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The Impact of Diagnostic Hysteroscopy on Treatment Outcomes in Patients with Recurrent IVF Failure

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Abstract

BACKGROUND/AIMS: To assess whether diagnostic hysteroscopy, performed alone or in combination with endometrial scratching, influences reproductive outcomes in women with recurrent implantation failure (RIF).

MATERIALS AND METHODS: This retrospective cohort study included women with unexplained infertility who experienced recurrent in vitro fertilization failures despite transfer of good-quality embryos. All patients had normal uterine imaging prior to enrollment. Diagnostic hysteroscopy was performed in all cases; and patients were divided into two groups according to whether endometrial scratching was also performed. Baseline demographic characteristics, stimulation parameters, embryological outcomes, and pregnancy results were compared between groups.

RESULTS: Baseline clinical and hormonal profiles were comparable between the two groups. While luteinizing hormone levels on the trigger day were modestly higher in the scratching group, other stimulation characteristics and embryological outcomes did not differ significantly ($p>0.05$). Although the scratching group had higher biochemical, clinical, and live-birth rates than the non-scratching group, the difference in overall pregnancy outcomes was not statistically significant ($p=0.172$).

CONCLUSION: In this selected cohort of women with RIF, endometrial scratching performed during diagnostic hysteroscopy did not significantly improve pregnancy or live-birth rates. These findings suggest that the benefit of endometrial scratching may be limited and highly dependent on patient selection. Larger, prospective, randomized studies that incorporate molecular markers of endometrial receptivity are needed to identify subgroups that may benefit from this intervention.

Keywords: Diagnostic hysteroscopy, endometrial scratching, recurrent implantation failure

INTRODUCTION

Infertility is a common and significant health problem in modern societies, adversely affecting couples' quality of life. Although advances in assisted reproductive technologies have provided effective treatment options for many infertile couples, cumulative pregnancy rates following in vitro fertilization/embryo transfer (IVF/ET) cycles remain approximately 30% even in the most experienced centers, highlighting the ongoing need to improve treatment success rates.[1] Moreover, recurrent IVF/ET failures are associated with increased psychological burden - including anxiety and depression, impaired social functioning, and loss of work productivity - and substantially increase healthcare expenditures, creating a considerable economic burden at the societal level.[2]

A standardized definition of recurrent implantation failure (RIF) has not yet been established in the literature. While some investigators describe RIF as the absence of pregnancy following three successive IVF/ET cycles

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with good-quality embryos, others apply a less stringent definition based on failure to achieve pregnancy after at least two consecutive IVF/ET attempts involving high-quality embryos.[3] This variability in diagnostic criteria likely contributes to the divergent and sometimes conflicting results reported among studies. Moreover, much of the existing RIF research has concentrated on identifying uterine structural abnormalities, potentially at the expense of consistent consideration of other critical factors, including embryo quality and ET strategies.

Beyond structural uterine abnormalities, increasing attention has been directed toward functional and molecular aspects of endometrial receptivity. Successful implantation may still be compromised by disrupted embryo-endometrium signaling, even when the uterine cavity appears morphologically normal and high-quality embryos are transferred. Endometrial receptivity is a complex, tightly regulated process involving hormonal signaling, immune modulation, angiogenesis, and expression of implantation-related genes and cytokines during the "window of implantation".[4] Subtle endometrial alterations that are undetectable by routine imaging modalities may therefore play a critical role in RIF.

Within this framework, diagnostic hysteroscopy provides a direct assessment of the uterine cavity and may reveal subtle abnormalities not detected by ultrasonography, whereas endometrial scratching has been suggested as a strategy to influence endometrial receptivity by inducing localized inflammatory and regenerative responses through controlled mechanical injury.[5,6] However, evidence regarding the clinical benefit of these interventions remains conflicting, particularly in patients with RIF, highlighting the need for further well-defined studies focusing on carefully selected populations. This study aimed to evaluate the effects of diagnostic hysteroscopy and endometrial scratching on treatment outcomes in patients with recurrent IVF failure.

MATERIALS AND METHODS

Ethical Permission

Ethical approval was obtained from the University of Health Sciences Türkiye, Zeynep Kamil Women and Children Diseases Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: 62, date: 25.09.2024). The study was conducted in compliance with the Declaration of Helsinki and with the institutional regulations. Written consent from patients was waived due to the retrospective nature of the study.

This retrospective cohort study comprised patients aged 18-45 years who were diagnosed with unexplained infertility at the Assisted Reproduction Unit of University of Health Sciences Türkiye Zeynep Kamil Women and Children Disease Training and Research Hospital between 2019 and 2024. Patients who underwent diagnostic hysteroscopy after at least two failed IVF attempts and who had no apparent uterine anomaly on transvaginal ultrasonography were enrolled; patients with a history of systemic disease and/or use of chronic medications, and those in whom an uterine anomaly was detected during hysteroscopy, were excluded.

Demographic and clinical information, including age, duration of infertility, and baseline hormonal parameters, was retrieved from the hospital's electronic database. Data on IVF cycle characteristics and outcomes within six months following diagnostic hysteroscopy were extracted from individual patient records. Recorded variables included the type and cumulative total dose of gonadotropins, ovarian stimulation duration, peak estradiol level and final endometrial thickness, total number of oocytes, the number and proportion of mature oocytes and of fertilized oocytes, total number of embryos, the number and grade of embryos transferred, transfer strategy (fresh or frozen), and subsequent pregnancy outcomes.

In Vitro Fertilization Steps

Controlled ovarian hyperstimulation was started following transvaginal ultrasonographic evaluation of ovarian follicles at early follicular phase, using follitropin alpha and/or human menopausal gonadotropin. The starting gonadotropin dose was individualized based on patient age, hormonal profile, and antral follicle count. Once the leading follicle reached a diameter of ≥12 mm, daily administration of a 0.25-mg gonadotropin-releasing hormone (GnRH) antagonist (cetrorelix) was initiated and continued until the day of ovulation triggering. Follicular development and serum estradiol concentrations were assessed on alternate days. When at least three follicles measured ≥17-18 mm in diameter, oocytes were triggered using either 250 µg recombinant human chorionic gonadotropin (hCG) or 0.2 mg GnRH agonist (triptorelin acetate). After 35 hours, oocyte retrieval was carried out transvaginally under ultrasound guidance.

Intracytoplasmic sperm injection (ICSI) was performed after denudation by an experienced embryologist. Fertilization was assessed 18-24 hours after ICSI, and embryo quality was evaluated according to the Gardner-Schoolcraft system.[7] The freeze-all approach was chosen for patients with a continued risk of ovarian hyperstimulation syndrome, insufficient luteal phase support, unfavorable endometrial conditions, or when ET was scheduled for a subsequent cycle. For analytical consistency, only the first frozen-thawed ET cycle was included in the study.

Luteal phase support was standardized with vaginal micronized progesterone at a total daily dose of 600 mg, initiated on the day of oocyte pickup, for patients undergoing fresh embryo transfer. For frozen-thawed cycles, a hormone-replacement protocol was used for endometrial preparation. A six-mg daily dose of oral estradiol was administered; after ultrasonographic evaluation on cycle day 12, progesterone supplementation was initiated with 600 mg vaginal and 25 mg subcutaneous progesterone.

Pregnancy was initially assessed 10-12 days after ET; serum β-hCG values ≥40 IU/L were considered indicative of biochemical pregnancy. At 6-7 weeks of gestation, the presence of fetal cardiac activity on ultrasonography was considered diagnostic of clinical pregnancy.

Hysteroscopy Procedure

Hysteroscopy was performed in the luteal phase of the cycle. Under sedo-analgesia, after antiseptic preparation of the perineum and vagina with povidone-iodine, the cervix was grasped with a tenaculum and dilated using cervical dilators. Diagnostic hysteroscopy was then performed to visualize the cervical canal, endometrial cavity, and both tubal ostia using a rigid hysteroscope with a 4-mm diameter and a 30° optical system (Olympus, Japan). Normal saline (0.9%) was used as the uterine distension medium. In 19 patients, endometrial scratching was performed with 3-mm hysteroscopic scissors selected to enable controlled and targeted endometrial injury under direct hysteroscopic visualization. The intervention was applied to the posterior-fundal region of the endometrium, chosen for its close proximity to the physiological implantation site, as supported by previous studies.[8]

After the procedure, all patients were observed for at least 6 hours and discharged with prophylactic antibiotic therapy (doxycycline 100 mg, 2x1 for 5 days).

Statistical Analysis

All statistical evaluations were performed using SPSS version 23 (Statistical Package for the Social Sciences). Quantitative variables were reported as mean ± standard deviation or as median with corresponding minimum and maximum values, depending on their distribution, whereas qualitative variables were presented as counts and percentages. The distribution of continuous data was assessed using the Shapiro-Wilk test. For intergroup comparisons, the Independent Samples t-test was applied to variables that were normally distributed, while the Mann-Whitney U test was used for variables that did not meet the assumption of normality. Comparisons of categorical variables were carried out using the chi-square test or Fisher's exact test, when appropriate. A two-tailed p-value below 0.05 was considered statistically significant, and analyses were performed at the 95% confidence level.

RESULTS

Among the 200 patients initially eligible for inclusion, 87 were excluded following hysteroscopic identification of endometrial polyps or intrauterine adhesions, and a further 73 were excluded because of inadequate embryo development or cancellation of ET after hysteroscopy. Consequently, in the main analysis, 40 patients were evaluated: 19 underwent diagnostic hysteroscopy combined with endometrial scratching, while 21 underwent diagnostic hysteroscopy alone. The baseline characteristics and hormonal profiles of the groups are summarized in Table 1.

No significant differences were observed between groups in age, infertility duration, or number of previous IVF attempts (p>0.05). Baseline hormonal profiles were also largely similar. Serum hormone concentrations were comparable between patients who underwent endometrial scratching and those who did not (p>0.05). In contrast, luteinizing hormone levels were higher in the endometrial scratching group than in the diagnostic hysteroscopy-only group (6.37±4.00 vs. 3.87±1.96 mIU/mL, p=0.038).

Table 2 presents the cycle characteristics and outcomes for the groups. No statistically significant differences were identified with respect to stimulation length, cumulative gonadotropin dose, or endometrial thickness (p>0.05). Although peak estradiol concentrations were numerically higher in the endometrial scratching group (2050.89±1487.03 pg/mL vs. 1210.52±809.75 pg/mL), this difference was not statistically significant (p=0.060). Endometrial thickness was comparable between groups (9.54±2.66 vs. 9.17±2.02 mm, p=0.413).

Likewise, embryological outcomes-including total number of oocytes, number and proportion of mature (metaphase II) oocytes, number of fertilized oocytes and fertilization rate, total number of embryos generated, number of embryos transferred, and embryo grade at transfer-did not differ significantly between the two groups (p>0.05).

As shown in Table 3, overall pregnancy outcomes were similar between the groups (p=0.172). Higher rates of biochemical pregnancy (36.85% vs. 23.81%), clinical pregnancy (36.85% vs. 14.28%), and live birth (31.57% vs. 14.28%) were observed in the endometrial scratching group compared with the non-scratching group.

DISCUSSION

Diagnostic hysteroscopy and endometrial scratching were evaluated in a strictly defined RIF population characterized by homogeneous baseline characteristics, including age, ovarian reserve parameters, oocyte maturity, and embryo quality. By limiting inclusion to patients without sonographically detectable uterine pathology and with comparable embryological parameters, we aimed to reduce confounding factors and better isolate the potential effect of endometrial intervention itself. Our findings suggest that although hysteroscopy and endometrial scratching are biologically plausible strategies, their clinical impact may be modest when applied to an already-selected cohort of patients with RIF. This observation aligns with growing evidence that RIF is a multifactorial condition in which endometrial receptivity, embryo competence, immunologic balance, and molecular signaling pathways interact in complex ways, making it unlikely that a single intervention can improve outcomes in all patients.[9,10]

Table 1. Baseline characteristics and hormonal profiles of the groups

Variables	Dx H/S + scratching n=19 Mean ± SD (min-max)	Dx H/S n=21 Mean ± SD (min-max)	p*
Age (years)	33.47±5.25 (25-42)	34.14±5.1 (26-45)	0.685
Infertility duration (months)	47.95±27.32 (19-108)	60.71±39.36 (18-168)	0.237
Number of IVF attempts	3.26±0.56 (3-5)	3.48±0.87 (3-6)	0.509
FSH (mIU/mL)	7.62±4.04 (2.77-21.4)	6.7±1.68 (4-9.8)	0.560
LH (mIU/mL)	6.37±4 (2-16.1)	3.87±1.96 (0.1-8.7)	0.038
E2 (pg/mL)	46.02±15.92 (22-82)	48.47±29.35 (14-148)	0.675
PRL (ng/mL)	22.77±12.15 (1.5-57.1)	20.69±12.42 (5-54.8)	0.350
TSH (mIU/L)	2.48±1.04 (0.68-4.3)	2.25±1.13 (0.7-5.4)	0.521
AMH (ng/mL)	2.59±2.29 (0.23-8.2)	3.16±3.83 (0.2-17.1)	0.860

*p<0.05.
Dx H/S: Diagnostic hysteroscopy, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, PRL: Prolactine, TSH: Tyroid-stimulating hormone, AMH: Anti-Müllerian hormone, SD: Standard deviation, min-max: Minimum-maximum.

Table 2. Cycle characteristics and outcomes of the groups			
	Dx H/S + scratch Mean ± SD (min-max)	Dx H/S Mean ± SD (min-max)	p*
Duration of stimulation (days)	9.32±2.11 (6-13)	9.95±2.27 (7-15)	0.449
Total gonadotropin dose (IU)	2005.26±1139.71 (1050-5850)	2498.1±1363.36 (1200-6750)	0.095
E2 on trigger day (pg/mL)	2050.89±1487.03 (428-5178)	1210.52±809.75 (276-3000)	0.06
ET on trigger day (mm)	9.54±2.66 (4.5-13.7)	9.17±2.02 (4-14.5)	0.413
Total oocyte number	11±7.23 (1-27)	8.86±6.14 (1-25)	0.283
MII oocyte number	7.74±5.43 (1-24)	6.43±4.63 (1-19)	0.384
MII oocyte rate (%)	73.6±19.31 (50-100)	74.68±19.78 (33-100)	0.615
Fertilized oocyte number	5.74±3.6 (1-14)	4.48±3.53 (1-14)	0.129
Fertilization rate (%)	80.27±19.33 (44.44-100)	69.24±27.65 (1-100)	0.248
Number of obtained embryo	3.68±1.8 (1-7)	3±1.82 (1-8)	0.155
Transferred embryo number	1.42±0.51 (1-2)	1.52±0.6 (1-3)	0.641
Transferred embryo grade	1.30±0.47 (1-2)	1.26±0.45 (1-2)	0.746

*p<0.05.
Dx H/S: Diagnostic hysteroscopy, E2: Estradiol, ET: Endometrial thickness, MII: Metaphase II, SD: Standard deviation, min-max: Minimum-maximum.

Table 3. Pregnancy outcomes of the groups					
	Dx H/S + scratch n=19		Dx H/S n=21		
	n	%	n	%	p*
No pregnancy	12	63.15	16	76.19	0.172
Biochemical pregnancy	7	36.85	5	23.81	
Clinical pregnancy	7	36.85	3	14.28	
Live birth	6	31.57	3	14.28	
Total	19	100.00	21	100.00	

*p<0.05.
Dx H/S: Diagnostic hysteroscopy.

An increasing number of studies have examined whether diagnostic hysteroscopy and endometrial injury can enhance reproductive outcomes in patients diagnosed with RIF. Demirol and Gurgan[11] reported a significant increase in pregnancy rates when hysteroscopy was performed prior to IVF-ICSI, even among patients with normal hysterosalpingography findings, suggesting that undetected intrauterine abnormalities or hysteroscopy-related endometrial disruption may improve implantation. Consistent findings were later reported by Tomaževič et al.[1] and Kilic et al.,[12] who observed improved pregnancy and live-birth outcomes, particularly when hysteroscopy was performed before the first IVF-ICSI attempt. The more favorable results reported in these studies, compared with the present findings, may be explained by differences in patient selection, because those cohorts largely consisted of treatment-naïve individuals rather than women with established RIF.

The therapeutic relevance of endometrial scratching remains a matter of debate, as findings reported in the literature have been inconsistent. Although current studies have proposed that localized endometrial injury may facilitate implantation by triggering inflammatory pathways and increasing the expression of cytokines and growth factors,[5,6] other investigations have not demonstrated a meaningful improvement in reproductive outcomes.[13] Notably, the multicenter, randomized SCRaTCH trial did not report an increase in live birth rates associated with endometrial scratching; however, only a limited subset of the study population met the criteria for RIF.[14] In addition, Baum et al.[15] reported no apparent benefit from the procedure, though the conclusions were constrained by the small sample size of their cohort.

Conversely, investigations specifically targeting women with RIF have yielded more encouraging results. Seval et al.[16] reported significantly increased biochemical and clinical pregnancy rates following endometrial scratching in patients with RIF. Similarly, Demirol and Gurgan[11] observed a marked improvement in reproductive outcomes after hysteroscopic endometrial injury in a clearly defined RIF cohort, despite comparable stimulation protocols and embryo quality between the intervention and control groups. These observations lend support to the concept that endometrial injury may confer benefit predominantly in carefully selected patients with RIF. Nevertheless, more recent systematic reviews and meta-analyses indicate that routine hysteroscopy prior to IVF does not uniformly enhance live birth rates in women without suspected intrauterine pathology, including those with prior implantation failure.[17,18] Variability in study design, patient selection, timing of hysteroscopy, and the inclusion of treatment-naïve versus RIF populations may contribute to the inconsistent results reported across studies.

Several biological pathways have been hypothesized to explain the benefit of endometrial injury, including the initiation of a localized inflammatory cascade, increased release of cytokines and growth factors, activation of implantation-associated genes such as HOXA10 and HOXA11, stimulation of endometrial regeneration, and enhancement of uterine microcirculation. Collectively, these processes may facilitate improved endometrial receptivity and more effective embryo-endometrium communication.[19]

The mechanistic rationale for endometrial scratching is largely grounded in the concept that controlled mechanical disruption of the endometrium provokes a transient inflammatory response. This response is characterized by immune cell recruitment, upregulation of cytokines, chemokines, and growth factors, and increased expression of implantation-related markers, including HOXA10, HOXA11, leukemia inhibitory factor, and integrins.[20,21] Such molecular and cellular alterations are thought to enhance endometrial-embryonic synchrony and support decidualization. However, accumulating evidence indicates

that these effects are not uniform across all patient populations. In women with an otherwise normal endometrial environment, injury-induced inflammation may offer limited benefit or potentially disrupt endometrial homeostasis. In contrast, patients with RIF may harbor subtle defects in endometrial receptivity or remodeling that render them more responsive to targeted endometrial interventions.[22,23] This biological and clinical heterogeneity likely underlies the inconsistent outcomes reported in clinical studies and meta-analyses, underscoring the critical role of appropriate patient selection when considering endometrial scratching or diagnostic hysteroscopy as adjunctive therapeutic strategies.

Study Limitations

The principal strength of this study lies in the inclusion of a highly selected patient population, limited to women with normal uterine imaging and who developed good-quality embryos, thereby reducing potential confounding related to underlying uterine pathology or embryonic competence. Consequently, our results align with evidence suggesting that any potential benefit of endometrial injury may be more evident in carefully defined populations with RIF.

Nonetheless, it should be acknowledged that the relatively modest sample size may have limited the statistical power of the study and increased the risk of a type II error, which may partly explain the absence of statistically significant differences in some reproductive outcomes. Additional limitations include loss to follow-up, exclusion of patients who required operative hysteroscopy despite normal preprocedural imaging, and cycle cancellations due to inadequate embryo development.

CONCLUSION

In conclusion, this study evaluated the impact of diagnostic hysteroscopy with or without endometrial scratching in a well-defined cohort of women with RIF who exhibited comparable baseline clinical characteristics and embryological outcomes. Although pregnancy rates were numerically higher in the endometrial scratching group, these differences did not reach statistical significance, likely due to the limited sample size resulting from strict inclusion criteria designed to ensure cohort homogeneity. The interventions were found to be safe and biologically plausible; however, their clinical benefit could not be conclusively demonstrated within this underpowered, highly selected population.

Given the heterogeneous and multifactorial nature of implantation failure and endometrial receptivity, larger, adequately powered, prospective, randomized studies that focus on carefully phenotyped RIF populations are warranted. Incorporation of molecular and immunological markers of endometrial function may help identify subgroups of patients who could benefit from hysteroscopic evaluation or endometrial injury, thereby supporting more personalized treatment strategies for patients with recurrent IVF failure.

MAIN POINTS

- In a selected cohort of women with recurrent implantation failure and normal uterine imaging, endometrial scratching performed during diagnostic hysteroscopy did not result in a statistically significant improvement in pregnancy or live birth rates.
- Although biochemical pregnancy, clinical pregnancy, and live birth rates were numerically higher in the endometrial scratching group, these differences did not reach statistical significance.
- No significant differences were observed between the groups with respect to cycle characteristics, embryological parameters, or embryo quality.
- While diagnostic hysteroscopy and endometrial scratching are biologically plausible and safe interventions, their clinical benefit appears to be highly dependent on careful patient selection.
- Larger, adequately powered prospective randomized studies incorporating molecular and immunological markers of endometrial receptivity are needed to identify patient subgroups that may benefit from endometrial scratching.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Zeynep Kamil Women and Children Diseases Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: 62, date: 25.09.2024).

Informed Consent: Written consent from patients was waived due to the retrospective nature of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.B.Y., Concept: G.A., M.B.Y., Design: G.A., M.B.Y., Data Collection and/or Processing: G.A., Analysis and/or Interpretation: M.B.Y., Literature Search: G.A., Writing: G.A., M.B.Y.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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