
Research Article,

The Role of Endometrial Scratching to Improve the Pregnancy Rate Among Infertile Couples

Awatif Andisha¹, Ismail Elfortia¹, Hanan Eljabu¹, Murjan Elaiwa¹, Fatma Daw¹, Hawa Ben-Salah¹,
Hawa Shalfuh¹, Ruwaydah Mletan¹, Ibrahim Hanaish¹

¹Libyan National Fertility Center - Misurata, Qaser Ahmed, Residential City, Misurata, Libya
Email Address: a.aljabu@lnfc.med.ly

Abstract:

Background: Different technologies have been used in order to improve the endometrial condition as well as the quality of embryos; however, still the implantation process could fail. Endometrial Scratching (ES) has been proposed by many studies and revealed conflicting results.

Objective: The study Aims to investigate the effect of ES on improving the Clinical Pregnancy Rate (CPR) and Live Birth Rate (LBR).

Methodology: This is a retrospective study was carried out at Libyan National Fertility Centre. 188 Infertile women were included in the study in two different groups. 95 patients who underwent ES and 93 as control group. Cases with male factor infertility, history of surgical sterilization, premature ovarian failure, endometriosis and other hormonal disturbance (thyroid /prolactin) had been excluded from the study.

Results: The CPR was positively affected by scratching procedure among infertile women after perform ES (p value 0.022). The secondary infertile patients have got significant benefit after performing ES by improving the CPR (P value 0.045). The ES has improved the CPR on patients with previous history of failed Intra-Cytoplasmic Semen Injection ICSI (P value 0.043). However, there was no statistically significant difference to the effect of ES on LBR.

Conclusion: The study found that the ES has a positive role to improve the implantation among specific group of infertile couples. It is recommended to perform ES for couples with secondary infertility and previously failed ICSI cycle.

Introduction:

Different technologies of assisted reproductive conception have been used around world in order to improve the CPR among infertile couples [1]. The endometrial receptivity and quality of embryos are considered as important factors affecting the pregnancy rate. The structural anomalies in the uterine cavity such as congenital problems, fibroid, polyp, endometrial adhesion and endometrial thickness are major factors affecting the implantation and so the pregnancy rate [2, 3].

Despite, the development in diagnostic and therapeutic technology in order to improve the endometrial condition (Transvaginal Ultrasound Scan and Hysteroscopy) as well as the quality of embryos, still the implantation of embryos could fail (35% of embryo transfer rate) [4,5].

Consequently, the improvement in the pregnancy rate is still under research [6, 7].

The implantation window is a process that involves activation of some inflammatory cells as well as its mediators such as macrophages, natural killer cells, interleukin and tumor necrosis factor [8, 9, 10, 11]. During this window, essential coordinated interactions between a healthy embryo and normal uterus take place and ended by pregnancy [12]. So, ES has been projected to stimulate the endometrium to catch the implantation window and so improve CPR [13].

The explanation how ES can improve the implantation is still under debate, however its potential to improve the endometrial implantation is crucial to be investigated [11, 14]. ES could be considered as a cost-effective procedure because it is an outpatient procedure and only requires

simple analgesics. On the other hand, it carries a risk of intra-uterine infection [15, 16]. Also, proven the efficacy of ES could help to apply a policy of single embryo transfer which will reduce the risk of multiple pregnancy as well as the unnecessary assisted conception cycles Intra Uterine Insemination (IUI), ICSI and In-vitro fertilization (IVF). So, is a cost-effective procedure [7, 9].

Various research has been carried out and studied the effect of ES on pregnancy rate before imparking in assisted conception cycles as well as natural conception, however; the results were not conclusive mostly due to heterogeneity in the data included as well as the time of ES had been done during the cycle [1, 4]. This study aims to evaluate the improvement in pregnancy rate and pregnancy outcome among sub-fertile couples after performing the endometrial scratching during the mid-luteal phase of the previous cycle.

Materials and Methods:

This is a retrospective study was carried out at Libyan National Fertility Centre. 201 Infertile women were included in the study in two different groups. 95 patients who underwent ES (scratching group) and 93 patients who did not perform ES (control group). Cases with male factor infertility, history of surgical sterilization, premature ovarian failure, endometriosis, poly-cyclic ovaries and other hormonal disturbance (thyroid /prolactin) have been excluded from the study.

The endometrial scratching was done during the luteal phase (18, 19, 20 and 21of menstrual cycle). The procedure was under general anesthesia, insertion of the vaginal speculum and the cervix became clear when the normal saline used as a distension media to stimulate the endometrium as well as wash the uterine cavity from any undetected pathology by trans-vaginal sonography that, could be act as an inhibitory factor for implantation process.

Patients from the two groups (study and control groups) went for assisted conception ICSI in steps. Controlled Ovarian Stimulation (COH) was applied on second day of menstrual cycle and the ovarian response was monitored by TVS and Estradiol level and when at least three follicles reach 18mm (mature follicles), Human Chorionic Gonadotrophin (HCG) was injected. Thirty-six hours later follicles collected by transvaginal ultrasonography-guide under general anesthesia and after fertilization of oocytes with sperm in the laboratory, embryos were transferred. Serum β-

hCG levels were measured 12-14 days after transfer the embryos.

Statistical analysis:

In this study, the statistical analysis for the Data was done by using software SPSS 23.0. The descriptive statistics were either continuous variables which presented by mean ± standard deviation or categorical data which presented by counts (percentage). The comparison of various data between the two groups was done by using chi square. The significant relation is considered when the level of P value achieves <0.05.

Results:

This study involves 201 cases (95 cases perform endometrial scratching and 93 without scratching as a control group). The all scratching procedures for the involved cases were done during the luteal phase of the menstrual cycle. There were 13 cases excluded from the study due to different day of scratching (day 12, 13 of menstrual cycle). The descriptive data were shown in table1 which involve age, duration of infertility, ovarian response markers Follicular Stimulating Hormone (FSH), Antra Follicular Count (AFC), Luteinizing Hormone (LH), Thyroid Stimulating Hormone (TSH) and Estradiol E2.

Table 1: Descriptive Data for both groups Scratching and Control groups.

Variable	Scratching group (n=95) mean±SD	Control group (n=93) mean±SD
Age(y)	32.34 ± 4.58	32.95 ±4.43
Infertility time (year)	4.28 ±2.559	3.96 ±2.738
FSH (IU/L)	6.84 ±1.91	7.17 ±1.72
LH (IU/L)	4.37 ±1.54	4.59 ±1.47
E2 (pg/mL)	35.58 ±15.13	36.47 ±16.26
TSH (IU/L)	2.083 ±0.68	2.14 ±0.79
AFC	4.28 ±2.64	7.78 ±2.57

The study revealed that the clinical pregnancy rate and rate of live birth clearly affected by the scratching procedure and *p value* was statistically significant (0.044, 0.042) respectively.

Table2: Effect of scratching procedure on the pregnancy rate and outcome.

Variable	Scratching Group N=95	Control Group N=93	P value
CPR	54 (56.84%)	35 (37.63%)	0.044
LBR	39 (41.05%)	23 (24.70%)	0.042
Abortion Rate	15 (15.70%)	12 (12.90%)	0.564

By analysis subgroup analysis among scratching group of patients according to the infertility type and in relation to the clinical pregnancy rate, its clear (table 4) that the patients with secondary infertility had got benefit after performing a scratching procedure by improving the clinical pregnancy rate as 62.96% who had negative pregnancy test were with primary infertility and this gives a significant relation (*P value* 0.045).

Table3: Compare the effect of scratching procedure on the types of infertility and clinical pregnancy rate

	Positive Pregnancy (n=41)	Negative Pregnancy (n=54)	P value
Primary infertility	21/41 (51.22%)	34/54 (62.96%)	0.045
Secondary infertility	20/41 (48.78%)	20/54(37.04%)	

There had been some cases with previous history of ICSI and when studied the effect of scratching on those group of people revealed that the scratching procedure has a positive effect in improving the pregnancy rate among patients with previous trials of assisted conception ICSI

Table4: Compare the effect of scratching procedure on the cases with previous failed ICSI and no trials before.

	Negative Pregnancy N (%)	Positive Pregnancy N (%)	P value
History of failed ICSI(51 cases)	30 (31.58%)	21 (22.11%)	0.043
History of no trial (44 cases)	24 (25.26%)	20 (21.05%)	

Discussion:

The present study has concluded that the endometrial scratching has a role to improve the implantation rate among infertile couples; however, LBR does not changed with the ES procedure. In the recent time, endometrial scratching has been proposed as a process to improve pregnancy rate as it involves superficial injury to the endometrium helping in a process of embryo's implantation by releases growth factors, chemical and gene switching that leaves the endometrium to grow healthy and ready for implantation [17, 18, 19, 20]. Barash *et al* [1] was first to demonstrate the positive effect of ES by doubling the implantation rates as well as the live birth rates in cases with Recurrent Implantation Failure (RIF) [1, 21, 22]. In addition, Neeta Singh *et al* [23] revealed that the implantation rate was statistically significant (*P* =0.028) in cases with RIF who were group1 with ES during the luteal phase 19.4% and group2 who had no ES 8.1%. However, the live birth rate and miscarriage rate were no significant difference between the two groups [22]. Moreover, Milan Reljić1 *et al* [24] performed study among cases 429 ICSI cycle with age less than 40 years and had previous failed trials of ICSI and found that the CPR significantly higher among group with ES (*P* =0.007). Furthermore, Emiko Kanazawa *et al* [3] studied three groups, group1 with ES, group2 with only hysteroscopy and group3 with no treatment received. The clinical pregnancy rate was statistically significant between group1 and 3 (*P* = 0.03) but with group 2 no statistically significant (*P* = 0.103). On the other hand, there has been various studies concluded that the ES has no significant role to improve the CPR. Mahnaz Ashrafi *et al* [12] studied 169 cases with more than one IUI cycle failure and normal uterine cavity which revealed no significant difference (*P* = 0.09) in CPR as well as LBR and miscarriage rate [25, 26]. In addition, various research was conducted on cases with RIF and normal uterine cavity before imparking in ICSI cycle and revealed no significant differences in improving the CPR between group with ES and groups with no treatment intervention [4, 13, 27, 28]. Moreover, variety of studies conducted on women who plane for frozen-thawed embryo transfer and applying ES to improve the pregnancy outcome which giving a result with no significant differences study and control group [29, 30, 31].

Limitations:

The current study has some limitations that because it's retrospective in nature missed other factors interfering with the embryo's implantation as well as limit the number of cases involved, for that reason, could not generalize the result. It is recommended that, large Randomized Control Trials to examine the role ES among subgroups of patients to prove the improvement in implantation rate and LBR as the question is performing ES will have to achieve a positive statistically significant result.

Conclusion:

The study's findings were in consistent with some previous research which proves that the endometrial scratching has a positive role to improve the implantation among infertile couples. However due to its limitations and the conflict with the results from other studies, it is recommended a multicenter randomized controlled clinical trial in order to identify the exact group of people as candidates who can get benefit from ES procedure and so answering the question about the possibility of performing the ES as a routine procedure for special group of infertile couples.

Abbreviation

Endometrial Scratching (ES), Clinical Pregnancy Rate (CPR), Live Birth Rate (LBR), Intra-Cytoplasmic Semen Injection (ICSI), Controlled Ovarian Stimulation (COH), Recurrent Implantation Failure (RIF), Human Chorionic Gonadotrophin (HCG), Follicular Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), Antra Follicular Count (AFC), Thyroid Stimulating Hormone (TSH). In-vitro fertilization (IVF), Intra Uterine Insemination (IUI)

Ethical Approval:

The approval of the study was obtained from the Research Ethics Committee at Scientific Research and Documentation Department, Libyan National Fertility Center - Misurata, Libya (PR 2021-11), and parental written consent has been collected and preserved by the author(s)

Competing Interests:

Authors have declared that no competing interests exist.

Authors' contributions:

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

References:

- [1] Barash A, Dekel N, Fieldust S, Segal I, Schechtman E, Granot I. Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization. *Fertility and sterility*. 2003 Jun 1;79(6):1317-22.
- [2] Dix E, Check JH. Successful pregnancies following embryo transfer despite very thin late proliferative endometrium. *Clinical and experimental obstetrics & gynecology*. 2010 Jan 1;37(1):15-6.
- [3] Kanazawa E, Nakashima A, Yonemoto K, Otsuka M, Yoshioka N, Kuramoto T, Mitao H, Imaishi H, Komai K, Ushijima K. Injury to the endometrium prior to the frozen-thawed embryo transfer cycle improves pregnancy rates in patients with repeated implantation failure. *Journal of Obstetrics and Gynaecology Research*. 2017 Jan;43(1):128-34.
- [4] Van Hoogenhuijze NE, Kasius JC, Broekmans FJ, Bosteels J, Torrance HL. Endometrial scratching prior to IVF; does it help and for whom? A systematic review and meta-analysis. *Human reproduction open*. 2019; 2019(1): hoy 025.
- [5] De Geyter C, Calhaz-Jorge C, Kupka MS, Wyns C, Mocanu E, Motrenko T, Scaravelli G, Smeenk J, Vidakovic S, Goossens V. ART in Europe, 2014: results generated from European registries by ESHRE: The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). *Human reproduction*. 2018 Sep 1;33(9):1586-601.
- [6] Lensen S, Osavyluk D, Armstrong S, Napier E, Sadler L, Hennes A, Stadelmann C, Hamoda H, Khalaf Y, Webber L, Bhide P. Endometrial scratching by pipelle biopsy in IVF (the PIP study): a pragmatic randomised controlled trial. *Hum Reprod*. 2018 Jul 1; 33(Suppl_1):i62.
- [7] Lensen S, Sadler L, Farquhar C. Endometrial scratching for subfertility:

- everyone's doing it. Human reproduction. 2016 Jun 1;31(6):1241-4.
- [8] Spencer EA, Mahtani KR, Goldacre B, Heneghan C. Claims for fertility interventions: a systematic assessment of statements on UK fertility centre websites. *BMJ open*. 2016 Nov 1;6(11):e013940.
- [9] Pye C, Chatters R, Cohen J, Brian K, Cheong YC, Laird S, Mohiyiddeen L, Skull J, Walters S, Young T, Metwally M. Induced endometrial trauma (endometrial scratch) in the mid-luteal menstrual cycle phase preceding first cycle IVF/ICSI versus usual IVF/ICSI therapy: study protocol for a randomised controlled trial. *BMJ open*. 2018 May 1;8(5):e020755.
- [10] Van Hoogenhuijze NE, Torrance HL, Mol F, Laven JS, Scheenjes E, Traas MA, Janssen C, Cohlen B, Teklenburg G, de Bruin JP, van Oppenraaij R. Endometrial scratching in women with implantation failure after a first IVF/ICSI cycle; does it lead to a higher live birth rate? The SCRaTCH study: a randomized controlled trial (NTR 5342). *BMC women's health*. 2017 Dec;17(1):1-7.
- [11] Lensen S, Martins W, Nastri C, Sadler L, Farquhar C. Pipelle for Pregnancy (PIP): study protocols for three randomised controlled trials. *Trials*. 2016 Dec;17(1):1-4.
- [12] Mahnaz A., Tehraninejad ES, Haghiri M, Masomi M, Sadatmahalleh SJ, Arabipoor A. The effect of endometrial scratch injury on pregnancy outcome in women with previous intrauterine insemination failure: A randomized clinical trial. *Journal of Obstetrics and Gynaecology Research*. 2017 Sep;43(9):1421-7.
- [13] Panagiotopoulou N, Karavolos S, Choudhary M. Endometrial injury prior to assisted reproductive techniques for recurrent implantation failure: a systematic literature review. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2015 Oct 1;193:27-33.
- [14] Santamaria X, Katzorke N, Simón C. Endometrial 'scratching': what the data show. *Current Opinion in Obstetrics and Gynecology*. 2016 Aug 1;28(4):242-9.
- [15] Nastri CO, Lensen SF, Gibreel A, Raine-Fenning N, Ferriani RA, Bhattacharya S, Martins WP. Endometrial injury in women undergoing assisted reproductive techniques. *Cochrane database of systematic reviews*. 2015(3).
- [16] Venetis, Christos A. "Endometrial injury before IVF: light at the end of the tunnel or false hope?" (2021): 1-2.
- [17] Ahmad Mahran MI, Bahaa H. The effect of endometrial injury on first cycle IVF/ICSI outcome: A randomized controlled trial. *International Journal of Reproductive BioMedicine*. 2016 Mar;14(3):193.
- [18] Kumbak B, Sahin L, Ozkan S, Atilgan R. Impact of luteal phase hysteroscopy and concurrent endometrial biopsy on subsequent IVF cycle outcome. *Archives of gynecology and obstetrics*. 2014 Aug;290(2):369-74.
- [19] Siristatidis C, Vrachnis N, Vogiatzi P, Chrelias C, Retamar AQ, Bettocchi S, Glujovsky D. Potential pathophysiological mechanisms of the beneficial role of endometrial injury in in vitro fertilization outcome. *Reproductive Sciences*. 2014 Aug;21(8):955-65.
- [20] Maged AM, Rashwan H, AbdelAziz S, Ramadan W, Mostafa WA, Metwally AA, Katta M. Randomized controlled trial of the effect of endometrial injury on implantation and clinical pregnancy rates during the first ICSI cycle. *International Journal of Gynecology & Obstetrics*. 2018 Feb;140(2):211-6.
- [21] Gnainsky Y, Granot I, Aldo P, Barash A, Or Y, Mor G, Dekel N. Biopsy-induced inflammatory conditions improve endometrial receptivity: the mechanism of action. *Reproduction*. 2015 Jan 1; 149(1):75-85.
- [22] Liang Y, Han J, Jia C, Ma Y, Lan Y, Li Y, Wang S. Effect of endometrial injury on secretion of endometrial cytokines and IVF outcomes in women with unexplained subfertility. *Mediators of inflammation*. 2015 Oct 26; 2015.
- [23] Singh N, Toshyan V, Kumar S, Vanamail P, Madhu M. Does endometrial injury enhances implantation in recurrent in-vitro fertilization failures? A prospective randomized control study from tertiary care center. *Journal of human reproductive sciences*. 2015 Oct;8(4):218.
- [24] Milan Reljič1, Knez J, Kovač V, Kovačić B. Endometrial injury, the quality of embryos, and blastocyst transfer are the most

important prognostic factors for in vitro fertilization success after previous repeated unsuccessful attempts. *Journal of assisted reproduction and genetics*. 2017 Jun;34(6):775-9.

- [25] Ghuman NK, Raikar S, Singh P, Gothwal M, Yadav G. Improving reproductive outcomes of intrauterine insemination: Does endometrial scratch injury help? A randomised controlled trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2020 Oct 1;253:225-31.
- [26] Sine Berntsena,b, Hare KJ, Løssl K, Bogstad J, Palmø J, Prætorius L, Zedeler A, Pinborg A. Endometrial scratch injury with office hysteroscopy before IVF/ICSI: A randomised controlled trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2020 Sep 1;252:112-7.
- [27] Ashrafi M, Tehraninejad ES, Haghiri M, Masomi M, Sadatmahalleh SJ, Arabipoor A. The effect of endometrial scratch injury on pregnancy outcome in women with previous intrauterine insemination failure: A randomized clinical trial. *Journal of Obstetrics and Gynaecology Research*. 2017 Sep;43(9):1421-7.
- [28] FIRAT CUYLAN Z, DEMİR B, DİLBAZ B, DİLBAZ S. Is There any Impact of Local Endometrial Injury on Implantation and Clinical Pregnancy Rates in the First in Vitro Fertilization Cycles. *Journal of Clinical Obstetrics & Gynecology*. 2019;29(4):129-35.
- [29] Gricius R, Balciuniene G, Jakubauskiene L, Ramasauskaite D. The Significance of Endometrial Scratching for Clinical Pregnancy Rate in Long Agonist and Antagonist Protocols. *Medicina*. 2019 Sep;55(9):527.
- [30] Aflatoonian A, Bagheri RB, Hosseinisadat R. The effect of endometrial injury on pregnancy rate in frozen-thawed embryo transfer: A randomized control trial. *International Journal of Reproductive BioMedicine*. 2016 Jul;14(7):453.
- [31] Matsumoto Y, Kokeyuchi S, Shiotani M. Effects of endometrial injury on frozen-thawed blastocyst transfer in hormone replacement cycles. *Reproductive medicine and biology*. 2017 Apr;16(2):196-9.