Effect of adding endometrial scratching to hysteroscopy on pregnancy rates in women with recurrent implantation failure in IVF/ICSI cycles

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Abstract: Assisted reproductive techniques (ART) is a recent tool for overcoming of several infertility problems in human beings. Implantation failure is remaining one of the foremost factors restraining IVF success. A successful implantation mainly depends on two basic factors including the quality of embryo and endometrial condition. In spite of several protocols were applied in vivo and in vitro to enhance the embryonic developing environment, like types of culture media, supported hatching, transfer of blastocyst embryos, and preimplantation genetic screening (PGS), but the rate of implantation remain lower. The endometrium of the uterus is a multifaceted dynamic tissue composed of two layers (basalis and functionalis), during the menstrual cycle several of morphological and biochemical alterations occur. For improving the implantation and consequently pregnancy rates following IVF, it is essential to improve plans to optimize endometrial receptivity. Induction of injury before IVF has been proposed as a tool to elevate the implantation rates via improving endometrial receptivity. 25% of infertile patients was found to had pathological lesions inside the uterus. Accordingly, routine hysteroscopy before IVF has been proposed to ensure normality of the uterine cavity before embryo transfer. The present study was designed to assess the impact of further scratching to the endometrium during hysteroscopy on ART cycle consequences in repeated transfer due to implantation failure in patients without uterine or endometrial anomalies on hysteroscopic evaluation in a prospective observational study. It was carried out at the Department of Obstetrics and Gynecology, Sayed Galal University Hospital. The present study included 50 infertile patients as eligible cases for the study and recruited for hysteroscopy and 50 women as a control group with no intervention. Our results had showed non-significant variations among control and experimental groups with regard to duration, age, body mass index, type of infertility and causes. There were non-statistical significant differences between study group and control group regarding follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin, duration of hormonal stimulation, the amount of recombinant FSH used (IU), endometrial thickness and previous failures. Also, there were non-statistical significant differences between study group and control group regarding retrieved oocytes, amount of oocytes injected, embryos number, frozen embryos number, and grade, except for grade 2 which exhibited statistically a high significant difference. The result of this study showed no statistically significant differences between both groups as regard mode of insemination, number of sacs and fetal pulsation, also there were non-statistical significant differences regarding pregnancy and implantation, but there was a significant variations among the two studied groups concerning rate of gestation.

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1. Introduction

Hysteroscopy is used for several purposes in the field of Gynecology and the diagnosis of many gynecological disordered. It has become essential tool in the hand of the gynecologic surgeons. It is used transcervical for dual purposed for diagnosis and treatment of the endometrial cavity [(1)].

Synchrony between embryo and endometrial development is considered as a serious factor for successful gestation, has supported the importance of elements for uterine receptivity to more improve in rates of implantation in couples under ART, like *in vitro* fertilization. The idea of endometrial receptivity is attributed to the capacity of the endometrium to permit implantation of embryo, where the blastocyst is attached to the epithelial cells of the uterus and penetrates via it. The mechanism of attachment is a complex procedures and required a synchronized interactions among the endometrium and the embryonic cells, which can be classified into three successive phases. The first phase is called the apposition of an embryonic pole of blastocyst to the endometrium. Through the 2nd phase (implantation stage) or connection phase, the embryonic throphoectodermal cells union to the epithelium of endometrium to form a strong contact. while during

the 3rd phase, blastocyst braches the epithelium of endometrium and occupies the entire endometrium accomplishment the inner 1/3 of the myometrium and renovation the uterine vasculature.

An accessibility of the endometrium is not long-lasting, so during most of the endometrial cycle, the uterus does not permit the embryo to be implanted. This special feature was first recorded in rats, while in mice is characterized by the presence of a 'window of implantation', which is governed by the steroid hormones released from the ovaries: A slight time setting in which the endometrium permits implantation of blastocyst [(2)].

Implantation comprises two chief elements, a healthy embryo capable for implantation and a receptive endometrium that should assist implantation processes [(3)].

The term of recurrent implantation failure (RIF) is meaning failure in implantation of embryo after many embryo transfer trials for successive IVF treatment cycles. Though, there are no proper measures describing the number of un-succeeded cycles or the total number of transferred embryos in these IVF trials. Therefore, interesting IVF fertility centers may call different expressions for RIF [(4)].

Failure in implantation after repeated embryo transfer, may be endorsed to many causes. These causes can be summarized into three topics: embryonic defects, reduced endometrial receptivity, and factors with collective influence.

Ben-Meir et al. [(3)] have proposed that women with RIF may profit from stimulation of endometrium convinced by local abrasion during insertion of catheter for endometrial biopsy in the cycle prior to the actual treatment cycle.

Narvekar et al. [(5)] Obtained two endometrial biopsy, during the luteal and follicular phases of the cycle of RIF women, prior to the embryo transfer cycle. They found a significant increase in the clinical pregnancy rate (32.7 % vs13.7 %), the live birth rate (22.4 % vs 9.8 %) and the implantation rate (13.07 % vs 7.1 %) in women who go through the intervention versus control one.

Endometrial scratching is a procedure performed to increase the IVF pregnancy rates. It is a quick and safe procedure which resembles a smear test and is performed the month prior startring IVF treatment [(6)].

Seval et al. [(7)]. They concluded that endometrial scratching during diagnostic hysteroscopy of RIF patients underwent ART appears to improve implantation and pregnancy rates in contrast to diagnostic hysteroscopy only.

The aim of this work is to investigate the effect of performing endometrial scratching during hysteroscopy on gestation rates in patients with recurrent implantation failure in IVF/ICSI cycles.

2. Patients and Methods

It is a prospective observational study, conducted at the Department of Obstetrics and Gynecology, Sayed Galal University Hospital on fifty women. All subjects gave informed consent.

Patients:

50 infertile patients were assessed as eligible cases for the study and recruited for hysteroscopy and 50 women were considered as a control group with no intervention.

Eligible participant subjects were randomly assigned to receive either a single, site-specific endometrial injury guided by hysteroscopy [study group (n = 50)] or no intervention [control group (n = 50)].

Inclusion criteria:

1. Age less than or equal to 37 years.

2. Patients with at least one previous failed IVF-ET/ICSI cycles undergoing fresh autologous IVF/ICSI cycles.

3. Good responders in the previous IVF cycle [the patients who had developed at least four good-quality embryos (grade 1 and 2 of Veeck's grading) in the previous IVF cycles].

4. Normal HSG.

5. Normal seminal profile.

6. Regular ovulation confirmed by mid-luteal progesterone.

7. Normal TVS criteria.

Exclusion criteria:

1. Patients detected to have endometrial tuberculosis in the past, including those treated with antituberculous treatment.

2. Presence of intramural fibroid distorting the endometrial cavity / submucous myoma / ashermans syndrome.

3. Presence of sonographically detected hydrosalpinx.

Mehods:

1- Written informed consent to share in this study.

2- History taking and examination [full personal history (e.g. age and past history of IVF/ICSI trials), menstrual history and medical history] are taken.

3- General, abdominal and local examination were done to all cases.

4- Investigations including hormonal profile (FSH and LH), HSG and transvaginal ultrasound).

Treatment protocol:

All patients were evaluated with baseline day 3 FSH, antral follicle count, and a hysteroscopy on 7 to 10 day of the cycle prior to the embryo transfer cycle. Records of previous stimulation protocols and embryology details were reviewed.

The patients in the intervention group underwent endometrial sampling with a biopsy catheter (Pipelle;

Gynetics Medical Products, Hamont Achel, Belgium). After the introduction of the Pipelle into the uterine cavity, it was rotated 360 degrees and moved up and down four times after withdrawing the piston.

Figure (1): Biopsy catheter

All patients were prescribed Diclofenac sodium 75 mg IV ampoule 30 minutes prior the procedure. Doxycyclin 100 mg was prescribed twice daily for 7 days after both the procedures. In order to avoid the possible confounding effect of antibiotic on IVF success, the control group was also prescribed Doxycyclin twice. Nonhormonal contraception was advised to the patients in both the groups in the nontransfer cycle.

Each woman recruited in the study underwent the same COH protocol that she had undergone in the previous IVF cycles.

Outcome measures:

Cases were followed up prospectively. The primary outcome was the clinical crude Pregnancy Rate (PR) per woman on the onging and subsequent cycles. Clinical pregnancy is defined as visualization of fetal cardaic pulsations on TVS, 2-3 weeks following a positive pregnancy test.

Statistical analysis:

Data were entered checked and analyzed using Epi-Info version 6 and SPP for Windows version 8.

Data were summarized using: the arithmetic mean, standard deviation, student t test and chi-squared test.

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value).

The results was considered:

- Significant when the probability of error is less than 5% ($p < 0.05$).
- Non-significant when the probability of error is more than 5% ($p > 0.05$).
- Highly significant when the probability of error is less than 0.1% ($p < 0.001$).

The smaller the p-value obtained, the more significant are the results.

3. Results

There were non-statistical significant differences between study group and control group regarding age, duration and body mass index ($p > 0.05$) (table 1).

Table (1): Comparison between study group and control group regarding demographic and clinical characteristics

	Control (n = 50)	**Study (n = 50)**	**t**	**p**
Age (years)				
Mean ± SD Range	30.8 ± 6.3 20-40	29.8 ± 6.8 20-41	0.7	0.46 (NS)
Duration of infertility				
Mean ± SD Range	10.5 ± 5.2 1-16	9.7 ± 5.2 1-16	0.84	0.4 (NS)
BMI				
Mean ± SD Range	28.8 ± 5.7 22-40	29.2 ± 7.2 22-41	0.3	0.75 (NS)

There were non-statistical significant differences between study group and control group regarding type of infertility and causes ($p > 0.05$) (table 2).

There were non-statistical significant differences between study group and control group regarding basal FSH, basal LH and basal E_2 ($p > 0.05$) (table 3).

There was a non-statistical significant difference between study group and control group regarding prolactin ($p > 0.05$) (table 4).

There were non-statistical significant differences between study group and control group regarding E_2, duration of hormonal stimulation and recombinant FSH at time of hCG administration ($p > 0.05$) (table 5).

There was a non-statistical significant difference between study group and control group regarding endometrial thickness ($p > 0.05$) (table 6).

There was a non-statistical significant difference between study group and control group regarding previous failures ($p > 0.05$) (table 7).

There were non-statistical significant differences between study group and control group regarding retrieved oocytes, number of injected oocytes, number of embryos, number of frozen embryos, and grade ($p > 0.05$), except for grade 2 which exhibited statistically a high significant difference ($p < 0.001$) (table 8).

There were non-statistical significant differences between study group and control group regarding mode of insemination, number of sacs and fetal pulsation ($p > 0.05$) (table 9).

There were non-statistical significant differences between study group and control group regarding pregnancy and implantation ($p > 0.05$), but there was statistically a significant differences between the two studied groups regarding pregnancy rate ($p < 0.05$) (table 10).

Table (2): Comparison between study group and control group regarding type of infertility and causes

	Control		Study		X^2	p
	No	%	No	%		
Type of infertility						
Primary	38	76	40	80	0.23	0.62
Secondary	12	24	10	20		(NS)
Cause of infertility						
Male factor	25	50	20	40	2.39	0.88 (NS)
Male tubal factor	5	10	5	10		
Ovarian factor	4	8	6	12		
Endometriosis	2	4	3	6		
Tubal factor	5	10	7	14		
Unexplained	6	12	4	8		
Unknown	3	6	5	10		

Table (3): Comparison between study group and control group regarding basal FSH (IU/L), basal LH (IU/L) and basal E_2 (pg/ml)

	Control (n = 50)	Study (n = 50)	t	p
FSH				
Mean ± SD	5.9 ± 2.2	5.6 ± 2.4	0.65	0.59
Range	2-8	2-9.9		(NS)
LH				
Mean ± SD	6.7 ± 3.1	7.5 ± 3.5	1.2	0.22
Range	2-8	2-9.9		(NS)
E_2				
Mean ± SD	95.7 ± 104.1	95.5 ± 78.9	0.01	0.99
Range	16-300	15-300		(NS)

Table (4): Comparison between study group and control group regarding prolactin (IU/ml)

PRL	Control (n = 50)	Study (n = 50)	t	p
Mean ± SD	19.6 ± 6.6	17.5 ± 5.3	1.73	0.08
Range	7-30	7-30		(NS)

Table (5): Comparison between study group and control group regarding hormonal assay at time of hCG administration

	Control (n = 50)	Study (n = 50)	t	p
E_2				
Mean ± SD	8.9 ± 2.3	9.3 ± 1.5	1.1	0.26
Range	5-12	7-11		(NS)
Duration of hormonal stimulation				
Mean ± SD	15.4 ± 4.3	14 ± 5.7	1.4	0.15
Range	10-21	9-25		(NS)
Recombinant FSH				
Mean ± SD	24.8 ± 14.3	28.8 ± 19.4	1.1	0.24
Range	13-55	11-68		(NS)

Table (6): Comparison between study group and control group regarding endometrial thickness of embryo transfer

Endometrial thickness	**Control (n = 50)**	**Study (n = 50)**	**t**	**p**
Mean ± SD **Range**	6.8 ± 3.2 4-14	7.3 ± 3.7 5-15	0.74	0.4 (NS)

Table (7): Comparison between study group and control group regarding previous failures

	Control		**Study**		**X^2**	**p**
	No	**%**	**No**	**%**		
1	40	80	38	76	1.1	0.77
2	9	18	10	20		
3	0	0	1	2		
4	1	2	1	2		

Table (8): Comparison between study group and control group regarding quality of oocyte and embryo

	Control (n = 50)	**Study (n = 50)**	**t**	**p**
Retrieved oocytes				
Mean ± SD Range	19.8 ± 7.5 5-30	20.8 ± 7.7 6-32	0.68	0.49 (NS)
Number of injected oocytes				
Mean ± SD Range	12 ± 6.1 2-20	11.8 ± 6.8 2-22	0.12	0.9 (NS)
Number of embryos				
Mean ± SD Range	4.1 ± 1.6 1-6	4.5 ± 1.7 1-6	1.3	0.18 (NS)
Number of frozen embryos				
Mean ± SD Range	3.86 ± 2.9 0-10	4.1 ± 3.1 0-10	0.45	0.64 (NS)
Grade Grade 1 *Mean ± SD* *Range* Grade 2 *Mean ± SD* *Range* Grade 3 *Mean ± SD* *Range*	 1.7 ± 0.9 0-3 2 ± 1.5 0-5 2.4 ± 1.3 0-4	 2.46 ± 1.3 0-4 3 ± 1.7 0-5 2.5 ± 1.3 0-4	 3.4 0.6 0.46	 < 0.001 (HS) 0.5 (NS) 0.6 (NS)

Table (9): Comparison between study group and control group regarding mode of insemination, number of sacs and fetal pulsation

	Control		**Study**		**X^2**	**p**
	No	**%**	**No**	**%**		
Mode					2.34	0.12 (NS)
ICSI	50	100	46	92		
IVF	0	0	4	8		
Number of sacs					0.41	0.81 (NS)
1	28	80	30	85.7		
2	4	11.4	3	8.6		
3	3	8.6	2	5.7		
Fetal pulsation -ve +ve	 0 12	 0 100	 2 22	 8.3 91.7	0.07	0.79 (NS)

Table (10): Comparison between study group and control group regarding study outcome measures (pregnancy and implantation)

	Control		Study		X^2	p
	No	%	No	%		
Pregnancy rate						
-ve	38	76	28	56	4.46	0.03
+ve	12	24	22	44		(S)
Implantation rate						
Mean ± SD	38 ± 22		45 ± 25		0.66	0.4
Range	20-100		25-100			(NS)
Clinical pregnancy	23	46	28	56	1	0.3 (NS)

4. Discussion

Implantation is the "rate-limiting step" in the achievement of IVF cycles but also in intrauterine insemination (IUI) cycles. Successful implantation of embryo requires a receptive uterus. Poor endometrial receptivity is an important cause of repeated implantation failure. Endometrial receptivity is modulated by various signaling molecules such as prostaglandins, cytokines, integrins, and leukemia inhibitory factor. Dysregulation in these factors may lead to repeated implantation failure [(8)].

Many factors are play a role in decreasing the endometrial receptivity, like changed expression of immunological factors, adhesive molecules and thin endometrium, may decrease endometrial receptivity [(9)].

Moragiann et al. [(10)] reported IVF success rates represented in cumulative live-birth rate (CLBR) per woman, therefore giving a more accurate assessment that suits the applicable to single couples. Generally, CLBR recorded was ranged from 45 and 55% after IVF. Increased mother`s age has been demonstrated to reduce significantly these values as has preimplantation genetic analysis**.**

Some authors reported that an increase in the fertilization or conception rates, do not necessarily followed by an increase in the pregnancy rates. Nearly 30% of naturally fertilized embryos are missing before implanted in the endometrium and more than 50% of IVF embryos succeeded to complete implantation [(11)].

The process of successful implantation based mainly on endometrial–embryonic communication and condition of receptive endometrium which is required for apposition, adhesion and invasion of blastocyst. Implantation failure is assumed to product from diminishing of embryo growth and/or from abnormal uterine receptivity. To complete the steps of implantation needs a proficient embryo, a receptive endometrium and a synchronized communication among maternal and embryonic tissues and is dependent on a timely advancement of a sequences of biological measures during which the embryo endures functional interactions with the uterus organized by the maternal factors [(12)]**.**

Several protocols have been proposed for successful endometrial receptivity and implantation rate in ART. Scratching of endometrium during insertion of catheter for biopsy has been suggested to augment embryo implantation after repeated failures of implantation after IVF technique [(13)].

Zhou et al. [(14)] observed that convincing local scratch to the endometrium in Controlled Ovarian Hyperstimulation (COH) cycles is accompanied with increased in the pregnancy rate. Conversely, **Karimzade et al.** [(15)] have demonstrated that local abrasion to the endometrium on the day of oocyte collection has a negative effect on implantation rate in IVF cycles due to interruption in the receptive endometrium.

The present study was designed to explore the impact of more of scratching to the endometrium during hysteroscopy on ART cycle products in repeated implantation failure in women free from endometrial or uterine anomalies on hysteroscopic evaluation in a prospective observational study.

It was carried out at the Department of Obstetrics and Gynecology, Sayed Galal University Hospital. The present study included 50 infertile patients as eligible cases for the study and recruited for hysteroscopy and 50 women as a control group with no intervention.

Concerning demographic and clinical data, our results had showed non-statistical significant variations among control and study groups with respect to age, duration, body mass index, type of infertility and causes. This in agreement with **Narvekar et al.** [(5)].

Petanovski et al. [(16)] demonstrated that obese women (increased BMI) enrolled in IVF has a bad effect on the final result and definitely decreases the success rate of pregnancy. So, both BMI and age interaction revealed a strong significant effect on the success of IVF represented in pregnancy rate.

Wadhwa and Mishra [(17)] evaluated the treatment efficiency of scratching of endometrium in

repeated ovarian hyperstimulation failure cycles. Overall clinical pregnancy rate (CPR) was found maximum (20%, 36.3% vs 11.11%) in the age group of 21–25 years of age. 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 ± 2.62, 7.38 ± 3.56, and 6.67 ± 3.07 years in Group A, B, and C, respectively.

The maximum cases were of unexplained infertility (UI) with distribution of 43.64%, 27.27%, and 30.91%, respectively, in Group A, B, and C (P = 0.355) followed by combined etiology (18.8%, 27.27%, and 14.5%, respectively, in Group A, B, and C) and male factor (16.36%, 20%, and 25.45% in Group A, B, and C, respectively) [17].

In our study, there were non-statistical significant differences between study group and control group regarding follicle-stimulating hormone, luteinizing hormone and estradiol. This is in agreement with **Narvekar et al.** [5]. **Ebbesen et al.** [18] established that increasing bFSH levels were accompanied with poor pregnancy rates following IVF.

In our study, there were non-statistical significant differences between study group and control group regarding prolactin and duration of hormonal stimulation. This is in agreement with **Barash et al.** [19].

The result of our study showed no statistically significant difference between both groups as regard the amount of recombinant FSH used (IU). This is in agreement with **Narvekar et al.** [5].

In our study, There were non-statistical significant difference between study group and control group regarding endometrial thickness and previous failures. This is in agreement with **Karimzadeh et al.** [20].

In our study, there were non-statistical significant differences between study group and control group regarding retrieved oocytes, numbers of injected oocytes, embryos, frozen embryos, and grade, except for grade 2 which exhibited statistically a high significant difference.

Heijnen et al. [21] suggested that a low number of oocytes in ovarian response after slight stimulation are accompanied with a noticeably higher conception rate. Because a mild stimulation symbolize a physiological response to the indirect interference with single dominant follicle selection and not returned to pathological decrease in ovarian response accompanied with ovarian ageing. The clinical impacts of low numbers of oocytes after slight stimulation may consequently be quite varied from the poor ovarian response recorded in conventional GnRH agonist suppression cycles.

Wadhwa and Mishra [17] found that the mean embryo transfer (ET) on day 2 were averaged 3.56 ± 0.89 mm; 3.83 ± 0.74 and 3.81 ± 0.75 mm in groups A, B, and C, respectively.

The result of this study showed no statistically significant differences between both groups as regard mode of insemination, number of sacs and fetal pulsation. This is in agreement with **Narvekar et al.** [5].

Our study showed that there were non-statistical significant differences between study group and control group regarding pregnancy and implantation, but there was a significant variations among the two studied groups concerning pregnancy rate.

Baysoy et al. [22] reported that pregnancy rates were not significantly different between the two groups. **Li and Hao** [23] had demonstrated the same favorable effect.

Zhou et al. [14] found that local harm to the endometrium during a COH cycle in ART enhanced implantation of embryos, clinical pregnancy, and live birth rates.

Karimzadeh et al. [20] observed the same results in their study. They indicated that the implantation rate was estimated as 10.9% in the biopsy group compared to 3.38% in the controls. The clinical pregnancy rate was high significantly in the case group (27.1%) than in control (8.9%) group.

Also, **Kalma et al.** [24] They hypothesized that the endometrial injury increases the expression of genes required for preparation of endometrial for implantation.

Narvekar et al. [5] reported that the live birth rate was significantly higher (P = 0.04) in the intervention group (22.4%) in comparison with control group (9.8%). The clinical pregnancy rate was 32.7% vs. 13.7%, in the intervention group versus control group, respectively. The implantation rate was significantly higher (P = 0.04) in the intervention group (13.07%) as compared to controls (7.1%).

Gnainsky et al. [25] reported that a biopsy-caused inflammatory reactions which may help the endometrium for proper implantation.

However, conflicting results were reported by **Karimzade et al.** [15]. They confirmed that local abrasion to the endometrium on the day of oocyte collection interrupted the receptive endometrium and had a adverse on implantationa rate in IVF cycles.

Hyodo et al. [26]. Postulated that the local scratch to the endometrium in a cycle might encourage an appropriate decidualization for implantation ability.

Li and Hao [23] proposed that endometrial abrasion upsurges the expression of estradiol receptor in endometrial leading to alterations in maturation of

endometrium. In addition, mechanical stimulation of endometrium with a microcurette or an oil injection had been known to encourage decidual tissue formation in guinea pigs and in mice. The mode of action of injury in increasing implantation rate may be during a healing processes which augment the release of cytokines and growth factors following induction of scratch to the endometrium might induce the noticed beneficial effect.

In addition, Cooper et al. [27] reported that scratching to the endometrium could have a beneficial endometrial healing action on the success of implantation. The effect proper healing may stimulate the secretions of biochemical mediators that could augment implantation.

Gibreel et al. [28] concluded that in in couples with unexplained infertility, endometrial scratching may increase clinical pregnancy rates.

Narvekar et al. [5] They have showed that implantation rates, clinical pregnancy and the live birth rates, significantly elevated post endometrial scratching in the non-transfer cycle in women with good-quality embryos. This increase may be returned to that injury-induced endometrial decidualization secondary to up regulation of genes encoding for locally acting mediators.

Huang et al. [29] demonstrated that a local injury induced during IVF procedures is valuable for implantation in women with repeated implantation failure.

Kara et al. [30] concluded that local endometrial scratch in the non-transfer cycle elevated the implantation rate and pregnancy rate in the subsequent IVF-ICSI cycle in women who had previous failed IVF-ICSI result.

Nastri et al. [31] demonstrated that inducing scratch to the endomterium before the embryo transfer cycle in patients with preceding ART failure and a normal endometrium increases clinical pregnancy rates and live birth post autologous fresh embryo transfer. Also, they not advise to do induction of injury in endometrium on the day of oocyte collection because it seems to significantly drop clinical pregnancy rates.

Chan [32] showed an improvement in IVF outcomes including live birth rates after an endometrial "scratch" which done in the menstrual cycle prior a fresh IVF cycle in patients with preceding recurrent IVF failure.

Menstruation and pregnancy are considered an inflammatory situation that lead to a degree of physiological ischaemia–reperfusion tissue harm, although much more hence in gestation. Repetitive exposures a harmful stimulus offer strong protection against, or tolerance to, the injurious impacts of a following more severe offense. [33].

Brosens and Gellersen [34] demonstrated that cyclic decidualization of the endometrium go after menstrual coming off preconditions saves uterine tissues from the sever hyperinflammation and oxidative stress accompanied with deep trophoblast invasion during gestation.

Wadhwa and Mishra [17] reported that pregnancy rate (P = 0.542) in the same cycle of EB scratch was (11.5%), (17.39%), and (13.7%). Pregnancy rate per cycle (P = 0.67) is (11.2%), (14.7%), and (14.03%) in Groups A, B, and C, respectively. Abortion rate (P = 0.313) was 1.92%, 4.35%, and 0% in Groups A, B, and C, respectively. Ovarian hyperstimulation syndrome rate (P = 0.195) was 5.77%, 0%, and 1.96%. No twins present in any of the three treated groups.

El-Toukhy et al. [35] recorded a significant increase in the clinical pregnancy rate in hysteroscopy group. The required number of hysteroscopy trials 7 to get high of pregnancy rate.

Gnainsky et al. [25] found that local mechanical scratching of the endometrium can augment the uterine receptivity and help the implantation of embryo. The method is easy to perform and simple and not coasty which can be used in selective unexplained infertility women who suffering from repeated failure in embryo implantation and leads to infertility. In addition, this method may help in reducing psychological tensions and high costs.

Potdar et al. [36] compared the efficacy of endometrial injury versus no intervention in women with RIF undergoing IVF. They demonstrated a beneficial effect of EB and hysteroscopy in significantly improving clinical pregnancy rates in women with RIF in IVF/ICSI cycles when intervention was done in luteal phase of preceding IVF cycle. Clinical pregnancy rates were twice as high with biopsy/scratch as opposed to hysteroscopy. 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.

Elbareg et al. [37] 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. In addition,

women who do not conceive will get the benefit of improved results of assisted reproductive techniques.

Makled et al. [38] 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 **Simón and Bellver** [39], 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.

Nastri et al. [31] demonstrated that endometrial injury was associated with increased clinical pregnancy rate when done between day 7 of preceding cycle and day 7 of ET, live birth rate or ongoing pregnancy rate in women undergoing more than two previous ETs. Thus, it was observed that endometrial injury improves pregnancy outcomes not only when done in luteal phase of preceding cycle but also when done in follicular phase of the same cycle.

Seval et al. [7] 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. **Lensen et al.** [40] 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.

Wadhwa et al. [41] **and Maged et al.** [42] 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 **Wadhwa et al.** [41], most women underwent scratching in first IUI cycle. **Wadhwa and Mishra** [17] concluded that endometrial scratching is a cost-effective and easy technique which may improve clinical pregnancy rates in previous COS failure cycles.

Conclusion

- Induction of injury to the endometrium in non transfer cycle increases the implantation and clinical pregnancy rates in the subsequent IVF-ET cycle in women having good quality embryos with a history of repeated IVF cycles failure.
- Scratching to the endometrium is a cost-effective and simple method which may enhance clinical pregnancy rates in preceding implantation failure cycles.
- More information is needed as regard the timing of site-specific hysteroscopic-guided endometrial snip and whether repeating the procedure in patients who failed to conceive after undering it once may be effective or not.

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