

# Targeted Hysteroscopic Endometrial Scratching in Patients with Previous Implantation Failure: A Retrospective Cohort Study

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## SUMMARY

**Background/Aim:** Previous Implantation Failure (IF) remains a major challenge in assisted reproduction. Mechanical endometrial injury has been proposed to improve receptivity, though the ideal target population is debated. This retrospective study evaluated targeted hysteroscopic endometrial scratching in specific IF subgroups.

**Patients and Methods:** The study included 152 IF patients in a private IVF center from June 2021 to June 2022, split into an intervention group (n=76) undergoing targeted scratching and a matched control group (n=76). During the follicular phase of the prior unmedicated cycle, the sharp edge of an inverted 30-degree rigid hysteroscope created localized linear scratches before starting a fixed GnRH antagonist protocol with day 5 ET. We compared baseline characteristics, stimulation parameters, and reproductive outcomes. Statistical analyses included subgroup evaluations and multivariable logistic regression using SPSS 28.0.

**Results:** No significant differences in baseline demographics or stimulation parameters ( $p > 0.05$ ). The scratching group showed higher clinical pregnancy (46.1% vs. 27.6%,  $p=0.019$ ) and ongoing pregnancy rates (40.8% vs. 23.7%,  $p=0.024$ ). Subgroup analysis revealed significant ongoing pregnancy benefits only in women under 35 (50.0% vs. 27.3%,  $p=0.028$ ) and those with 2-3 prior failed cycles (48.1% vs. 28.0%,  $p=0.038$ ). No significant improvements were seen in women over 35 or with 4 or more failures. Multivariable analysis confirmed endometrial scratching (aOR 2.45,  $p=0.025$ ), age under 35 (aOR 2.15,  $p=0.036$ ), and 2-3 prior failures (aOR 1.95,  $p=0.042$ ) as independent predictors of ongoing pregnancy.

**Conclusion:** Targeted hysteroscopic endometrial scratching enhances pregnancy rates in patients with previous IF, especially in women under 35 with moderate prior failures.

## INTRODUCTION

In *Vitro* Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI) have revolutionized infertility treatment, but embryo implantation remains a major challenge in Assisted Reproductive Technology (ART). Despite advances in embryo selection and ovarian stimulation, implantation failure still limits success, causing psychological and financial stress [1]. Recurrent Implantation Failure (RIF), defined as the failure to achieve pregnancy after multiple transfers of good-quality embryos ( $>3$ ), presents a complex issue [2]. Its causes include embryonic genetic issues, suboptimal culture conditions, and reduced endometrial receptivity [3]. Ensuring a receptive endometrium during the implantation window is crucial, as embryo-endometrial cross-talk determines early pregnancy success [4].

To improve endometrial receptivity, endometrial scratching, a form of local mechanical injury, has become a debated adjunct in IVF. Originating from animal studies showing that uterine trauma prompts rapid decidualization [5], it gained clinical attention when studies reported increased pregnancy success following injury before IVF, especially in previous failure cases [6]. The mechanism is thought to involve a localized inflammatory response that releases cytokines, interleukins, and macrophages, aiding embryo attachment [7]. Additionally, this controlled trauma may counteract endometrial issues caused by ovarian hyperstimulation, restoring synchronization between the embryo and uterus [8].

Despite initial enthusiasm, research on endometrial scratching shows mixed results, with no clear consensus on its universal use. Some systematic reviews suggest it improves clinical pregnancy rates, especially in women with recurrent implantation failure [9]. However, large randomized trials indicate no benefit when applied routinely to unselected women or those undergoing their first IVF cycle [10]. These conflicting findings often reflect differences in timing, surgical technique, and patient characteristics [11]. Therefore, identifying which patient groups truly benefit from this procedure is crucial to avoid unnecessary interventions [12].

This retrospective study evaluates how endometrial scratching affects reproductive outcomes in patients with previous failed IVF undergoing ICSI cycles. We hypothesize that meticulous localized endometrial injury enhances clinical and ongoing pregnancy rates by creating a more receptive immunomodulatory environment.

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## PATIENTS AND METHODS

This retrospective, single-center cohort study assessed the impact of intentional endometrial injury on reproductive outcomes in patients with previous implantation failure. Conducted at a private IVF center (Bnoon Medical Center, Riyadh, Saudi Arabia) and ART center in Riyadh, Saudi Arabia, it used electronic medical records from ICSI cycles between June 2021 and June 2022. The Institutional Review Board of our center approved the study (IRB no: 2021-011), and it was conducted in accordance with the Declaration of Helsinki. Because it relied on anonymized historical data, the ethics committee waived written informed consent.

### Participants

Eligible participants were women aged 20 to 40 years with a documented history of implantation failure (at least one) who underwent an ICSI cycle utilizing a long GnRH antagonist protocol. We selected participants by reviewing the center's database. Inclusion criteria required a diagnosis of tubal factor, unexplained infertility, or mild male factor infertility. Patients were strictly excluded if they presented with severe male factor infertility requiring surgical sperm retrieval, endometriosis, adenomyosis, or untreated uterine cavity abnormalities such as submucosal fibroids or polyps. Routine post-transfer follow-up was standardized for all participants and consisted of a serum  $\beta$ -hCG test approximately 14 days after embryo transfer, followed by transvaginal ultrasound assessments for those with positive biochemical results.

The study compared an intervention cohort of women who underwent endometrial scratching from day 6 to day 14 of the preceding cycle of ovarian stimulation with a historical control cohort of women who received standard Intracytoplasmic Sperm Injection (ICSI) protocols without any mechanical endometrial intervention. The data collection period captured baseline evaluations, the duration of controlled ovarian stimulation and exposure to endometrial injury, and the follow-up period from the day of embryo transfer through the end of the first trimester to accurately capture ongoing clinical pregnancies.

### Procedure

#### Pre-Cycle Evaluation and Hysteroscopic Endometrial Injury

All patients underwent a comprehensive medical history and baseline assessment in the month before their scheduled ICSI cycle. On day 6 of this cycle, a baseline Transvaginal Ultrasound (TVUS) was performed. Patients then had an office hysteroscopy during the follicular phase once their endometrial thickness reached 7 to 9 mm. The procedure involved using a rigid 30-degree hysteroscope to carefully examine the uterine cavity and confidently rule out cervical polyps or signs of endometritis. During the same hysteroscopic assessment, the intervention group received targeted endometrial scratching by inverting the hysteroscope to use its sharp edge, creating distinct lines of mechanical injury along the anterior, posterior, and lateral uterine walls, mimicking localized curettage. Importantly, no medications or hormonal treatments were given during this cycle.

### Controlled Ovarian Stimulation with GnRH

Following the unmedicated preceding cycle, Controlled Ovarian Stimulation (COS) commenced on day 2 or day 3 of the subsequent menstrual cycle. Ovarian stimulation was initiated with daily subcutaneous injections of recombinant follicle-stimulating hormone (rFSH; Gonal-f®, Merck Serono, Darmstadt, Germany). The initial gonadotropin dose was carefully individualized based on the patient's predicted ovarian response, age, body mass index, and ovarian reserve markers. Follicular development and endometrial response were closely monitored using serial TVUS and serum estradiol measurements. To effectively prevent a premature Luteinizing Hormone (LH) surge, subcutaneous injections of a GnRH antagonist (Cetrotide® 0.25 mg, Merck Serono, Darmstadt, Germany) were routinely introduced on day 6 of the stimulation cycle and continued daily until the day of the ovulation trigger. The control cohort underwent this identical fixed antagonist protocol without the preceding hysteroscopic endometrial injury.

#### Dual Trigger, Oocyte Retrieval and Embryo Transfer

Once TVUS confirmed the presence of an optimal cohort of mature follicles, specifically, at least two to three follicles measuring 17 mm or more, the final oocyte maturation was triggered using a dual approach. This involved administering a GnRH agonist (Decapeptyl® 0.2 mg, Ferring Pharmaceuticals, Saint-Prex, Switzerland) combined with recombinant hCG (Ovitrelle® 250 µg, Merck Serono, Darmstadt, Germany). Transvaginal ultrasound-guided oocyte retrieval (OPU) was then performed under conscious sedation approximately 36-38 hours after the trigger. In the embryology lab, we denuded the retrieved metaphase II (MII) oocytes and fertilized them via standard ICSI methods. Based on the number of viable oocytes and embryonic development, we selected up to two high-quality embryos for transfer on day 5 (blastocyst stage). We performed embryo transfer with a soft semirigid catheter under continuous transabdominal ultrasound guidance to ensure precise placement.

#### Luteal Phase Support and Pregnancy Assessment

Luteal phase support began on the day of oocyte retrieval with twice-daily vaginal progesterone (Crinone® 8% gel, Merck Serono, Darmstadt, Germany). About 14 days after embryo transfer, a quantitative serum  $\beta$ -hCG pregnancy test was performed. If positive, luteal support continued until the 12th week of pregnancy. Clinical pregnancy was defined as the visual detection of an intrauterine gestational sac with a fetal heartbeat via TVUS between 6 and 8 weeks of gestation. The primary outcomes included ongoing pregnancy, defined as at least one fetus alive and progressing past 12 weeks, and the clinical pregnancy rate.

The primary outcomes were the clinical pregnancy rate, defined as the presence of at least one intrauterine gestational sac with a visible fetal heartbeat on transvaginal ultrasound at 6 to 8 weeks, and the ongoing pregnancy rate, indicating a viable pregnancy extending beyond the 12th week. Secondary outcomes included

the biochemical pregnancy rate (positive serum  $\beta$ -hCG), implantation rate, and fertilization rate. The primary exposure was targeted mechanical endometrial injury affecting the anterior, posterior, and lateral uterine walls, performed via office hysteroscopy during the follicular phase before treatment. To evaluate the intervention's independent effect, we identified and documented potential confounders, including maternal age, BMI, baseline antral follicle count, infertility type and duration (primary or secondary), and endometrial thickness on the day of dual trigger.

## Bias

To reduce selection and information bias in this retrospective cohort study, we implemented strict measures. Rigorous inclusion and exclusion criteria created a homogeneous group of patients with at least one implantation failure, excluding confounders like untreated uterine pathologies and severe male infertility. We standardized clinical and laboratory protocols; all patients received the same fixed GnRH antagonist protocol, the same surgeon performed hysteroscopic procedures uniformly. All patients had day 5 Blastocyst ET. We defined outcomes using objective measures: serum  $\beta$ -hCG levels and ultrasound-confirmed fetal cardiac activity, minimizing observer bias.

## Sample size justification

We determined the sample size based on the primary outcome of clinical pregnancy from a previous study by Kalyoncu et al [13] on luteal phase hysteroscopy and endometrial biopsy; we estimated a 67% pregnancy rate in the endometrial scratching group and 45% in the control group. To detect this 22% difference with 80% power and a 5% significance level using a 1:1 ratio, we needed at least 76 patients per group, for a total of 152 participants. We achieved this by reviewing electronic medical records of all eligible patients treated from June 2021 to June 2022 who met the strict inclusion and exclusion criteria.

## STATISTICAL ANALYSIS

All statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean  $\pm$  standard deviation and compared using the independent Student's t-test. Categorical variables are presented as frequencies and percentages and analyzed with the Pearson Chi-square or Fisher's exact test as appropriate. To assess interaction effects, we performed predefined subgroup analyses, stratifying outcomes by maternal age, previous failed cycles, and embryo

transfer stage. To account for baseline confounders and identify independent prognostic factors, we developed a multivariable logistic regression model and reported adjusted odds ratios with 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

Table 1 presents the baseline demographic and clinical features of both the endometrial scratching and control groups. All evaluated parameters, including maternal age, body mass index, infertility duration, and baseline ovarian reserve markers, showed no significant differences ( $p > 0.05$ ), suggesting the groups were well matched and comparable before the intervention.

Table 2 displays data on controlled ovarian stimulation parameters, embryological outcomes, and reproductive results. Although there were no significant differences in stimulation duration, gonadotropin dose, and oocyte parameters ( $p > 0.05$ ), the rates of biochemical, clinical, and ongoing pregnancies differed significantly ( $p < 0.05$ ). The miscarriage rate differences between groups were not statistically significant.

Table 3 presents subgroup analyses of ongoing pregnancy rates after consistent Day 5 blastocyst transfers. Significant differences ( $p < 0.05$ ) were found in patients under 35 and those with 2-3 previous failed cycles. In contrast, groups categorized by advanced maternal age and four or more prior failures showed no significant differences.

Table 4 presents the multivariable logistic regression model predicting ongoing pregnancy in the Day 5 transfer cohort. Endometrial scratching, maternal age below 35, and having 2-3 previous failures were identified as statistically significant independent predictors ( $p < 0.05$ ). Conversely, body mass index showed a non-significant odds ratio in this particular model.

Statistical comparisons between the endometrial scratching and control groups were performed using the independent Student's t-test for continuous data and the Pearson Chi-square or Fisher's exact test for categorical data.

Continuous variables regarding ovarian stimulation and embryological data are expressed as mean  $\pm$  standard deviation and analyzed using the independent Student's t-test. Categorical reproductive outcomes (pregnancy and miscarriage rates) are presented as frequencies (percentages) and compared utilizing the Pearson Chi-square or Fisher's exact test. \*Statistically significant ( $p < 0.05$ ).

**Tab. 1.** Baseline demographic and clinical characteristics of the study groups.

| Parameter                            | Endometrial Scratching Group (n=76) | Control Group (n=76) | p-value |
|--------------------------------------|-------------------------------------|----------------------|---------|
| Age (years)                          | 32.1 $\pm$ 6.8                      | 33.5 $\pm$ 7.2       | 0.21    |
| Body mass index (kg/m <sup>2</sup> ) | 30.4 $\pm$ 5.6                      | 29.3 $\pm$ 5.5       | 0.21    |
| Duration of infertility (years)      | 5.8 $\pm$ 3.8                       | 6.8 $\pm$ 4.2        | 0.12    |
| Type of infertility (Primary), n (%) | 51 (67.1%)                          | 49 (64.5%)           | 0.73    |
| Number of previous failed cycles (n) | 2.7 $\pm$ 1.4                       | 3.0 $\pm$ 1.6        | 0.21    |
| Baseline FSH (IU/L)                  | 7.1 $\pm$ 3.5                       | 8.0 $\pm$ 3.9        | 0.14    |
| Baseline estradiol (pg/mL)           | 48.2 $\pm$ 28.5                     | 55.4 $\pm$ 32.1      | 0.14    |
| Baseline antral follicle count (n)   | 12.8 $\pm$ 6.8                      | 11.2 $\pm$ 7.1       | 0.15    |

**Tab. 2.** Controlled ovarian stimulation parameters, embryological data, and reproductive outcomes.

| Parameter                                     | Endometrial Scratching Group (n=76) | Control Group (n=76) | p-value |
|-----------------------------------------------|-------------------------------------|----------------------|---------|
| Stimulation & Embryology                      |                                     |                      |         |
| Stimulation duration (days)                   | 9.6 ± 2.8                           | 10.2 ± 3.1           | 0.21    |
| Total gonadotropin dose (IU)                  | 2580 ± 1150                         | 2810 ± 1250          | 0.24    |
| Endometrial thickness on trigger day (mm)     | 9.3 ± 2.2                           | 9.8 ± 2.5            | 0.19    |
| Total oocytes retrieved (n)                   | 9.8 ± 8.1                           | 8.3 ± 7.2            | 0.23    |
| MII oocytes (n)                               | 7.0 ± 7.2                           | 5.8 ± 6.4            | 0.28    |
| Number of blastocysts (Day 5) transferred (n) | 1.7 ± 0.5                           | 1.6 ± 0.5            | 0.22    |
| Pregnancy Outcomes                            |                                     |                      |         |
| Biochemical pregnancy, n (%)                  | 39 (51.3%)                          | 25 (32.9%)           | 0.021*  |
| Clinical pregnancy, n (%)                     | 35 (46.1%)                          | 21 (27.6%)           | 0.019*  |
| Ongoing pregnancy, n (%)                      | 31 (40.8%)                          | 18 (23.7%)           | 0.024*  |
| Miscarriage, n (%)                            | 4 (11.4%)                           | 3 (14.2%)            | 0.75    |

**Tab. 3.** Subgroup analyses of ongoing pregnancy rates stratified by maternal age, prior failures, and embryo developmental stage.

| Subgroup Parameter  | Endometrial Scratching (n=76) | Control (n=76) | p-value |
|---------------------|-------------------------------|----------------|---------|
| Maternal Age        |                               |                |         |
| < 35 years          | 23/46 (50.0%)                 | 12/44 (27.3%)  | 0.028*  |
| ≥ 35 years          | 8/30 (26.7%)                  | 6/32 (18.8%)   | 0.46    |
| Prior Failed Cycles |                               |                |         |
| 2-3 prior failures  | 25/52 (48.1%)                 | 14/50 (28.0%)  | 0.038*  |
| ≥ 4 prior failures  | 6/24 (25.0%)                  | 4/26 (15.4%)   | 0.4     |

**Tab. 4.** Multivariable logistic regression model of variables related to the probability of ongoing pregnancy.

| Variable                            | Odds Ratio (OR) | 95% Confidence Interval (CI) | p-value |
|-------------------------------------|-----------------|------------------------------|---------|
| Endometrial Scratching (Yes vs. No) | 2.45            | 1.12 – 5.34                  | 0.025*  |
| Maternal Age (< 35 vs. ≥ 35 years)  | 2.15            | 1.05 – 4.40                  | 0.036*  |
| Prior Failures (2-3 vs. ≥ 4)        | 1.95            | 1.02 – 3.75                  | 0.042*  |
| Body Mass Index (continuous)        | 0.98            | 0.89 – 1.07                  | 0.45    |

Table 3. Subgroup analyses of ongoing pregnancy rates stratified by maternal age, prior failures, and embryo developmental stage.

Statistical differences between the intervention and control groups within each specific subgroup were evaluated using the Pearson Chi-square or Fisher's exact test.

## DISCUSSION

### Our Results and Their Interpretation

This retrospective cohort study examined targeted hysteroscopic endometrial scratching in patients with at least one implantation failure. It found significantly higher clinical ( $p=0.019$ ) and ongoing pregnancy rates ( $p=0.024$ ) than in matched controls. No significant differences were observed in baseline demographics (maternal age,  $p=0.21$ ), ovarian reserve markers (baseline FSH,  $p=0.14$ ), or ovarian stimulation parameters (total gonadotropin dose,  $p=0.23$ ) between groups. These results indicate that performing precise mechanical endometrial injury specifically on day 6 of the previous cycle can positively modify the uterine environment. By triggering localized inflammation and tissue repair, the procedure might improve endometrial receptivity and embryo implantation, potentially addressing barriers in these studied groups.

Our study found that endometrial scratching significantly benefits women under 35 ( $p=0.028$ ). For women aged 35 and above, ongoing pregnancy rates did not increase significantly ( $p=0.46$ ). This likely stems from different causes of IVF failure in each group: younger women often experience implantation failure (IF) due to endometrial

receptivity issues, which scratching can help improve. In contrast, older women's failures are more often due to diminished oocyte quality and higher rates of embryonic aneuploidy, making endometrial scratching less advantageous when embryonic quality is the core problem.

Our subgroup analysis by severity of Implantation Failure (RIF) provided mechanistic insights. Patients with two to three failed cycles experienced a significant increase in ongoing pregnancy rates ( $p=0.038$ ). However, those with four or more failures did not see a significant benefit ( $p=0.40$ ). Fewer than 3 RIFs may stem from treatable local issues such as insufficient decidualization or immune dysregulation, which could respond to the immunomodulatory effects of mechanical scratching. Conversely, more than 3 IFs, involving at least four failed transfers, probably indicate a complex, multifactorial problem, potentially genetic, systemic immunological, or anatomical, that cannot be fixed with simple local mechanical injury. Multivariable logistic regression revealed that targeted endometrial scratching, younger maternal age, and fewer previous failures are independent predictors of ongoing pregnancy, confirming the intervention's therapeutic benefit. Our method involved using an inverted 30-degree rigid hysteroscope from day 6 to 14th day of an unmedicated cycle to create targeted linear scratches, allowing direct visualization to exclude cavitory pathologies and ensure consistent injury depth and placement. Performing the procedure in the cycle prior to the GnRH antagonist protocol prevents interference with endometrial synchronization during stimulation. This precise technique likely boosts the local inflammatory response conducive to implantation while reducing structural disruption during this vital period.

## Comparison of our results to similar studies

Our research indicates a notable advantage of endometrial scratching in patients with implantation failure and normal ovarian reserve, in contrast to Kalyoncu et al.'s [13] conclusion of no benefit. Their study targeted poor ovarian responders with reduced oocyte yield and embryonic quality, whereas our group consisted of IF patients with typical ovarian reserve. The significant clinical pregnancy rate ( $p=0.019$ ) supports that mechanical endometrial injury may improve uterine receptivity and help bypass localized implantation obstacles. Nevertheless, it does not address the substantial oocyte quality and quantity challenges faced by poor responders.

Our findings corroborate the positive therapeutic effect reported by Bar et al. [14], who examined endometrial scratching in patients with unexplained RIF. However, our results offer a more realistic perspective of typical practice. Bar et al. observed a striking difference in clinical pregnancy rates, 38.4% in the intervention group compared to 0.9% in controls, based on an imbalanced sample. In contrast, our matched 1:1 cohort demonstrated a more expected increase, 46.1% versus 27.6%. Furthermore, while Bar et al. noted overall benefits in RIF, our subgroup analyses suggest mechanical injury is most effective in younger patients (under 35) with a moderate history of two to three failed cycles, rather than in severe, highly resistant cases.

Our findings support the reproductive benefits noted by Kumbak et al. [15], despite variations in timing and stimulation protocols. While Kumbak et al. conducted hysteroscopy and endometrial biopsy during the luteal phase using a long GnRH agonist protocol, our study performed hysteroscopic scratching in the early follicular phase of an unmedicated cycle prior to a fixed GnRH antagonist protocol. This method minimizes the risk of interfering with a primed luteal endometrium or cycle hemodynamics. Nonetheless, both studies demonstrated significant improvements in pregnancy outcomes, suggesting that the immunomodulatory effects of mechanical injury are consistent and effective across different hormonal stimulation strategies.

Our study confirms the significant improvements in clinical and ongoing pregnancy rates in IF patients documented by Seval et al. [16], but our technique for inducing local injury differs. Seval et al. used electrocoagulation via a monopolar needle during diagnostic hysteroscopy to create endometrial lesions. We used a strict "cold" mechanical injury, using the sharp edge of an inverted 30-degree rigid hysteroscope to make linear scratches resembling curettage. Although Seval's electrocoagulation triggers a strong inflammatory response, it carries a risk of thermal necrosis and unintended damage to the basal endometrial layer. Our mechanical approach produces a similar inflammatory cascade, as shown by comparable increases in clinical ( $p=0.019$ ) and ongoing ( $p=0.024$ ) pregnancies, without thermal risks and preserving the structural integrity of the regenerative endometrium.

Our findings closely match the recent meta-analysis by Kang et al. [17], which reviewed 16 randomized controlled trials involving women with previous ART failures. Like our results, the meta-analysis found that endometrial scratching significantly boosts clinical pregnancy rates

without notably increasing miscarriage rates. Kang et al. also mention that performing the scratching in the cycle before treatment improves pregnancy outcomes. They propose that mechanical trauma triggers a localized inflammatory response and helps synchronize embryo and endometrial development. This supports our protocol of doing targeted hysteroscopic scratching precisely on day 6, before the active GnRH antagonist phase. While the meta-analysis shows the general effectiveness of endometrial scratching for patients with previous failures, our study offers important clinical insight, showing that the benefit is especially evident in younger women under 35 with moderate IF (two to three prior failures).

## Clinical Implications

The clinical implications of our findings suggest that targeted hysteroscopic endometrial scratching should not be universally applied to all patients undergoing ICSI. Instead, it offers a highly effective, low-cost adjunctive therapy specifically for women under 35 years old experiencing moderate recurrent implantation failure (two to three prior unsuccessful cycles). Integrating this targeted mechanical injury during a pre-cycle hysteroscopy allows for simultaneous cavity evaluation and optimal endometrial priming.

## STUDY STRENGTHS AND LIMITATIONS

A primary strength of this study is the highly homogeneous cohort achieved through stringent inclusion criteria, which successfully minimized confounding variables often present in implantation failure research. Crucially, the strict standardization of all embryo transfers to Day 5 blastocysts eliminated major embryological variables that could otherwise skew implantation data. Additionally, utilizing a standardized, targeted mechanical scratching technique via an inverted rigid hysteroscope precisely on day 6 of an unmedicated preceding cycle ensured procedural consistency. The uniform application of the fixed GnRH antagonist protocol further isolates the independent therapeutic effect of the mechanical injury.

Despite its strict inclusion criteria, our study faces several limitations. The retrospective, single-center design inherently introduces selection bias and reduces the applicability of our findings to different clinical environments. Although our sample of 152 patients was statistically sufficient to identify differences in clinical pregnancy rates, larger, multicenter randomized controlled trials are needed to confirm these results. Additionally, our analysis depended solely on clinical and sonographic data without histological or molecular assessments. Therefore, we can only suggest, rather than definitively establish, the cellular or immunomodulatory mechanisms responsible for the observed improvements in receptivity.

## RECOMMENDATION FOR FUTURE RESEARCH

Future research should focus on large, multicenter randomized controlled trials involving women under 35 who have experienced two to three previous implantation failures, as they showed the most benefit.

Prospective studies should also include transcriptomic and immunological profiling of the endometrium to better understand the molecular mechanisms behind mechanically induced receptivity. Moreover, standardizing the injury method, tools, and timing across studies is crucial for developing clear, universal clinical guidelines.

## CONCLUSION

Targeted hysteroscopic endometrial scratching in the preceding unmedicated cycle significantly enhances clinical and ongoing pregnancy rates for a specific subset of patients with at least one implantation failure. The therapeutic benefits are predominantly realized in women under 35 years of age with a history of two to three prior failed Day 5 blastocyst transfers. Future large-scale randomized controlled trials are warranted to validate these tailored protocols and confirm the underlying immunomodulatory mechanisms.

## DECLARATION

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Review Board (IRB) of Bnoon Medical Center approved the study (IRB no: 2021-011). All procedures followed the ethical standards of the Declaration of Helsinki. Because the study was retrospective and used anonymized historical data, the ethics committee officially waived the need for informed written consent.

## CONSENT FOR PUBLISH

This retrospective study used anonymized data and does not include any personal or clinical details or identifying images that would need consent for publication.

## AVAILABILITY OF DATA AND MATERIAL

The datasets utilized and examined in this study can be obtained from the corresponding author, Asim F Alwohaibi, upon reasonable request.

## COMPETING INTERESTS

The authors declare no conflict of interest.

## FUNDING

This research received no external funding.

## AUTHORS CONTRIBUTIONS

All authors jointly contributed to the conception and design of the study.

**Asim F Alwohaibi:** Conception and design of the study, performed the ICSI cycles and hysteroscopic procedures, data collection, drafting of the initial manuscript, and submission to the journal.

**Hend El-Hossary:** Reviewing the literature, data analysis, statistical analysis, and critical revision of the manuscript.

**Mahmoud Amr Nadim:** Interpretation of results, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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