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Therapeutic endometrial scratching and implantation after in vitro fertilization: a multicenter randomized controlled trial

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Objective: To study whether endometrial scratching in the luteal phase before ovarian stimulation increases clinical pregnancy rates in women with one or more previous implantation failures.
Design: A nonblinded multicenter randomized clinical trial.
Setting: Fertility clinics.
Patient(s): Three hundred four eligible patients scheduled for IVF/intracytoplasmic sperm injection were randomized. The intervention group (n = 151) underwent endometrial scratching in the luteal phase before controlled ovarian stimulation, while no intervention was performed in the control group (n = 153).
Intervention(s): Endometrial scratching with a Pipelle de Cornier catheter in the luteal phase before ovarian stimulation.
Main Outcome Measure(s): Clinical pregnancy rate and prenatal and birth data.
Result(s): There was no overall significant improvement in clinical pregnancy rates between the control and intervention groups (38.5% vs. 44.4%; relative risk = 1.15; confidence interval [0.86–1.55]). However, subgroup analyses revealed that women with three or more previous implantation failures had a significant increase in clinical pregnancy rate (31.1% vs. 53.6%; relative risk = 1.72; confidence interval [1.05–2.83]) after scratching. No difference was seen as regards prenatal and birth data between the two groups.
Conclusion(s): Endometrial scratching in the luteal phase before ovarian stimulation significantly enhances the clinical pregnancy rate in women with three or more prior implantation failures. This result seems to corroborate previous reports, which found that particularly women with repeated implantation failure seem to gain a positive effect from endometrial scratching. Importantly, there were no significant differences in prenatal data and birth data between the groups.
Clinical Trial Registration Number: NCT01963819. (Fertil Steril® 2019;112:1015-21. Copyright ©2019 The Authors. Published by Elsevier Inc. on behalf of the American Society for Reproductive Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Key Words: Endometrial scratching, endometrial injury, Pipelle de Cornier, pregnancy rate, repeated implantation failure

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Implantation is the rate-limiting step of pregnancy (1); however, previous studies have indicated that therapeutic endometrial scratching may enhance implantation in assisted reproductive technology (ART) (2–4). The benefit of endometrial scratching in humans was initially reported as a serendipitous finding because a high pregnancy rate was observed in IVF women who had undergone repeated endometrial biopsies during their preceding natural menstrual cycle. This led to the first published study on 134 patients, which showed a twofold increase in live birth rate (48.9% vs 22.5 %) (5). Subsequently, a number of studies have indicated a potential clinical value of this intervention (4, 6, 7), particularly in repeated implantation failure (RIF) patients (5, 8–10), while others failed to detect a benefit in patients, mainly in those undergoing their first or second IVF attempt (11–15). In contrast, a randomized controlled trial (RCT) showed that endometrial scratching carried out on the day of oocyte pickup resulted in a reduction of approximately two-thirds in the implantation rate in comparison with the control group (16). Since there is no consensus regarding the timing and optimal number of scratchings, heterogeneity exists in the current studies, and caution has been advised against extrapolating from these studies (17, 18). Only a few studies (4, 6, 11, 15) reported live birth rates, and only one study reported prenatal and birth data on the children born (15). Furthermore, only two studies had adequate power to draw reliable conclusions (11, 15).

The aim of this study was to investigate the impact of endometrial scratching on the clinical pregnancy rate in a nonblinded multicenter randomized controlled trial in women with one or more prior implantation failures. Secondary outcomes were implantation rate (defined as the number of gestational sacs observed at vaginal ultrasound after transfer divided by the number of transferred embryos), ongoing pregnancy rate, live birth rate, miscarriage rate (defined as the number of miscarriages per cycle initiated), multiple pregnancy rate, prenatal data, and offspring data.

MATERIALS AND METHODS

Ethics

The study was approved by the local Research Ethics Committee (1-10-72-72-13) and the Danish Data Protection Agency (1-16-02-115-13) and was registered at www.clinicaltrials.gov (NCT01963819). The study is reported according to the CONSORT guidelines.

Study Design and Participants

Patients were recruited during the period of February 2014 to December 2017 at four public fertility clinics in Denmark: Horsens Regional Hospital, Aalborg University Hospital, Skive Regional Hospital, and Herlev University Hospital. Eligible patients were IVF or intracytoplasmic sperm injection patients with one or more prior implantation failures, despite top-quality embryo or blastocyst (19) transfer(s). Further inclusion criteria were regular menstrual cycle (28–32 days), age 18–40 years, and a body mass index (BMI) 18–32 kg/m^2. Women with congenital uterine abnormalities, fibroids, or polyps were excluded, as were women with suspected hydrosalpinges and adenomyosis.

Randomization

After providing informed consent, the participants were randomized into blocks of 10 for each participating clinic in a ratio of 1:1, according to an Internet-based randomization list that was sealed in consecutively numbered opaque envelopes. The study was nonblinded, and no sham procedure was carried out in the control group.

Endometrial Scratching

Scratching was performed, using a Pipelle de Cornier (Laboratoires Prodimed) in the luteal phase before ovarian stimulation at cycle day 18–22 for the intervention group. The scratching was carried out with the patient lying in a lithotomy position and was performed once in each quadrant of the endometrium. Biopsies were snap frozen at −80°C.

ART

Participants were cotreated in a GnRH-antagonist protocol using recombinant FSH (rFSH) for controlled ovarian stimulation starting on cycle day 2 or 3 and a GnRH antagonist (0.25 mg/day Orgalutran, MSD) from stimulation day 5 to prevent premature luteinization. Patients were triggered with 6,500 IU hCG (Ovitrelle, Merck). Oocytes were retrieved and fertilized by either IVF or intracytoplasmic sperm injection, and a maximum of two embryos were transferred after 2–5 days of culture. Luteal-phase support was provided by vaginal P gel (Crinone 90 mg/dose, Merck) from the day after oocyte retrieval until the day of hCG testing (12–14 days after transfer).

Sample Size Calculation

The sample size for the RCT was based on a clinical pregnancy rate of 31% in the four participating clinics. To detect a 50% increase in clinical pregnancy rate (i.e., from 31% to 47%) at a significance level of $P = .05$ and a power of 0.80, we needed 146 participants in each group, in total, 292 participants.

Statistical Methods

Comparisons of the cycle characteristics were performed using a t test, Mann-Whitney U test, or χ^2 test. An intention to treat (ITT) analysis included all participants who were randomized, regardless of whether they completed full treatment or dropped out. Further, a per-protocol (PP) analysis of the participants who complied with their randomized treatment was performed to compare reproductive outcomes. A subgroup analysis was performed comparing reproductive outcome according to previous implantation failure (i.e., one, two, or three or more previous failed implantations). Two-sided $P < .05$ was considered statistically significant. Confidence intervals (CIs) were given at 95%. All statistical work was performed in STATA, 15.0 (StataCorp).

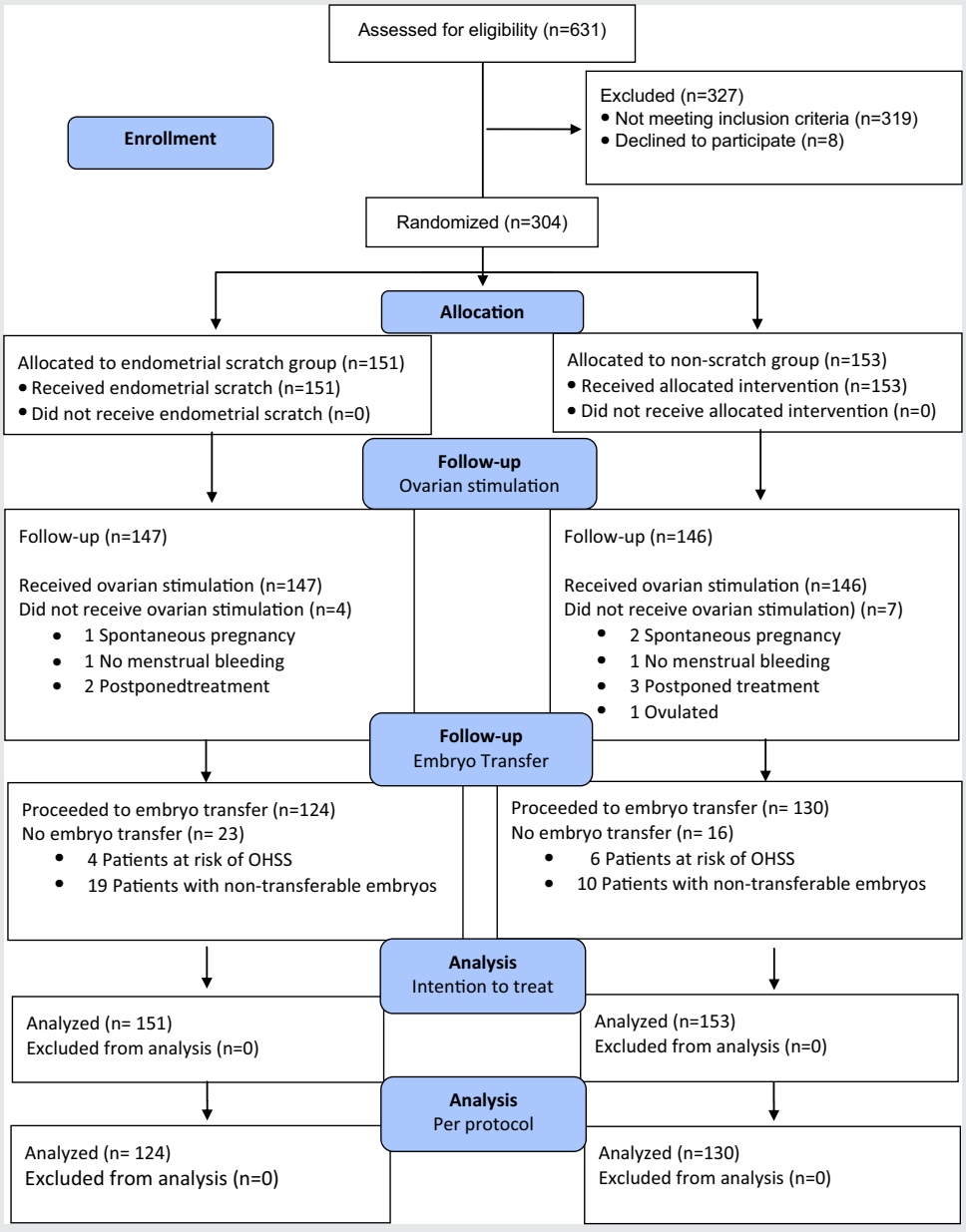
RESULTS

In total, 304 Caucasian women were included according to the CONSORT guidelines (Fig. 1). Of the 304 patients, 151 women were randomized to endometrial scratching and 153 patients to the control group. In all, 254 women completed the study with ET. There were no uterine infections, bleeding, or adverse events reported, besides a short pain during the endometrial scratching procedure.

Patients and Cycle Characteristics

Patients' baseline characteristics were well balanced with respect to age, BMI, indication of infertility, smoking, alcohol consumption, sum of previous transfers (including fresh and frozen transfers), and prior parity in both groups (Supplemental Table 1). Furthermore, there were no significant differences between the two groups with respect to cycle characteristics, as shown in Supplemental Table 2.

FIGURE 1



CONSORT 2010 flow diagram.

Olesen. Scratching for RIF patients only. Fertil Steril 2019.

Reproductive Outcomes

Reproductive outcomes of the endometrial scratch and nonscratch groups are listed in Table 1. There was no overall significant difference in the clinical pregnancy rate when comparing the scratch group to the nonscratch group based on ITT analysis: 36.4% versus 32.7%; relative risk (RR) = 1.11; CI (0.82–1.52), P=.492; and based on PP analysis: 44.4% versus 38.5%; RR = 1.15; CI (0.86–1.55), P=.340. Furthermore, no significant differences were found in implantation rate, ongoing pregnancy rate, live birth rate, miscarriage rate, and multiple pregnancy rate between the scratch and nonscratch group.

Subgroup Analyses

Subgroup analyses were performed by stratifying according to previous implantation failure (i.e., one, two, or three or more previous failed implantations). We found no significant difference between the scratch and nonscratch group within the two subgroups with one and two previous implantation failures.

Conversely, the subgroup of women with three or more previous implantation failures had a significant increase in reproductive outcome after scratching based on ITT analyses, namely, we found a significant increase in clinical pregnancy rate in the scratch group: 45.5% versus 27.5%; RR = 1.66; CI (1.01–2.78), P=.046. Based on PP analysis, when comparing the scratch and nonscratch groups, the following results were found with respect to clinical pregnancy rate: 53.6% versus 31.1%; RR = 1.72, CI (1.05–2.83), P=.024; ongoing pregnancy rate: 46.4% versus 26.7%; RR = 1.74, CI (1.00–3.05), P=.042); and live birth rate: 46.4% versus 26.7%; RR = 1.74, CI (1.00–3.05), P=.042. The subgroup analyses are listed in Table 2.

Subgroup analyses of baseline and cycle characteristics according to previous implantation failures are given in Supplemental Table 3. No significant differences were found, except for a significant difference in male factor infertility in the subgroup of women with three or more previous implantation failures (P=.043). Due to the Danish national policy of single ET, the multiple pregnancy rate was overall low, with three pairs of twins in total; the multiple pregnancy rate was therefore not given for the subgroup analyses. Furthermore, pregnancy rates by diagnosis are shown in Supplemental Table 4.

Prenatal Data and Birth Data

In total 87 children were born. In the endometrial scratch group, 50 children were born, including three pairs of twins. Prenatal data were comparable with respect to preeclampsia, intrauterine growth restriction (IUGR), gestational diabetes (GDM), and preterm birth (gestational age < 36 + 6 weeks). Furthermore, no significant differences in birth data were observed, including sex, length and birth weight, malformations/birth defects, and placenta malformations. The prenatal and birth data are listed in Table 3.

DISCUSSION

This multicenter RCT shows that endometrial scratching in the luteal phase before ovarian stimulation does not increase overall clinical pregnancy rates in women with one or more prior implantation failures. However, subgroup analyses indicate an increase in the clinical pregnancy rate in women with three or more previous implantation failures. These results are consistent with previous research that reported that women with RIF in particular may benefit from endometrial scratching (5, 8–10, 12), while no significant improvement could be demonstrated in unselected subfertile women (11, 13, 15).

Since embryo quality has been estimated to account for two-thirds of all implantation failures, a nonreceptive endometrium could be responsible for the remaining one-third

TABLE 1

Reproductive outcomes of the endometrial scratch and nonscratch groups using an ITT analysis of the randomized participants and a PP analysis of the participants complying with their randomization.

		ITT analysis (n = 304)		
Variable	**Scratch group (n = 151)**	**Nonscratch group (n = 153)**	**RR (95% CI)**	***P* value**
Clinical pregnancy rate	55/151 (36.4)	50/153 (32.7)	1.11 (0.82–1.52)	.492
Ongoing pregnancy rate	47/151 (31.1)	37/153 (24.2)	1.29 (0.89–1.86)	.176
Live birth rate	47/151 (31.1)	37/153 (24.2)	1.29 (0.89–1.86)	.176
Miscarriage rate	11/151 (7.3)	16/153 (10.5)	0.70 (0.33–1.45)	.331
		Analysis per protocol (n = 254)		
	Scratch group (n = 124)	**Nonscratch group (n = 130)**	**RR (95% CI)**	***P* value**
Clinical pregnancy rate	55/124 (44.4)	50/130 (38.5)	1.15 (0.86–1.55)	.340
Ongoing pregnancy rate	47/124 (37.9)	37/130 (28.5)	1.33 (0.94–1.90)	.110
Live birth rate	47/124 (37.9)	37/130 (28.5)	1.33 (0.94–1.90)	.110
Miscarriage rate	11/124 (8.9)	16/130 (12.3)	0.72 (0.35–1.49)	.374
Implantation rate	58/153 (37.9)	50/158 (31.6)	1.20 (0.88–1.63)	.246
Multiple pregnancy rate	3/55 (5.5)	0/50 (0)		.094

Note: Data in parentheses are percentages unless otherwise indicated.

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TABLE 2

Subgroup analyses.

		One previous failed implantation (n = 108)		
ITT	**Scratch group (n = 47)**	**Nonscratch group (n = 61)**	**RR (95% CI)**	***P* value**
Clinical pregnancy rate	18/47 (38.3)	19/61 (31.1)	1.23 (0.73–2.07)	.438
Ongoing pregnancy rate	15/47 (31.9)	14/61 (23.0)	1.39 (0.75–2.59)	.297
Live birth rate	15/47 (31.9)	14/61 (23.0)	1.39 (0.75–2.59)	.297
Miscarriage rate	4/47 (8.5)	8/61 (13.1)	0.65 (0.21–2.03)	.450
PP	**Scratch group (n = 37)**	**Nonscratch group (n = 49)**	**RR (95% CI)**	***P* value**
Clinical pregnancy rate	18/37 (48.6)	19/49 (38.8)	1.25 (0.77–2.03)	.360
Ongoing pregnancy rate	15/37 (40.5)	14/49 (28.6)	1.42 (0.79–2.56)	.245
Live birth rate	15/37 (40.5)	14/49 (28.6)	1.42 (0.79–2.56)	.245
Miscarriage rate	4/37 (10.8)	8/49 (16.3)	0.66 (0.22–2.03)	.465
Implantation rate	18/45 (40)	22/61 (36.1)	1.11 (0.68–1.81)	.680
		Two previous failed implantations (n = 79)		
ITT	**Scratch group (n = 38)**	**Nonscratch group (n = 41)**	**RR (95% CI)**	***P* value**
Clinical pregnancy rate	7/38 (18.4)	14/41 (34.1)	0.54 (0.24–1.19)	.114
Ongoing pregnancy rate	6/38 (15.8)	11/41 (26.8)	0.59 (0.24–1.44)	.233
Live birth rate	6/38 (15.8)	11/41 (26.8)	0.59 (0.24–1.44)	.233
Miscarriage rate	2/38 (5.3)	6/41 (14.6)	0.36 (0.08–1.67)	.168
PP	**Scratch group (n = 31)**	**Nonscratch group (n = 36)**	**RR (95% CI)**	***P* value**
Clinical pregnancy rate	7/31 (22.6)	14/36 (38.9)	0.58 (0.27–1.25)	.151
Ongoing pregnancy rate	6/31 (19.4)	11/36 (30.6)	0.63 (0.27–1.51)	.294
Live birth rate	6/31 (19.4)	11/36 (30.6)	0.63 (0.27–1.51)	.294
Miscarriage rate	2/31 (6.5)	6/36 (16.7)	0.39 (0.08–1.78)	.199
Implantation rate	8/38 (21.1)	14/45 (31.1)	0.68 (0.32–1.44)	.301
		Three or more previous failed implantations (n = 117)		
ITT	**Scratch group (n = 66)**	**Nonscratch group (n = 51)**	**RR (95% CI)**	***P* value**
Clinical pregnancy rate	30/66 (45.5)	14/51 (27.5)	1.66 (1.01–2.78)	.046[a]
Ongoing pregnancy rate	26/66 (39.4)	12/51 (23.5)	1.67 (0.94–2.98)	.069
Live birth rate	26/66 (39.4)	12/51 (23.5)	1.67 (0.94–2.98)	.069
Miscarriage rate	5/66 (7.6)	2/51 (3.9)	1.93 (0.39–9.35)	.409
PP	**Scratch group (n = 56)**	**Nonscratch group (n = 45)**	**RR (95% CI)**	***P* value**
Clinical pregnancy rate	30/56 (53.6)	14/45 (31.1)	1.72 (1.05–2.83)	.024[a]
Ongoing pregnancy rate	26/56 (46.4)	12/45 (26.7)	1.74 (1.00–3.05)	.042[a]
Live birth rate	26/56 (46.4)	12/45 (26.7)	1.74 (1.00–3.05)	.042[a]
Miscarriage rate	5/56 (8.9)	2/45 (4.4)	2.01 (0.41–9.87)	.378
Implantation rate	32/70 (45.7)	14/52 (26.9)	1.70 (1.01–2.84)	.034[a]

Note: Data in parentheses are percentages unless otherwise indicated. Reproductive outcomes stratified for one, two, and three or more implantation failures using an ITT and PP analysis.
[a] Statistically significant.

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(1). The subgroup of women with RIF are therefore more likely to have an endometrium-associated implantation failure, in contrast to the subgroup of women with one or two previous implantation failures. This result echoes a recent finding in which RIF patients were reported to have a specific endometrial gene expression profile predictive of RIF when compared with non RIF patients (20). To conclude that endometrial scratching may enhance the clinical pregnancy rate in RIF patients, we compared baseline and cycle characteristics in the subgroups as well (Supplemental Table 3). We found no differences except for male factor infertility in the subgroup of women with three or more implantation failures. However, none of the other parameters significantly differ from each other, especially the quality of the transferred embryos. Moreover, patients with male factor infertility had similar rates of clinical pregnancy, ongoing pregnancy, and live birth rate compared with patients with other causes of infertility (Supplemental Table 4). We therefore find this difference of minor importance and unlikely to create bias.

The studies of Yeung et al. (11) and Lensen et al. (15) were well powered (n = 300 patients and n = 1,364, respectively). Our study differs from that of Lensen et al. in that their study allowed marked heterogeneity, that is, fresh and frozen ETs, and a broad timing of endometrial scratching; also their definition of RIF differs from our study. This makes it a very generalizable and pragmatic study but difficult to compare with our study. Conversely, our study resembles the study of Yeung et al. in timing, number of endometrial scratchings,

TABLE 3

Prenatal and birth data of the endometrial scratch group and nonscratch group (84 women, 87 children).

Variable	Scratch group (50 children, 47 women)	Nonscratch group (37 children, 37 women)	*P* value
Preeclampsia	5/47 (10.6)	2/37 (5.4)	.389
IUGR	2/47 (4.3)	3/37 (8.1)	.439
GDM	2/47 (4.3)	2/37 (5.4)	.806
Preterm birth (gestational age < 36+6 wk)	7/47 (14.9)	4/37 (10.8)	.396
Sex male	22/50 (44.0)	20/37 (54.1)	.354
Sex female	28/50 (56.0)	17/37 (45.9)	.354
Length at birth, cm	50.26 ± 2.97	50.84 ± 2.85	.367
Weight at birth	3,242 ± 623	3,358 ± 699	.427
Birth defects/malformations	0	0	
Placenta malformations	4/47 (8.5)	3/37 (8.1)	.947

Note: Data in parentheses are percentages.

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and sample size, but our patient population is different because we included only women with one or more previous implantation failures. Noticeably, 69.7% of the recruited women were first-attempt IVF patients in the aforementioned study, which could be the reason why the results may not be generalizable to all women undergoing IVF, as also mentioned by the authors (11). This emphasizes how important it is to distinguish between patient populations, for example, previous implantation failures, when evaluating the effect of endometrial scratching. Further, a standard definition of RIF would be required as well as a consensus regarding the optimal number and timing of endometrial scratching(s).

A major strength of our RCT is that we included live birth rate, prenatal data, and birth data. This allows us not only to investigate whether endometrial scratching enhances reproductive outcomes in women with one or more prior implantation failures, but also to verify that no adverse effects are induced in pregnancy or in the children born after this intervention. In this context especially, implantation-related disorders such as preeclampsia and IUGR are of interest. Although our sample size was too small to claim any statistical significance of this observation, it is certainly of importance.

An additional strength is the sample size, which increases the statistical accuracy and strengthens our knowledge of endometrial scratching as a possible therapeutic intervention.

Some limitations of the study are that it was nonblinded and no sham procedure was used, but because clinical pregnancy rate is an objective outcome, these factors are unlikely to create bias.

Further, during recruitment for this study, a paradigm shift from cleavage culture to extended culture was impending at the different participating clinics. Another potential limitation of this study is, therefore, that it allowed marked heterogeneity, that is, combining the transfer of cleavage- and blastocyst-stage embryos and transfer of one or two embryos. Ideally, the study protocol should have been more standardized. However, randomization should reduce the chance of biasing the *results*. Lastly, our sample size calculation did not plan for more than 10% dropouts during the study (i.e., 304 women were randomized, and 254 women completed the transfer); therefore, the results of the PP analysis should be interpreted with caution. Despite these limitations, our study contributes to knowledge regarding a possible therapeutic intervention in ART for a subgroup of patients.

In conclusion, this multicenter RCT found that endometrial scratching in the luteal phase before ovarian stimulation does not increase overall clinical pregnancy rates in women with one or more previous implantation failures. However, subgroup analyses show that women with three or more previous failed implantations have a significant increase in clinical pregnancy rate with scratching. Importantly, no differences in prenatal and birth data were seen between scratched and nonscratched cycles.

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