementary Appendix). Neither the days between endometrial scratch and embryo transfer

Table 2. Characteristics of Fresh IVF Cycle.*

Characteristic	Endometrial Scratch (N=447)	Control (N=431)
Stimulation protocol — no. (%)		
Long agonist	176 (39.4)	178 (41.3)
Short agonist or flare	32 (7.2)	18 (4.2)
Antagonist	231 (51.7)	231 (53.6)
Ultralong agonist	6 (1.3)	2 (0.5)
Missing data	2 (0.4)	2 (0.5)
Contraceptive pills used for IVF scheduling — no. (%)		
Yes	148 (33.1)	130 (30.2)
No	294 (65.8)	294 (68.2)
Missing data	5 (1.1)	7 (1.6)
Median level of total FSH (IQR) — IU†	2220 (1500–2925)	2100 (1500–3000)
Use of long-acting FSH — no. (%)‡	13 (2.9)	22 (5.1)
Median no. of oocytes retrieved (IQR)§	8 (5–11)	8 (5–12)
Insemination method — no. (%)		
IVF	179 (40.0)	171 (39.7)
ICSI or IVF–ICSI split	266 (59.5)	256 (59.4)
Missing data	2 (0.4)	4 (0.9)
Status with respect to embryo transfer — no. (%)		
No embryo transfer	50 (11.2)	68 (15.8)
Freeze-all cycle	31 (6.9)	35 (8.1)
No embryos to transfer	19 (4.3)	33 (7.7)
Embryo transfer	397 (88.8)	363 (84.2)
Single	322 (72.0)	292 (67.7)
Double	75 (16.8)	70 (16.2)
Triple	0	1 (0.2)
Day of embryo transfer — no./total no. (%)¶		
2	62/397 (15.6)	44/363 (12.1)
3	189/397 (47.6)	163/363 (44.9)
≥5	146/397 (36.8)	155/363 (42.7)
Missing data	0/397	1/363 (0.3)
Median no. of embryos frozen from trial cycle (IQR)‖	0 (0–2)	1 (0–2)

* Data include participants who underwent oocyte retrieval during the trial period, including 2 women who underwent randomization as planning a frozen-embryo transfer but who instead underwent an in vitro fertilization (IVF) cycle with fresh-embryo transfer within the 3-month trial period. The only characteristic that differed significantly between the two groups was the proportion of women who underwent embryo transfer (P=0.047); there was no adjustment made for multiple testing. Percentages may not total 100 because of rounding. FSH denotes follicle-stimulating hormone, and ICSI intracytoplasmic sperm injection.

† Data on the level of total FSH were missing for 15 participants in the endometrial-scratch group and 5 participants in the control group.

‡ Participants who used long-acting FSH were excluded from the median calculation.

§ Data on the number of oocytes retrieved were missing for 1 participant in the endometrial-scratch group and 2 participants in the control group.

¶ The denominator is the number of women who underwent embryo transfer.

‖ Data on the number of embryos frozen from the trial cycle were missing for 4 participants in the endometrial-scratch group and 2 participants in the control group.

Table 3. Characteristics of Frozen Embryo Transfer Cycle.*

Characteristic	Endometrial Scratch (N=201)	Control (N=193)
Stimulation protocol — no. (%)†		
Natural	106 (52.7)	94 (48.7)
Stimulated	30 (14.9)	34 (17.6)
Programmed	57 (28.4)	56 (29.0)
Missing data	8 (4.0)	9 (4.7)
Insemination method — no. (%)		
IVF	85 (42.3)	89 (46.1)
ICSI or IVF–ICSI split	110 (54.7)	98 (50.8)
Missing data	6 (3.0)	6 (3.1)
Status with respect to embryo transfer — no. (%)		
No embryo transfer	12 (6.0)	22 (11.4)
Embryo transfer	189 (94.0)	169 (87.6)
Single	163 (81.1)	141 (73.1)
Double	26 (12.9)	28 (14.5)
Missing data	0	2 (1.0)
Day of embryo transfer — no./total no. (%)‡		
2	7/189 (3.7)	7/169 (4.1)
3	23/189 (12.2)	21/169 (12.4)
≥5	158/189 (83.6)	140/169 (82.8)
Missing data	1/189 (0.5)	1/169 (0.6)

* Data include participants who planned to undergo or who underwent a frozen-embryo transfer during the trial period, including 67 women (33 in the endometrial-scratch group and 34 in the control group) who underwent randomization as planning a fresh IVF cycle but who instead underwent a freeze-all cycle and subsequent frozen-embryo transfer within the 3-month trial period. Not included are 2 women in the endometrial-scratch group who underwent randomization as planning a frozen-embryo transfer but who instead underwent an IVF cycle with fresh-embryo transfer within the 3-month trial period. There were no significant between-group differences. Percentages may not total 100 because of rounding.

† A stimulated cycle involved administration of FSH, clomiphene, or letrozole. A programmed cycle involved administration of estrogen and progesterone, usually with a gonadotrophin-releasing hormone antagonist. A natural cycle did not involve any of these medications. However, all three types of cycles may have involved luteal-phase support.

‡ The denominator is the number of women who underwent embryo transfer.

nor pain during the procedure was a predictor of live birth in the endometrial-scratch group (Table S6 in the Supplementary Appendix). In women undergoing endometrial scratching, pain was unrelated to previous cervical surgery or use of contraceptive pills for IVF scheduling but appeared to be slightly greater with the use of a tenaculum (Table S7 in the Supplementary Appendix).

DISCUSSION

The PIP trial was a large, pragmatic, multicenter, randomized trial of endometrial scratching as compared with no procedure before an IVF cycle. Endometrial scratching did not result in higher rates of the primary outcome of live birth than no procedure in intention-to-treat or in post hoc per-protocol analyses.

Subgroup analyses did not identify any populations of women who might benefit. There was no benefit observed in the subgroup of women in whom implantation had failed at least twice; the point estimate in an interaction analysis was in the direction of lower effectiveness of endometrial scratching in these women than in women in whom implantation had failed no more than once, as was reported in another large trial,[13] and the confidence interval suggests that a benefit is unlikely.

The median pain score during the procedure was 3.5 of 10, and there were 14 adverse reactions. Additional potential harms of endometrial scratching include cost and inconvenience; most procedures were scheduled as an extra clinic appointment, and in practice an endometrial scratch costs patients up to £400 when offered in a private fertility setting.[14]

The results from multiple previous trials have been inconsistent but have generally favored endometrial scratching in women undergoing IVF.[8,22-26] Many of these studies were small and underpowered or suffered from a high risk of bias, such as lack of concealment of trial-group assignments (which is known to be associated with exaggeration of treatment effect)[27,28] and other biases (e.g., stopping early for a positive effect).[8] The current trial had a large sample size, concealed trial-group assignments to limit the potential for selection bias, and had minimal attrition; four women withdrew from the trial, and the pregnancy outcome of only one other participant is unknown. The rate of single-embryo transfer was similarly high in both groups in this trial, which reflects current recommended practice and limits the potential for performance bias. Furthermore, the pragmatic trial design and the recruitment in 13 fertility clinics across five countries improves the generalizability of the results. Despite availability of the procedure privately in many fertility centers,[14] only eight participants in the control group are known

Table 4. Trial Outcomes (Intention-to-Treat Analysis).*

Outcome	Endometrial Scratch (N=690)	Control (N=674)	Adjusted Odds Ratio (95% CI)†
	number (percent)		
Live birth‡	180 (26.1)	176 (26.1)	1.00 (0.78–1.27)
Single	168 (24.3)	167 (24.8)	
Twin	11 (1.6)	9 (1.3)	
Triplet	1 (0.1)	0	
Biochemical pregnancy‡	273 (39.6)	269 (39.9)	0.98 (0.79–1.22)
Clinical pregnancy‡			
≥1 Gestational sac	217 (31.4)	210 (31.2)	1.01 (0.80–1.27)
≥1 Heartbeat	195 (28.3)	194 (28.8)	0.97 (0.76–1.23)
Ectopic pregnancy§	3 (0.4)	3 (0.4)	0.98 (0.18–5.32)
Multiple pregnancy§	15 (2.2)	12 (1.8)	1.22 (0.57–2.67)
Twin	14 (2.0)	11 (1.6)	
Triplet	1 (0.1)	1 (0.1)	
Ongoing pregnancy§	181 (26.2)	183 (27.2)	0.96 (0.76–1.23)
Miscarriage§	36 (5.2)	30 (4.5)	1.17 (0.10–1.94)
Stillbirth	0	2	NC
Termination§	1	2	0.48 (0.02–4.98)

* Data were imputed in one case: one woman with no pregnancy-test result was assumed to not be pregnant. Biochemical pregnancy is defined by a positive pregnancy test. Multiple pregnancy is defined by any scan with more than one heartbeat or gestational sac at the stage of clinical pregnancy (approximately 6 weeks). Miscarriages are losses of clinical pregnancy before 20 weeks, excluding ectopic pregnancy. Stillbirths are all losses of clinical pregnancy at or after 20 weeks (not including loss of one fetus in multiple pregnancies). Terminations are losses of an intrauterine pregnancy, through intervention by medical, surgical, or unspecified means. CI denotes confidence interval, and NC not able to be calculated.

† Confidence intervals have not been adjusted for multiple testing, and inferences drawn from the intervals may not be reproducible.

‡ The odds ratio was adjusted for both stratification factors: recruiting site and type of embryo transfer planned (fresh or frozen).

§ The odds ratio was adjusted for the type of embryo transfer planned (fresh or frozen) but not for recruiting site.

to have had the endometrial scratch during the trial and 92.9% of the women in the endometrial-scratch group completed the procedure.

An important limitation of our trial is the lack of blinding. It is possible that knowledge of trial-group assignments may have contributed to the higher proportion of participants in the control group than in the endometrial-scratch group who did not undergo embryo transfer. There were imbalances favoring the endometrial-scratch group both in the proportion of women starting an IVF cycle and in the number of women with embryos available for transfer after oocyte retrieval (Fig. 1). Women in the endometrial-scratch group may have been more likely to start their cycle in order to capitalize on their exposure to the endometrial scratch. However, results were materially unchanged in a per-protocol analysis. Another potential limitation is that the definition of recurrent implantation failure in this trial was two or more previous unsuccessful transfers and did not involve consideration of the stage or quality of the transferred embryos.[29] Last, because the outcomes of pain and bleeding were captured only in the endometrial-scratch group, it is not possible to compare the frequency of these adverse events between trial groups.

In conclusion, in this large, multicenter, pragmatic, randomized trial of endometrial scratching before IVF, endometrial scratching did not result in a higher live-birth rate than no endometrial scratching. The procedure was associated with a mild amount of pain and a small number of adverse events.

Supported by the University of Auckland, New Zealand; the A+ Trust, Auckland District Health Board, New Zealand; the Nurture Foundation, New Zealand; and the Maurice and Phyllis Paykel Trust, New Zealand.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the participants in this trial, and all the trial staff at each recruiting center.

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