The Effect of Endometrial Injury by Office Hysteroscopy on The Outcome of Intrauterine Insemination

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ABSTRACT

Background: Evaluating the uterine cavity is a basic step in investigating infertile women. Both the condition of the endometrium as well as the uterine cavity are thought to be important factors in determining receptivity for embryo implantation. **Aim of the Work:** In our study we conducted a trial to assess the effect of endometrial injury by hysteroscopy in the outcome of intrauterine insemination (IUI).

Patients and Methods: This interventional prospective randomized controlled clinical trial was conducted at ElSayed Galal University Hospital during the period from January 2016 to October 201
7. The study comprised 200 of women diagnosed as unexplained infertility or with mild male factor.

Results: The biochemical and clinical pregnancy rates were higher in women of group I when compared to women of group II [28 (28%) vs. 8 (8%), p=0.012 and 25 (25%) vs. 4 (4%), p= 0.034, respectively.

Conclusion: Performing endometrial scratch using hysteroscopy in the preceding cycle of intra uterine insemination is a simple cheap maneuver that improves the chemical and clinical pregnancy outcome.

Keywords: endometrial injury, hysteroscopy, intrauterine insemination.

INTRODUCTION

Intra uterine insemination (IUI), together with ovarian stimulation, is a less expensive and invasive treatment in comparison with other assisted reproductive technique (ART) , and has been widely used for the treatment of infertile couples with a variety of indications, such as non-severe male factor infertility, unexplained infertility, cervical mucus hostility and ovulatory disturbances . Ovarian stimulation with exogenous gonadotropins, combined with intrauterine insemination (IUI), is a valid treatment for infertility. Its effectiveness in terms of pregnancy rate is 10–14% per cycle reaching cumulative values of 40–90% after 3–10 treatment cycles [(1)].

An important cause of infertility would be a failure of uterine receptivity and failure of implantation. Implantation divided into four steps: apposition, adhesion, attachment and invasion [(2)]. The mid-secretory phase of the menstrual cycle (days 19–23), is the most receptive period of the endometrium which is called the window of implantation (WOI) [(3)].

Endometrial scratching is a simple, minimally invasive, low-cost procedure that may boost biochemical and clinical pregnancy rates in women with infertility. The questions regarding the underlying mechanism of the procedure action remain unanswered; however some hypotheses have been made to explain its beneficial effect. It was hypothesized that the local injury to the endometrium in a cycle might induce proper decidualization for implantation competency [(4)].

There are three possible mechanisms by which endometrial sampling may increase the receptivity and improve the clinical pregnancy rate of IVF-ET which may be effective in IUI cycles too. First, local injury to the endometrium might induce the decidualization of the endometrium and increase its implantation rate. Loeb reported that scratching guinea-pig uteruses provoked the rapid growth of the endometrial cells which are similar to the decidual cells of pregnancy [(5)].

Second, local injury to the endometrium might provoke the wound healing process, involving a massive secretion of different cytokines and growth factors, including leukemia inhibitory factor, interleukin-11, and heparin-banding endothelial growth factor, which are beneficial for embryo implantation [(5)]. The last and the most possible mechanism is COH performed during IVF therapy that may negatively affect the embryo implantation [(6)].

A recent Cochrane review found that we can improve the endometrial receptivity by scratching the endometrium by any mean such as curette or biopsy [(7)].

Hysteroscopy is the gold standard procedure for uterine cavity exploration through direct visualization in patients with recurrent implantation failure. However, the World Health Organization (WHO) recommends HSG alone for the management of infertile women. Office hysteroscopy (OH) is only recommended by the WHO when clinical or complementary exams (ultrasound, HSG) suggest intrauterine abnormality or after in vitro fertilization (IVF) failure [(8)].

Hysteroscopy is known as the most accurate test for diagnosing intrauterine pathology

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[9]. Hysteroscopy detects uterine cavity pathology by direct visualization of the endometrial lining making use of a vaginally inserted endoscope. Due to the development of thinner working channels and the vaginoscopic insertion technique, it has become easy to perform in an outpatient setting without anesthesia. Moreover, hysteroscopy enables instant treatment of small uterine pathology. Therefore, it is frequently referred to as the golden standard [10,11].

AIM OF THE WORK

In our study we conducted a trial to assess the effect of endometrial injury by hysteroscopy in the outcome of intrauterine insemination (IUI).

PATIENTS AND METHODS

Setting:

The study was conducted at ElSayed Galal University Hospital during the period from January 2016 to October 2017.

Study Design:

The study was an interventional prospective randomized controlled clinical trial to compare the effect of endometrial scratching by using hysteroscopy with non-endometrial scratching for women with unexplained infertility.

Population:

This Study comprised 200 of women diagnosed as unexplained infertility or with mild male factor.

Sample Size Justification:

The required sample size has been estimated using the IBM© SPSS© Sample Power© version 3.0.1 (IBM© Corp., Armonk, NY, USA). The primary outcome measure was the biochemical pregnancy rates.

Patients Selection

***Inclusion Criteria*:** Inclusion criteria were

① Mild male factor infertility.
② Unexplained infertility.
③ Women partner aged <39 years with regular menstrual cycles, body mass index "BMI" (calculated as weight in kilograms divided by the square of height in meters) <32 kg/m^2.
④ Normal uterine cavity with normal thin endometrium (<5 mm; to exclude the presence of endometrial lesion as polyp) on day 4 of menstruation, and normal fallopian tubes as documented by hysterosalpingography and/or laparoscopy.
⑤ Normal hormonal profile including follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), testosterone (T) and prolactin (PRL) serum levels.
⑥ Male factor infertility is defined as a sperm count of <15000,000/mL, a total motility of <40%, or normal forms <4% per WHO criteria [10].
⑦ Mild male factor infertility is defined as the presence of abnormal semen parameters but with >5% normal morphology and >5000000/mL motile spermatozoa recovered after sperm preparation.
⑧ Ovulation will be documented with mid-luteal serum progesterone (P) levels exceeding 5 μg/ml.
⑨ The diagnosis of unexplained infertility is based on normal semen analysis using WHO criteria, documentation of ovulation with a mid-luteal serum P level exceeding 5 μg/ml, normal hysterosalpingography and/or diagnostic laparoscopy.

***Exclusion criteria*:** Couples will be excluded if they are

① Diagnosed with infertility due to other causes.
② Significant cardiovascular, pulmonary, renal, neurologic, or hepatic problems.
③ Presence of ovarian cyst >2 cm before stimulation.
④ Abnormal endometrial cavity due to submucous myoma encroaching on the cavity, endometrial polyp, IU synechia (Asherman syndrome), septate or bicornuate uterus.

Informed consents from participants will be attained before randomization.

All patients will be subjected to careful history taking, general examination and local gynecologic examination.

Randomization:

Was done by using computer generated randomization sheet using MedCalc© software version 12.5.

Study Groups:

Two hundred patients admitted to the study, and were randomly distributed according to computer generated randomization sheet into two groups (one hundred in each group).

Hysteroscopic group with scratch (Group I):

One hundred patients were endometrial scratching was done by using the hysterocope for each patient at the day (21-26) from the last menestrual cycle.

Hysteroscopic group without scratch (Group II):

One hundred patients were undergoing hysteroscopy without scratch at all was done .

All patients will do postmenstrual hysteroscopy between days 21 and day 26 of the cycle that precedes IUI cycle. A rigid 30 degree 2.7 mm hysteroscopy was used. The uterine cavity was distended with normal saline solution at a pressure of 100-120 mmHg.

In the intervention group (I), hysteroscopy and endometrial scratching was done once in the luteal phase at day (21-26) in the cycle proceeds the IUI cycle using a grasping forceps with teeth.

In the control group (II), hysteroscopy was done without endometrial scratching.

In the next cycle.

All women took the same mild controlled ovarian stimulation protocol.

Clomiphene citrate 100 mg/day was administered orally from day 3 to day 7 of the cycle. Human menopausal gonadotropin (hMG) 75 IU/day was administered intramuscularly (IM) from day 6 to day 8.

Transvaginal ultrasonography (TVU) was performed on day 9 of the cycle for assessment of the number and diameter of follicles, as well as endometrial thickness and pattern. The administration of hMG was continued and the dose was adjusted, if necessary.

When 2-3 follicles with a diameter of at least 18 mm was present, Human chorionic gonadotropin (HCG) 10,000 IU was administered IM.

A single insemination was performed 36 h after hCG administration.

Oral supplementation with 30 mg of dydrogesteron was given daily to support the luteal phase, which started two days after the administration of HCG, and this continued until a pregnancy test was performed.

Clinical pregnancy is defined as the presence intrauterine gestation with fetal heart pulsations demonstrated by transvaginal US at 6-7 weeks' gestation.

Outcome measures

The outcome measure was being clinical pregnancy rate.

Allocation concealment

Allocation of patient in both groups was sealed, numerical, opaque, sequential and enveloped, randomly by 1:1 allocation ratio.

Data Collection and Schedule

Enrollment (recruitment) Data (CRF) (Annex I)**:**

Following admission into the study, the record of the case form was filled, including demographic information was collected, entailing patient's age, parity, medical and surgical histories.

Checkup Schedule:

***First session*:** Inclusion and exclusion criteria were reviewed, clinical examination was done and hormonal profile, HSG, and semen analysis were reviewed to be normal. If any of investigations weren't done, the patient was asked to do it and bring it in the next session.

***Second session*:** Women were asked to present themselves and contact investigators in the morning on the day of the procedure. They were instructed for not receiving any medication before presenting themselves. Each woman received a Case Record Form (CRF) in which the data were recoded.

Patients in control group (group II) were followed for six months without any intervention. Each patient in group I was subjected to the intervention according to the randomization sheet.

Group I: Hysteroscopy with scratching was done.

Group II: Hysteroscopy without scratching was done.

Outcome measures:

Outcome:

Pregnancy was detected by serum βhCG test performed 14 days after IUI for patients who had no menstruation. Chemical pregnancy was defined as a positive serum βhCG test (βhCG >10 mIU/ml. Clinical pregnancy was defined as the presence of gestational sac on vaginal ultrasound. Both chemical and clinical pregnancies were recorded. Vaginal ultrasound was performed 2 weeks after the first positive βhCG.

Case record form (CRF)

Ethical and legal aspects:

Good Clinical Practice (GCP):

The procedures set out in this study protocol, pertaining to the conduct, evaluation and documentation of this study, were designed to ensure that the investigators abide by the principles of good clinical practice and the ethical principles laid down in the current revision of the Declaration of Helsinki.

Delegation of Investigator Responsibilities:

The investigator ensured that all persons assisting with the trial were adequately informed

about the study, any amendments to the study, the study treatments, and their trial-related duties and functions. The investigator maintained a list of sub-investigators and other appropriately qualified person to whom he or she had delegated significant trial-related duties.

Patient Information and Informed Consent:

Before being admitted to the clinical study, the patient was obtained after the nature, scope, and consequences of the clinical study had been explained in a form understandable to her [CRF 01]. An informed consent document, in Arabic language, contains all locally required elements and specifies who informed the patient [CRF 02]. After reading the informed consent document, the patient must give consent in writing. The patient's consent was confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

If the patient was unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to patients took place in the presence of an impartial witness. Consent was confirmed orally and by the personally dated signature of the patient or by a local legally recognized alternative (e.g., the patient's thumbprint or stamp). The witness and the person conducting the informed consent discussions also signed and personally date the consent document.

The original signed consent document was retained by the investigator. The investigator did'nt undertake any measure specifically required only for the clinical study until valid consent had been obtained.

Confidentiality

Only the patient number and patient initials were recorded in the CRF, and if the patients name appeared on any other document (e.g., pathologist report), it was kept in privacy by the investigators.

The investigator maintained a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

Protocol Approval:

Before the beginning of the study and in accordance with the local regulation followed, the protocol and all corresponding documents had been declared for ethical and research approval by the council of OB/GYN department, Al-Azhar University. Furthermore, the approval of the study protocol had been granted by Ethics Research Committee (ERC), Faculty of Medicine, Al-Azhar University, with presentation of patient's information leaflet, consent form, and case record data form (CRF).

8. Statistical analysis:

Data were analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 13 (MedCalc© Software bvba, Ostend, Belgium). The D'Agostino-Pearson test was used to examine the normality of numerical data distribution.

RESULTS

Two hundred women attended to Elsayed Galal University Hospital were assessed for eligibility and offered to participate in the study.

The cases randomly divided in to two groups (I and II) each group included one hundred patients.

Hysteroscopic scratching group (Group I):

One hundred patients subjected to endometrial scratching by using the hysteroscope for each patient at the day (21-26) from the last menstrual cycle.

Non-scratching group (Group II):

One hundred patients subjected to hysteroscopy without any intervention.

All patients from the two groups (I and II) were received a trial of intrauterine insemination in the next month.

Table (1): Description of socio-demographic data among both study groups

		Mean	±SD
Age (year)		29.8	4.2
BMI (k/m^2)		29.3	3.0
Marriage duration (year)		5.9	1.4
Parity	None (n %)	80	(80.0%)
	P1 (n %)	15	(15.0%)
	P2 (n %)	5	(5.0%)

Age of all included females in study ranged between 21 and 35 years with mean of 29.8±4.2 years. The mean BMI and marriage duration was 29.3±3, and 5.9 ±3.4years respectively. The parity was zero among 80 females (80%).

Table (2): Description of Duration, types and Cause of Infertility and previous IUI among both study groups.

		Mean	**±SD**
Infertility duration (year)		5.00	1.35
Type of infertility	Primary (n %)	62	(62%)
	Secondary (n %)	39	(39%)
Cause of infertility	Male cause (n %)	65	(65.0%)
	Unexplained Infertility (n %)	35	(35%)
Previous IUI	No (n %)	77	(77%)
	Yes (n %)	23	(13%)
Number of previous IUI	None (n %)	63	(19%)
	Once (n %)	13	(13%)
	Twice (n %)	19	(19%)
	Three times (n%)	5	(5%)

Among all included women, 62 (62%) had primary infertility, while 24 (39%) had secondary infertility. The mean duration of infertility was 5.0 (range: 1-9 years). IUI was performed for male factor infertility in majority of cases 65 (65%). Among all included 100 women, 23 (23%) underwent previous IUI with 13% performed it only once.

Table (3): Description of hormonal profile among both study groups

	Mean	±SD
FSH (miu/mL)	6.51	1.8
LH (miu/mL)	6.26	1.7
E2 (pmol/L)	48.68	13.2
Prolactin	14.03	3.8

The above table show a description for FSH, LH, E2 and prolactin level among all females included in the study

Table (4): Description of semen characteristics among both study groups

	Mean	±SD
Semen Volume (mL)	1.92	0.41
Count (million/mL)	36.56	7.78
Motility (a+b)	54.13	11.52
Abnormal Forms	77.95	16.59

The above table shows a description for semen characteristics among all females included in the study.

The biochemical and clinical pregnancy rates were 28% and 25 respectively.

Table (5): Description of Duration, types and Cause of Infertility and previous IUI among control group.

		Mean	**±SD**
Infertility duration		4.55	1.05
Type of infertility	Primary	77	(77%)
	Secondary	23	(23%)
Cause of infertility	Male cause	85	(85.0%)
	Unexplained Infertility	15	(15.0%)
Previous IUI	No	57	(57%)
	Yes	43	(43%)
Number of previous IUI	None	57	(57%)
	Once	20	(20%)
	Twice	23	(23%)

Table (6): Description of hormonal profile among control group

	Mean	±SD
FSH	6.38	1.36
LH	8.17	1.74
E2	51.10	10.87
Prolactin	15.11	3.21

Table (7): Description of semen characteristics among control group.

	Mean	±SD
Semen Volume	1.75	0.37
Count	44.00	9.36
Motility (a+b)	48.12	10.24
Abnormal Forms	74.25	15.80

Table (8): Comparison between groups as regard Duration, types and Cause of Infertility and previous IUI.

		Group	P	Sig	±SD		
		Control	Study		3.38	0.474‡	NS
Age (years)	Mean	±SD	Mean	62	(62%)	0.143*	NS
	29.73	4.09	29.95	39	(39%)		
BMI (kg/m2)	29.33	3.12	29.35	65	(65.0%)	0.053**	NS
Marriage duration	5.43	1.16	6.35	35	(35%)		
Parity				77	(77%)	0.056*	NS
				23	(23%)		

N.S: non signifiant
‡student t test
*Chi-Square Tests

Fisher exact test

There were no significant differences between women in both groups regarding the duration, type and cause of infertility. The mean Infertility duration was 4.5 years in group 1 and 5 years in group 2 (p 0.474), primary infertility was present among 77% of group 1 cases compared to 62% of group 2 cases (p= 0.143), male cause of infertility was present among 85% of group 1 cases compared to 65% of group 2 cases (p= 0.053), previous IUI was done in 43% of group 1 cases compared to 23% of group 2 cases (p= 0.056)

Table (9): Comparison between groups as regard clinical and chemical pregnancy

		Group				P	Sig	**RR (95% CI)**
		Control (N=100)		Study (N=100)				
Chemical pregnancy rate (no%)	Positive	8	8%	28	28%	0.012 (S)	S	0.289 (0.14-0.59)
	Negative	92	92%	72	72%			
Clinical pregnancy rate (no%)	Positive	4	4%	25	25%	0.034 (S)	S	0.160 (0.06-0.44)
	Negative	96	96%	75	75%			

*Chi-Square Tests
**fisher exact test

The biochemical and clinical pregnancy rates were higher in women of group I when compared to women of group II [28 (28%) vs. 8 (8%), p=0.012 and 25 (25%) vs. 4 (4%), p= 0.034, respectively.

DISCUSSION

This current randomized clinical study aimed to estimate the effect of local endometrial injury induced by hysteroscopy on midluteal phase by day 21 of the spontaneous menstrual cycle before the IUI treatment on improving the pregnancy rates among patients undergoing IUI. This study was done on 200 infertile females where IUI was indicated for their management, divided randomly into two groups, 100 patients undergo IUI after hysteroscopy and endometrial injury done on day 21 of the preceding cycle and

100 patients underwent IUI after hysteroscopy without scratch. Evaluating the effect of endometrial injury on IUI outcome.

The results of the present study demonstrated that performing the endometrial biopsy in the cycle prior to the cycle of IUI, yield significant increase in pregnancy rates with comparison to control group without endometrial biopsy. Clinical Pregnancy rates were 25 %, versus 4% in the control group. Chemical pregnancy rates were 28%, versus 8% in the control group.

However, there are studies that show that no benefit from endometrial scratch like:

Ashrafi *et al.* [12] concluded that No significant beneficial effect of endometrial scratch injury (ESI) on fertility outcome in patients with repeated IUI failure was detected when it was carried out on day 8 or 9 of the same IUI stimulation cycle. Also, however, no negative impact secondary to ESI was observed. Therefore, confirmation or refutation of this hypothesis requires further studies with a larger sample size.

Aflatoonian *et al.* [13] concluded that local injury to endometrium in luteal phase prior to *Frozen-thawed embryo transfer* FET cycle had a negative impact on implantation and clinical pregnancy rates. But they suggested to perform larger studies with larger study of patients.

Dan Levin et al. [14] in their trial to assess the effect of endometrial scratching (ES) on *in vitro* fertilization-embryo transfer outcome (IVF-ET) on 238 patients they concluded that mechanical endometrial stimulation did not improve implantation and pregnancy rates. Furthermore, no factors that may predict which patients could benefit from ES were identified. Further prospective studies are warranted to evaluate possible benefits in different subsets of patients such as patients with recurrent implantation failures.

Although this study is similar to our study protocol the result was different which indicate that the presence of other factors which may affect the outcome which may need more studies.

There are number of studies support the idea of effect of endometrial injury on increasing pregnancy rate and implantations:

On a Cochrane review, **Nastri *et al.*** [7] they concluded that Moderate-quality evidence indicates that endometrial injury performed between day 7 of the previous cycle and day 7 of the embryo transfer (ET) cycle is associated with an improvement in live birth and clinical pregnancy rates in women with more than two previous embryo transfers. Although current evidence suggests some benefit of endometrial injury, we need evidence from well-designed trials that avoid instrumentation of the uterus in the preceding three months, do not cause endometrial damage in the control group, stratify the results for women with and without recurrent implantation failure (RIF) and report live birth.

Seval *et al.* [15] in their study to investigate 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.

The available evidence points towards a potential benefit of endometrial biopsy in women with RIF when performed in the cycle preceding the IVF treatment cycle. Current evidence on the value of the procedure in women undergoing their first IVF cycle is lacking [4].

Vitagliano *et al.* [16] in their study suggested that endometrial scrtch injury performed once, preferably during the follicular phase of the same cycle of IUI with flexible aspiration catheters, may improve clinical pregnancy and ongoing pregnancy rates in IUI cycles. Endometrial scratch injury does not appear to increase the risk of multiple pregnancy, miscarriage, or ectopic pregnancy.

Almog *et al.* [18] described that in the studies where hysteroscopy were carried out, this intervention was the only factor that increased the embryo implantation rate. Similarly, **Bozdag *et al.*** [19] concluded that pregnancy rates improved in women with normal hysteroscopy findings and repeated implantation failure. Although there is evidence regarding improved outcome with hysteroscopy only as an intervention.

Li *et al.* [20] ***and Hayodo*** [21] suggested that endometrial injury increases the expression of estradiol receptor in endometrial stroma causing changes in endometrial maturation.

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; **Rubel et al.** [22].

A proper healing effect, implemented through the released cytokines and growth factors

after endometrial scratching, might induce the observed favorable effect [4,23].

CONCLUSION

Performing endometrial scratch using hysteroscopy in the preceding cycle of intra uterine insemination is a simple cheap maneuver that improves the chemical and clinical pregnancy outcome.

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