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Original Research

Use of Endometrial Scratching in IVF/IUI – A Worldwide Opinion and Clinical Practice Survey

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Abstract

Background: Following recent publications regarding the use of the controversial procedure, endometrial scratching (ES), we wish to gain insights into *in vitro* fertilization (IVF) clinicians' knowledge and practice, including an updated literature review, current versus past utilization, patient selection, timing and frequency. **Methods**: Internet-based self-report multiple-choice/multiple-answer survey of IVF clinics. **Results**: Of the 143 IVF units completing the survey, 119 have used ES in IVF/intrauterine insemination (IUI). Of the respondents with ES experience, 94% recommended ES to patients with repeated implantation failure, 32.3% to patients with a thin endometrium, and 3.5% to general IVF/IUI patients. The majority of respondents performed ES only once prior to an IVF cycle. Of current or past ES users, 73% stopped or reduced ES frequency after reading recent ES-related publications. This was despite the finding that 57.2% believed that ES increased implantation and live-birth likelihood in selected IVF/IUI patients. **Conclusions**: Despite previous widespread utilization of ES, the lack of consensus regarding patient selection, timing, and benefits of the procedure, has prompted many IVF clinicians who used the procedure in the past to abandon the intervention. According to our study, ES is practiced most commonly for patients with repeated implantation failure and performed once during the luteal phase. Further research is needed to obtain definitive practice guidelines based on ES successes and failures–specifically a prospective randomized controlled study according to the methodology used by Barash *et al*., original publication.

Keywords: endometrial scratching; infertility; survey; IVF; pregnancy outcomes

1. Introduction

Over the past several decades, assisted reproductive technology (ART) has witnessed significant improvements and advances, leading to increased success rates [1] due to new methods and techniques that were integrated into routine practice [2]. As embryo implantation remains the most significant rate limiting step in the ART cycle, emerging research in this field focuses on improved embryo selection and endometrial receptivity.

One intervention that potentially enhances embryo implantation through improvement of endometrial receptivity is endometrial scratching (ES), defined as an intentional endometrial injury caused by a pipelle biopsy or curettage prior to embryo transfer [3]. Several theories have been proposed to explain how this local intervention may facilitate endometrial receptivity. One assumption is that the injury improves synchronicity between the development of the endometrium and embryo [4]. In addition, this technique could cause a local inflammatory response [5] or induce endometrial decidualization, which mimics the endometrial changes in early pregnancy and thus provides the anatomical site for implantation [4]. Another hypothesis, not yet investigated in humans, is the potential benefit of histamine release during endometrial injury, which was found to be a chemical stimulant of decidual response in rats [6].

In 2003, Barash *et al*. [7] published their preliminary findings in *Fertility and Sterility*, which suggested that "local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing *in vitro* fertilization (IVF)". This non-randomized controlled trial of ES in women undergoing ART showed a significant improvement in the implantation rate (27.7% vs. 14.2%, $p < 0.001$) and a two-fold higher live birth rate (48.9% vs. 23.6, $p = 0.016$) when women with previous high-order implantation failures underwent 2–4 ES procedures compared with controls [7]. Subsequently, many clinicians started recommending ES, and ES became a widely used intervention in ART practice. However, a plethora of studies—both prospective and retrospective, as well as opinion papers, systematic reviews, and meta-analyses have also produced conflicting results, making ES the subject of intense debate and one of the most controversial and intriguing add-on procedures in reproductive medicine [3,8,9].

Table 1. Endometrial scratching survey respondent demographics.

Continent	Total		Do not perform endometrial scratching in IVF/IUI		Do perform endometrial scratching in IVF/IUI	
	Annual IVF cycles	Number of IVF units	Annual IVF cycles	Number of IVF units	Annual IVF cycles	Number of IVF units
USA & Canada	17,800	17	8100	6	9700	11
Central & South America	13,300	20	600	3	12,700	17
Australia & New Zealand	500	2	100	1	400	1
Asia	49,300	47	1600	2	47,700	45
Europe	36,200	46	8400	12	27,800	34
Africa	7100	11	0	0	7100	11
Total	124,200	143	18,800	24	105,400	119
Percentage			15.1%	16.8%	84.9%	83.2%

While many studies have generally found ES effective, several clinical trials have doubted its effect. Simon and Bellver found methodological problems in previously published systematic reviews and meta-analyses, and questioned the biological plausibility of the intervention [10]. Lensen *et al*. [11] recently published a large multicenter randomized trial showing that ES did not result in higher live birth rates in intention-to-treat or in post hoc per-protocol analyses. In addition, a systematic review and meta-analysis by Vitagliano *et al*. [12], regarding first-time embryo transfer attempts in patients did not support performing ES to improve success rates of first ART cycles. A study in which a single endometrial biopsy performed per cycle did not show improved ongoing pregnancy rates in unselected sub-fertile women undergoing IVF [13]. In other studies, ES was found non-beneficial during the first IVF attempt [12], but was associated with improved outcomes in cases of repeated IVF failures, especially after two or more failures [14,15]. Adding to the controversy, not only was ES found useless in some previous studies, several investigators found it detrimental to implantation, ongoing pregnancy, and live birth rates when performed on the day of oocyte retrieval [16] or in cases of repeated ART cycles [13]. Performing ES during the follicular phase of current ovarian stimulation cycle was found to increase the miscarriage rate [17]. Moreover, several studies have shown decreased implantation or clinical pregnancy rates after a single ES procedure [16,18]. Two consecutive scratching procedures during the luteal phase of preceding cycles (on day 21 and day 23 or day 26) produced both higher and lower implantation, ongoing pregnancy, and live birth rates [14,19].

Endometrial scratching research has also been performed for infertile patients who did not undergo IVF. ES was found effective among couples with unexplained infertility who tried to conceive by regular intercourse, when done during the luteal phase of a spontaneous menstrual cycle [20] or during the pre-ovulatory stage following controlled ovarian stimulation [21]. In cases of intrauterine insemination (IUI) cycles, results of ES were inconclusive. Two IUI studies found an association between ES and higher clinical and ongoing pregnancy rates when done during the proliferative phase of either the current IUI cycle or the preceding IUI cycle–compared with IUI alone [22,23]. In contrast, a third IUI study in which ES was conducted on the same days of the preceding cycle did not show the same effect [24].

Our paper summarizes findings from a recent web-based survey that was conducted to analyze the subjective experiences and personal opinions of IVF clinicians worldwide about this controversial intervention, especially in light of the most recent publications. Findings may help IVF professionals better understand the role of ES in the management of infertility and daily clinical practice.

2. Material and Methods

We conducted the multiple-choice self-report survey titled *Use of endometrial scratching in IVF/IUI*. The survey was accessible from June 2019 through November 2019 [25]; an initial invitation and two reminders were sent to registered IVF-Worldwide.com units. Two questions were presented to all survey respondents, one of which determined whether respondents had performed ES. Respondents who did not perform ES were asked one follow-up question, while respondents who had performed ES were asked to answer ten additional questions.

2.1 Quality Assurance

To prevent duplicate clinical unit survey responses and eliminate possible false data, we used a software program developed by Community Surveys Pro [26], which compared three parameters from the surveyed clinics' self-reported data with existing IVF-Worldwide registration data. Methods used were described in previously reported research from the IVF-Worldwide network [27]. Thirteen out of the 167 (7.7%) survey responses were incomplete and 11/167 (6.5%) were duplicates that were removed. A total of 143/167 (85.6%) responses were complete and unique.

2.2 Statistical Analysis

The relative proportion of answers reflected the total proportion of annually IVF cycles represented rather than the proportion of individual survey respondents. We set the maximum number of IVF cycles per clinic to 4500 in order to limit the influence of large-scale centers.

Survey results were calculated using the formulas described in previously reported research from the IVF-Worldwide network [28].

3. Results

A total of 143 IVF units out of 3883 registered IVF units completed the survey, which, in aggregate, performed 124,200 IVF cycles annually. This annual cycle total accounts for approximately five percent of the estimated 2.5 million ART cycles performed worldwide each year [29]. A total of 85% (representing 105,400 IVF cycles) reported that they used ES in IVF/IUI (See unit demographics and cycles in Table 1, and survey questions and summarized results by percentage of cycles in Table 2). The initial question for all respondents was whether they had read recent publications on ES in the *New England Journal of Medicine* (NEJM), *Human Reproduction*, and/or *Fertility and Sterility* [11,30,31]. Nearly all (96.4%) of the respondents had read all or some of the articles.

The question for the respondents who had not performed the procedure (15.1%—representing 18,800 cycles) was to state why they did not perform ES or any other mechanical endometrial injury technique to facilitate implantation for IVF/IUI. Of this population, 51.1% believed that it did not make sense to perform the procedure, 34% thought that the data on this procedure was confusing and not reliable, 9% were not aware of this procedure, and 5.9% did not perform ES due to other reasons.

The following questions were targeted to the survey respondents who did perform or had performed ES in the past. Of this population, only 46.6% continued doing the procedure, while 53.4% stopped doing the procedure. Overall, a total of 39.5% of ART clinicians are currently performing ES. The analysis comparing clinic-based and IVF-cycle-based results showed no statistically significant difference. While the main objective of ES was for IVF, and 96.2% of the population performed the procedure for IVF, only 3.8% performed it for both IVF and IUI.

When asked to select: prior to what IVF procedure types they performed ES (with multiple answers allowed), 61.1% performed ES only for a specific indication, 38.2% performed it for fresh IVF cycles, 36.1% for frozen IVF cycles, and 27.5% for egg donation cycles. Regarding ES for IVF/IUI patients (with multiple answers allowed), 94% recommended ES to patients with repeated implantation failure (RIF), 32.3% to patients with a thin endometrium, and 3.5% to the general IVF/IUI population. A large majority (93.5%) recommended ES be performed only once prior to an IVF cycle, 4.6% recommended it be performed twice, 1% recommended it be conducted three times, and under 1% recommended ES more than three times prior to an IVF cycle.

In preparing to perform ES, 50.5% monitored cycles in order to time ES, 26.3% did not, and 23.2% only monitored patients with irregular cycles. Regarding the timing of the procedure, with multiple answers allowed, 57.8% performed ES during the midluteal phase, 53.6% during the late luteal phase, 11.4% during menstruation, and 11% during the follicular phase, while 5% believed it did not matter when the procedure was performed. Almost half (41.7%) sent the tissue obtained from ES for histological evaluation, 36.2% did not, and 22.1% sent the tissue for evaluation occasionally.

After reading recent publications, including randomized control trials (RCTs) and meta-analyses, 23.7% did not change their practices, continuing to perform ES in managing infertility, while 40.5% changed their practices and reduced ES frequency, and 32.5% stopped performing ES.

When asked about how best to describe their attitudes toward ES, 57.2% expressed that ES increased the likelihood of implantation and live birth rates in selected IVF/IUI patients, 41.1% believed that ES had no influence on these outcomes, and 1.7% believed ES increased likelihoods for all patients.

4. Discussion

Our study reports findings from a worldwide web-based survey of IVF physicians regarding their awareness of, and attitudes toward ES, the study included respondents from 143 IVF units, representing 124,200 annual ART cycles.

We have previously demonstrated that when survey responses reach a critical mass, the findings can reflect medical opinion and common clinical practice of the ART community [32]. While ES was considered controversial ever since it was first published in 2003 [7] the controversies regarding ES intensified following recent publications in leading journals, including a publication in the NEJM, which showed that the procedure was not efficacious [11]. The above paper was then followed by a series of debates [31,33,34], raising further the level of controversy. These papers were, to a large extent, the force driving the conduction of our survey, in an attempt to assess the impact of recent publications on the scientific community. During times of tremendous advances in reproductive medicine, it is important to stay current both on innovations that can potentially improve outcomes of ongoing treatments–and on findings that disprove their efficacy.

Before discussing the survey results, it is important to highlight that in the original Barash *et al*. [7] study, ES was done twice during the follicular phase and twice during the luteal phase (four biopsies altogether). None of the research papers published on ES ever repeated this exact procedure, methodology, timing, or population, and therefore, it is not

Table 2. Endometrial scratching survey results presented as percentages of annual IVF cycles[‡].

Are you aware of the recent publications in the NEJM, human reproduction and/or fertility and sterility about the use of endometrial scratching to facilitate implantation?				
Yes	No	Only some of them		
79.8	3.6	16.6		
Have you ever performed or do you currently perform endometrial scratching in the management of infertility?				
Yes	No			
84.9	15.1			
If your answer to this question is NO, please share with us why you did or do not perform endometrial scratching or any other endometrial injury technique to facilitate implantation for IVF/IUI				
I am not aware of this procedure	I think that the data on this procedure is confusing and not reliable	In my opinion, it does not make sense to do the procedure	Other	I do perform or have performed endometrial scratching
9	34	51.1	5.9	0
Do you currently perform endometrial scratching in the management of infertile patients?				
Yes	I did in the past, but stopped doing it			
46.6	53.4			
For which of the following patient procedures have you performed endometrial scratching:				
IUI	IVF	Both IUI and IVF		
0	96.2	3.8		
Prior to which types of IVF cycles do you perform endometrial scratching? (multiple answers allowed)				
Fresh IVF cycles	Frozen IVF cycles	Egg donation cycles	Only for a specific indication	
38.2	36.1	27.5	61.1	
For which types of IVF/IUI patients do you recommend endometrial scratching? (multiple answers allowed)				
General IVF/IUI population	Patients with repeated implantation failure	Patients with a thin endometrium		
3.5	94	32.3		
How many times prior to an IVF cycle do you perform endometrial scratching?				
Once	Twice	Three times	More than three times	
93.5	4.6	1	0.9	

Table 2. Continued.

At what stage of the cycle do you perform endometrial scratching? (multiple answers allowed)				
During menstruation	During the follicular phase	During the midluteal phase	During the late luteal phase	Any time, does not matter
11.4	11	57.8	53.6	5
Do you monitor the cycle in order to time the endometrial scratching?				
Yes		No		Only in case of irregular cycles
50.5		26.3		23.2
Do you send the tissue obtained from endometrial scratching for histological evaluation?				
Yes		No		Occasionally
41.7		36.2		22.1
To what extent have recent publications (RCTs and meta-analyses) changed your attitude towards endometrial scratching?				
I have read the publications, but have not changed my practice, and I perform endometrial scratching in the management of infertility	I have read the publications and have stopped performing endometrial scratching in the management of infertility		I have not read recent publications on endometrial scratching	I have read the publications and have changed my practice by reducing the frequency of endometrial scratching
23.7	32.5		3.3	40.5
In your opinion, which sentence best describes your attitude toward endometrial scratching?				
Endometrial scratching increases the likelihood of implantation and live birth rates in all IVF/IUI patients	Endometrial scratching increases the likelihood of implantation and live birth rates in select IVF/IUI patient populations			Endometrial scratching has no influence on the likelihood of implantation and live birth rates in IVF/IUI patients
1.7	57.2			41.1

‡There was no statistically significant difference between the analysis results by annual IVF cycles and by IVF units.

possible to compare the original findings with any of the subsequent studies. Our survey allowed choices for a range of cycle timings and frequencies during the cycle. In the survey results, the time points in the cycle when ES was done varied, as stated above, with the most being performed during the luteal phase. Nevertheless, a large majority (93.5%) performed it only once in the cycle, while only 0.9% did the procedure more than three times (at least as many times per cycle as Barash *et al*. [7]).

Indeed, ES has become well known and practiced worldwide. Almost 85% of respondents in our survey confirmed performing ES, and only two of the 143 clinics (1.4%) were not aware of it. High ES performance rates were also seen in a recent survey across the United Kingdom, Australia, and New Zealand, in which 83% of clinicians offered ES, especially in cases of recurrent implantation failure [35].

Survey results showed that most physicians (96%) were familiar with all or some of the recent publications. The conflict between previous supporting publications and newer disappointing results appeared to have a significant impact on daily practice. First, one-third of physicians who never performed ES declared that they were confused by the published data. Second, of those who read the publications, 32.5% stopped performing it and 40.5% reduced ES frequency. In contrast, although ES success was not supported by all studies, about 46.6% of respondents still performed ES, and more than 57% believed it increased implantation and live birth rates in selected populations, despite the recent negative publications.

The survey requested clinician opinion on which patients were best candidates for the intervention to potentially enhance endometrial receptivity. It appears that ES is being mostly utilized (96%) as part of IVF cycles. However, it is possible that this intervention may be useful for infertile women during other fertility treatments and stages. Given previous research results [22], physicians may still want to consider performing ES as part of IUI.

Repeated implantation failure was the primary patient characteristic for which a large majority of respondents (94%) recommended ES. It is reasonable that after several implantation failures, patients may have lower fertility potential. In these cases, an intervention such as ES could be offered to potentially improve receptivity and enhance implantation and pregnancy outcomes to carefully selected patients [14,36]. The efficacy of ES may be higher than what was already established; as mentioned in the NEJM's recent RCT, one of the limitations was that the definition of RIF did not consider the stage or quality of transferred embryos [11]. In a recent RCT, where the study design included only good-quality embryos, the results suggested ES was beneficial in RIF patients to increase the odds of implantation, clinical pregnancy, and live birth [37].

The variety of ES methods conducted can dramatically influence effectiveness and safety. There is still no consensus in the medical literature regarding the degree of injury needed, mode of scratching, timing, or number of procedures required to achieve the maximum effect. Our survey tried to shed light on some common methods used by IVF specialists. We investigated the number of reported scratching procedures per cycle required to achieve the desired effect on endometrial receptivity. The prominent practice was to perform ES once per cycle (93.5%); only 6.5% of physicians performed scratching multiple times. However, this tendency was not necessarily justified by previous studies. Current evidence suggests that the optimal number of scratching procedures needed is currently unknown, and studies are inconsistent. The lack of comparative studies about the number of interventions required during a single cycle suggests that further research and longitudinal trials, numerous observations of the same subjects over a period of time, are needed.

Timing of ES during specific phases of the menstrual cycle may play an important role in ES effects. The survey respondents share this concept as 80.3% (111.4/138.8) recommend that ES should be conducted during the luteal phase [mid (57.8%)- and/or late (53.6%)-luteal phase], and only 4% (5/138.8) of respondents believe that the timing of ES does not matter. However, no research has yet confirmed the effectiveness of ES during specific phases of the cycle. It has been suggested that injuries made in the luteal phase are more likely to enhance endometrial decidualization [38]. The biological assumption is that progesterone secretion from the corpus luteum during the luteal phase is important for transforming the endometrium to a state receptive to embryo implantation [39], and as a result, interventions such as ES can better enhance receptivity if performed during the luteal phase. Such interventions should be carried out preferably during the previous cycle due to ES's long-lasting effects, specifically, from the monocytes that the body recruits to the injured site, which can potentially reside in the uterine tissue until the subsequent cycle [5]. A recent study, in which ES was performed during the proliferative phase of the current cycle (days 6–8 of ovarian stimulation) was stopped prematurely because a higher clinical miscarriage rate was observed in the ES arm after an interim analysis [17]. Most recent updated systematic reviews and meta-analyses found significantly increased clinical pregnancy and live birth rates in the ES group overall, but also substantiated the need for better definitions of methodology and target populations in future studies [40,41].

Our survey revealed that IVF specialists were highly aware of ES and the latest ES-focused publications. Despite widespread ES use, the lack of consensus regarding patient selection and ideal working methods, as well as its questionable benefits, confused many IVF clinicians and caused many to abandon the intervention. The survey concludes that ES is most commonly practiced for specific IVF patient populations, especially for patients with RIF, and a

single ES procedure is most commonly performed during the luteal phase of the previous cycle while the patient's cycle is monitored.

5. Limitations

It is important to state a number of research limitations. Although a large number of IVF units responded to the survey, the number of annual IVF cycles does not enable us to generalize the results worldwide.

The survey has several drawbacks including selection bias, which is typical of optional self-report surveys. The survey was designed to represent opinions and self-report statistics from experts in the field; however, it does not capture actual clinician performance or patient data. In addition, in retrospect, some of the questions could have been phrased differently to minimize leading bias and reporting bias and to allow us to perform additional statistical analyses.

6. Conclusions

Our study reflects the knowledge and experience of the IVF-Worldwide.com community, and as showed in previous studies, indicates the opinions of the infertility community. To the best of our knowledge, this is the first survey that is based on leading experts in the field. Further work and comparative studies are needed to improve our understanding of the possible role that ES can play in clinical practice, to be precise, a prospective randomized controlled study that will duplicate the methods of the Barash *et al*. [5,7], as there is not even a single study that did so, especially since 57.2% believe that ES has the potential to improve live birth rates, but overall only 39.5% of survey respondents currently perform the procedure.

Author Contributions

GS—analysis of data, statistical analysis and drafting of the manuscript, HA—analysis of data ,statistical analysis and drafting of the manuscript , ML—revision of manuscript, AS—design and revision of manuscript, AW—design and revision of manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The Kaplan Medical Center Ethics Committee confirm that this study does not involve any collection of patients' data, thus does not require an IRB authorization. The survey was conducted as an open-access questionnaire to IVF-Worldwide.com members who voluntarily answered the study questions.

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Conflict of Interest

The authors declare no conflict of interest. AW is serving as one of the Editorial Board members. We declare that AW had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to AT.

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