

## Is Hysteroscopic Endometrial Scratching Affect Outcome of Intracytoplasmic Sperm Injection in Women with Primary Infertility?

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### Abstract

Implantation rate per embryo transferred usually does not exceed 30%, although higher rates with use of blastocysts have been reported, depending on age. Successful implantation depends on development of high-quality embryos and the acquisition of endometrial receptivity. Implantation failure is attributed to the failure of uterus to acquire receptivity. Implantation failure remains a major factor limiting success in vitro fertilization (IVF) treatment. Mechanical manipulation of the endometrium can enhance receptivity by modulating gene expression of factors required for implantation like glycodefin A, laminin alpha 4, integrin alpha 6 and matrix metalloproteinase 1. Value of hysteroscopic endometrial scratching in improving pregnancy rates in patient undergoing ICSI in the next cycle in a randomized controlled study. The study was carried out at the Benha Fertility Centre, including 91 infertile patients as eligible cases for the study and recruited for hysteroscopic endometrial scratching in early follicular phase of the cycle between the 7<sup>th</sup> and 11<sup>th</sup> day of the cycle and 91 women as a control group without endometrial scratching. Our results had showed non-significant differences between case group and control group regarding age, body mass index and duration. There were non-significant differences between interventional group and non-interventional group regarding number of follicles, number of oocytes retrieved, number of embryos, endometrial thickness, pregnancy rate, implantation rate and ongoing pregnancy and a high significant difference between the two studied groups regarding microbiota. Endometrial scratching does not result in improving clinical pregnancy rates and implantation rate in the subsequent IVF-ET in women with primary infertility.

**Keywords:** Hysteroscopy, Implantation, Fertilizaion, Implantation Failure, Hysteroscopy, Endometrial Scratching.

### 1.Introduction

Despite the numerous advances in the field of IVF and intra-cytoplasmic sperm injection (ICSI), the implantation rate per embryo transferred usually does not exceed 30%, although higher rates with the use of blastocysts have been reported, depending on female age [1].

Successful implantation depends on development of high-quality embryos and the acquisition of endometrial receptivity [2,3].

Various factors have been proven to contribute to the success of implantation[4][5] have suggested a favorable effect of endometrial injury (EI) on the implantation success rate, especially in women with recurrent implantation failure.

Implantation failure is attributed to the failure of the uterus to acquire receptivity[6,7] To improve implantation rate, many methods have been suggested in the last two decades. Intrauterine administration of autologous peripheral blood mononuclear cells (PBMC) freshly isolated from patients, was suggested by [8].

[9] suggested personalized embryo transfer (PET), Endometrial Receptivity Array (ERA) test to determine whether the endometrium is receptive or not, ET performed on the day designated by the ERA: 50.0% PR and 38.5% IR.

[10]studied the effect of endometrial scratching on the pregnancy outcome. They hypothesized that the injury inflicted on the endometrium could lead to a massive secretion of growth factors and cytokines during the process of wound healing, which could help in implantation.

With respect to the mechanism of injury-induced improvement of endometrial receptivity, [11]reported that local injury to the endometrium causes significant changes in the pattern of expression of genes related to implantation. [12] suggested that injury-induced local injury induces an inflammatory reaction which favors implantation. Natural killer cells, macrophages and dendritic cells are recruited to the injured site and increased quantities of cytokines, growth factors, and chemokines are secreted, thus resulting in successful implantation.

Endometrial injury was done in the same cycle of ovarian stimulation<sup>(13, 14)</sup>.<sup>(15)</sup> performed the injury one cycle before the targeted cycle.

This study evaluated the value of hysteroscopic endometrial scratching in improving pregnancy rates in patients undergoing ICSI in the next cycle.

## 2. Patients and methods

Our study is randomized controlled study. It was performed at the Benha Fertility Centre. One hundred and eighty two women undergoing ICSI were included in this study.

### I-Inclusion criteria

- 1-Age between 20-35 years.
- 2-Body mass index 18-29 Kg/m<sup>2</sup>.
- 3-Complaining of primary infertility for more than two year and planning for IVF/ ICSI trial.

### II-Exclusion criteria

Associated chronic medical condition e.g. cardiac disease diabetes, renal disease.....etc.

### 2.1 Methods

All patients included in this study were subjected to the following:

- Full history taking.
- General, abdominal and local examination.
- The 182 patients were divided randomly into two groups: 91 signed as group I and other 91 signed as group II.

### I.Group I

- 1- Patients of this group underwent hysteroscopic endometrial scratching in early follicular phase of the cycle between the 7<sup>th</sup> and 11<sup>th</sup> day of the cycle.
- 2- Protocol of stimulation in subsequent IVF/ ICSI attempt: next cycle after hysteroscopy.

### II.Group II

The patients of this group underwent ovarian stimulation without Endometrial scratching.

### Outcome

#### 1- Primary outcome

Pregnancy rate.

#### 2- Secondary outcome

- a- Implantation rate.
- b- Ongoing pregnancy rate.
- c- Live-birth rate.

### 3. Results

A total of 200 women were included in the study. There were non-significant differences between 100 cases and 100 controls regarding age, body mass index and duration ( $p > 0.05$ ) Table (1).

Among the 200 women, 18 were excluded from the study as embryo transfer was not done on them and so the sample size was 182; 91 cases and 91 women served as a control group. From Table (2), we concluded that the number of oocyte retrieved were similar among studied groups ( $p = 0.06$ ).

In Table (3), most of the studied participant received 1-2 embryo (78.0% and 75.8% in cases and control respectively) and the difference was not statistically insignificant ( $p = 0.72$ ).

There were non-significant differences between cases and control group ( $p > 0.05$ ) regarding pregnancy rate Table (4), implantation rate Table (5) and ongoing pregnancy tTable (6).

There was statistically a high significant difference between cases and control group regarding microbiota ( $p < 0.001$ ) Table (7).

**Table (1)** Comparison between cases and control group regarding demographic data

	Cases n = 100	Controls n = 100	t	P
<b>Age(years)</b>				
<b>X±SD</b>	28.2 ±4.7	27.6 ± 3.2	0.7	0.46
<b>Range</b>	22-35	22-33		
<b>Bini (k,g1m) X+sd</b>				
<b>range</b>	26.3+4.8 20-33	25.6+3.0 20-32	0.73	0.47
<b>Duration (years)</b>				
<b>X+sd</b>	3.6+1.1	3.56+1.2	0.25	0.79
<b>range</b>	2-6	2-6		

**Table (2)** Comparison between cases and control group regarding number of oocyte retrieved.

No.of oocyte retrieved	Cases n = 91	Control n = 91	T	P
<b>X±SD</b>	9.8±1.4	9.5±1.5		
<b>Range</b>	8-12	7-12	1.8	0.06

**Table (3)** Comparison between cases and control group regarding number of embryos

Number of embryos	Cases (n = 91)		Control (n = 91)		X <sup>2</sup>	p
	No	%	No	%		
1-2	71	78	69	75.8	0.12	0.72
3	20	22	22	24.2		

**Table (4)** Comparison between cases and control group regarding pregnancy rate.

	Cases n = 91	Controls n = 91	X <sup>2</sup>	P
Pregnancy n (%)	40(43.95%)	34(37.4%)	83	0.36

**Table (5)** Comparison between cases and control group regarding implantation rate.

	Cases (n = 91)		Control (n = 91)		X <sup>2</sup>	p
	No	%	No	%		
Implantation	56	61.54	48	52.75	0.83	0.36

**Table (6)** Comparison between cases and control group regarding ongoing pregnancy

	Cases n = 91	Controls n = 91	X <sup>2</sup>	P
Ongoing pregnancy N (%)	38 (41.76%)	30(33.0%)	1.5	0.22

**Table (7)** Comparison between cases and control group regarding microbiota

	Cases n = 91	Controls n = 91	X <sup>2</sup>	P
Microbiota N (%)	50(54.9%)	10(11.0%)	39.78	< 0.001

#### 4. Discussion

Hysterosalpingography, transvaginal ultrasonography, saline infusion sonography and hysteroscopy are the tools to assess the inner architecture of the uterus [16].

Office hysteroscopy is only recommended by the WHO when clinical or complementary exams (ultrasound, HSG) suggest intrauterine abnormality or IVF failure [17].

I. Moragianni et al., [18] reported IVF success rates in terms of cumulative live-birth rate (CLBR) per woman, thus providing a more realistic estimate that becomes applicable to individual couples. Increased maternal age has been shown to significantly reduce these rates.

Implantation failure is thought to result from impairment of embryo development and/or from abnormal uterine receptivity. Successful implantation requires a competent embryo, a receptive endometrium and a synchronized dialogue between maternal and embryonic tissues. Successful implantation is dependent on a timely progression of a series of biological events during which the embryo undergoes functional interactions with the uterus prepared by the maternal factors [19].

Many strategies have been suggested for improving endometrial receptivity and implantation rate in ART. Endometrial scratching (or injury) has been suggested to boost embryo implantation following recurrent implantation failure after IVF [20].

A link between endometrial scratching and increased chance of pregnancy in subsequent ART procedures was first described a decade ago. Although the underlying mechanism remains unknown, hypotheses include: that endometrial scratching during the previous cycle might induce decidualization, increasing the chance of implantation; that it induces a significant increase in the secretion of cytokines, interleukins, growth factors, macrophages and dendritic cells, all of which might be beneficial to embryo implantation; and that endometrial scratching might lead to better synchronicity between the endometrium and the transferred embryo [21].

In order to evaluate properly the effect of endometrial scratching, one should compare the main reproductive outcomes (live birth, clinical pregnancy, miscarriage) in women who received this intervention before undergoing ART with those in women who did not. Endometrial scratching improved the main reproductive outcomes. The most important

side effect is pain during the procedure. Endometrial scratching was performed in women who were not using oral contraceptive pills (OCP). OCPs are a frequently used pretreatment in fertility centers as this allows greater flexibility to start COS, and can be used to optimize oocyte retrieval during week days [22].

M.A.Karimzade et al., [23] have shown that local injury to the endometrium on the day of oocyte retrieval disrupts the receptive endometrium and has a negative impact on implantation in IVF cycles.

The present study was designed to the value of hysteroscopic endometrial scratching in improving pregnancy rates in patient undergoing ICSI in the next cycle in a randomized controlled study.

It was carried out at the Benha Fertility Centre. The present study included 91 infertile patients as eligible cases for the study and recruited for hysteroscopic endometrial scratching in early follicular phase of the cycle between the 7<sup>th</sup> and 11<sup>th</sup> day of the cycle and 91 women as a control group without endometrial scratching.

Our results had showed non-significant differences between case group and control group regarding age, body mass index and duration.

Z.Petanovski et al., [24] demonstrated that increased body mass of patients entering IVF has a negative impact on the final outcome and certainly reduces the success of the process resulting in reduced clinical pregnancy. Interaction of BMI and age showed a strong significant impact on the outcome of IVF seen through the achievement of clinical pregnancy.

K. Jayakrishnan et al., [25] assessed the efficacy of hysteroscopy in identifying the uterine pathologies and assessed the pregnancy rate following the endometrial scratching. The mean age of the mothers was 36.25 years and their mean duration of marriage life was 5.75 years. For majority of the study population, it was the 2nd attempt for IVF.

L.Wadhwa et al., [26] evaluated the therapeutic efficacy of endometrial scratching in repeated controlled ovarian stimulation (COS) failure cycles. A total of 165 patients were recruited and randomly allocated into three groups: Group A ( $n = 55$ ) underwent endometrial scratching on D2–D4 of the same COS cycle, Group B ( $n = 55$ ) on D7–D9, and Group C ( $n = 55$ ) no intervention done. Women of age group 20–38 years were included in the study. Majority of cases were in 26–30 year age group and distribution of cases in this age group was 49%, 54.5%, and 54.5% in Group A, B, and C, respectively.

Overall clinical pregnancy rate (CPR) was found maximum in the age group of 21–25 years of age. In this age group, CPR was 20%, 36.3% versus 11.1% in Group A, B, and C, respectively. A maximum number of cases recruited had a duration of 6–10 years of infertility; distribution of which was 47.27%, 49.09%, and 50.91% in Group A, B, and C, respectively. Mean duration of infertility was similar in all three groups which was  $6.22 \pm 2.62$ ,  $7.38 \pm 3.56$ , and  $6.67 \pm 3.07$  years in Group A, B, and C, respectively.

In our study, there were non-significant differences between interventional group and non-interventional group regarding number of follicles, number of oocytes retrieved and number of embryos.

L.Wadhwa et al., [26] found that the mean embryo transfer (ET) on day 2 was  $3.56 \pm 0.89$  mm in Group A,  $3.83 \pm 0.74$  mm in Group B, and  $3.81 \pm 0.75$  mm in Group C.

In our study, there was a non-significant difference between case group and control group regarding endometrial thickness. This is in agreement with [27].

Our study showed that there were non-significant differences between case group and control group regarding pregnancy rate, implantation rate and ongoing pregnancy.

Barash et al., [28] reported two-fold higher pregnancy rates, among women with recurrent implantation failure who underwent endometrial biopsy prior to IVF treatment, compared to controls. Subsequently, R.Li [29] had demonstrated the same favorable effect.

However, conflicting results were reported by [23]. They evaluated the effect of local injury to the endometrium on the day of oocyte retrieval on implantation and pregnancy rates in assisted reproductive cycles. They demonstrated that local injury to the endometrium on the day of oocyte retrieval disrupted the receptive endometrium and had a negative impact on implantation in IVF cycles.

S.Hyodo et al., [30] attributed this favorable effect to the diagnostic capability of this procedure and had not examined its potential therapeutic effect. Endometrial scratching is a simple, noninvasive, low-cost procedure that may boost pregnancy rates in women with unexplained infertility. The questions regarding the underlying mechanism of the procedure action remains unknown; however, some hypotheses have been made. It was hypothesized that the local injury to the endometrium in a cycle might induce proper decidualization for implantation competency.

T.G. Cooper et al., [31] suggested that endometrial scratching could have a favorable endometrial healing effect on the implantation

process. This favorable healing effect may trigger the release of biochemical mediators that could enhance implantation. Since an impairment of endometrial receptivity may be a cause of subfertility in a group of couples diagnosed with unexplained infertility, endometrial injury may help a group of couples with unexplained infertility.

A.Gibreel et al., [32] examined the effect of endometrial scratching in women with unexplained infertility undergoing expectant management in a randomized controlled setting. They concluded that endometrial scratching may improve clinical pregnancy rates in couples with unexplained infertility.

M. Kara et al., [33] detected the efficacy of the endometrial biopsy performed in the non-transfer cycle preceding the IVF-ICSI cycle. They concluded that local endometrial injury in the non-transfer cycle increases the implantation rate and pregnancy rate in the subsequent IVF-ICSI cycle in patients who had previous failed IVF-ICSI outcome.

C.O. Nastri et al., [34] assessed the effectiveness and safety of endometrial injury performed prior to embryo transfer in women undergoing ART. They concluded that endometrial injury prior to the embryo transfer cycle in women with previous ART failure and a normal uterus improves live birth and clinical pregnancy rates after autologous fresh embryo transfer. It is advisable not to perform endometrial injury on the day of oocyte retrieval because it appears to significantly reduce clinical and ongoing pregnancy rates.

C.C .Chan et al., [35] provided an evidence-based update on the use of the endometrial "scratch" technique in assisted conception. They showed an improvement in IVF outcomes including live birth rates after an endometrial "scratch". An endometrial "scratch" seems to be of most benefit when it is performed in the menstrual cycle preceding a fresh IVF cycle in women with previous recurrent unsuccessful IVF. An endometrial "scratch" may be achieved by either a hysteroscopy or an endometrial biopsy technique.

C.O.Nastri et al., [36] investigated the effect of endometrial scratching, performed once during OCP pretreatment, on reproductive outcome, pain and ultrasound markers of endometrial receptivity, in unselected women undergoing ART procedures. They believed that endometrial scratching performed once, during OCP pretreatment 7–14 days before starting COS, increases the chance of live birth and clinical pregnancy, but might cause considerable pain.

Both menstruation and pregnancy are inflammatory conditions that cause a degree of physiological ischaemia–reperfusion tissue injury, albeit much more so in pregnancy. Repetitive brief exposures of any organ to a harmful stimulus at a dose below the threshold for tissue injury provide robust protection against, or tolerance to, the injurious effects of a subsequent more severe insult. This paradoxical yet ubiquitous biological phenomenon is termed 'preconditioning' [37].

J.J. Brosens et al., [38] indicated that cyclic decidualization of the endometrium followed by menstrual shedding preconditions protects uterine tissues from the profound hyperinflammation and oxidative stress associated with deep trophoblast invasion during pregnancy.

N .Potdar et al. [39] compared the efficacy of endometrial injury versus no intervention in women with RIF undergoing IVF. They suggested that inducing injury is 70% more likely to result in a clinical pregnancy as opposed to no treatment. Furthermore, scratching of the lining was 2-times more likely to result in a clinical pregnancy compared with telescopic evaluation of the lining of the womb. In women with RIF, inducing local injury to the womb lining in the cycle prior to starting ovarian stimulation for IVF can improve pregnancy outcomes.

A.M .Elbareg et al., [40] assessed the value of hysteroscopy in evaluating a women with unexplained infertility in whom standard infertility investigation have failed to reveal any abnormalities and assessed the effect of treating subtle uterine abnormalities on pregnancy rate. They suggested that correction of any uterine abnormalities even if small and minor improves the chance of conception in infertile women who have no other causes for infertility.

A.K. Makled et al., [41] evaluated the role of hysteroscopy and endometrial biopsy in women with unexplained infertility. They concluded that routine hysteroscopy and endometrial biopsy should be used as a basic part of the work-up for women with unexplained infertility.

In a paper published by C.Simón et al., [42], the quality of evidence-based data supporting endometrial scratching as a means to improve pregnancy rates in ART was criticized and concluded that well-designed studies and well-performed meta-analysis are needed to generate good quality scientific information regarding endometrial scratching.

M.M. Seval et al., [43] investigated the effect of additional endometrial scratching procedure during hysteroscopy on assisted

reproductive technology (ART) cycle outcomes in repeated implantation failure (RIF) patients without endometrial or uterine abnormalities on hysteroscopic evaluation. They concluded that endometrial scratching during diagnostic hysteroscopy seems to enhance implantation and as well pregnancy rates in comparison to diagnostic hysteroscopy alone. S.F.Lensen et al., [44] concluded that it is uncertain whether endometrial injury improves the probability of pregnancy and live birth/ongoing pregnancy in women undergoing IUI or attempting to conceive through sexual intercourse.

A.M. Maged et al., [46] reported a significant improvement in clinical pregnancy rate when endometrial scratching was done in follicular phase of same COS with IUI cycle. However, in the study conducted by [45], most women underwent scratching in first IUI cycle.

S.Lensen et al., [47] investigated whether endometrial scratching, delivered by an endometrial pipelle biopsy, increases the probability of live birth in women undergoing IVF. They concluded that endometrial scratching did not result in a higher live-birth rate than no endometrial scratching. The procedure was associated with a mild amount of pain and a small number of adverse events.

S.Frantz et al., [48] concluded that endometrial scratch in the luteal phase of the cycle preceding the ovarian stimulation does not improve CPR in patients undergoing a first or second IVF/ICSI attempt.

Our study showed that there was statistically a high significant difference between the two studied groups regarding microbiota.

Knowledge regarding the interactions between the microbiome and the human reproductive axis is growing rapidly. A deeper understanding of normal physiology, identification of different dysbioses, and characterizing the microbiome's impact on reproductive outcomes promise meaningful enhancements in clinical care. While much has been learned since the early contributions of Semmelweis, the most insightful and powerful findings may lie just ahead [49].

## 5. Conclusion

- The role of hysteroscopy in patients undergoing IVF seems to be vital for patients in whom an IVF is being contemplated, for treatment of infertility.
- Endometrial injury in non transfer cycle does not improve the clinical pregnancy and implantation rates in the subsequent IVF-ET cycle in patients with previous

unsuccessful IVF cycles in patients with good-quality embryos.

- Endometrial scratching did not result in a higher rate of live birth than no intervention among women undergoing IVF.

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