Pregnancy after endometrial scratching in infertile couples undergoing ovulation induction and intrauterine insemination cycles—a randomized controlled trial

Tuhina Goel¹ · Reeta Mahey¹ · Neerja Bhatla¹ · Mani Kalaivani² · Sangeeta Pant¹ · Alka Kriplani¹

Received: 22 January 2017 / Accepted: 9 May 2017 / Published online: 27 May 2017
© Springer Science+Business Media New York 2017

Abstract

Purpose To study the effect of endometrial scratching in infertile couples undergoing ovulation induction and intrauterine insemination (IUI) cycles.

Methods A prospective randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, AIIMS, New Delhi, India. One hundred forty-four women with primary/secondary infertility were recruited. Couples were either unexplained or male factor infertility. Subjects were randomized into intervention (scratching) and control group. All patients received ovulation induction with clomiphene citrate (day 2–6) 50 mg/day +75 IU HMG on days 6 and 7. In addition, endometrial scratching was done on day 8 of ovulation induction cycle in intervention group. All couples were planned for three cycles of ovulation induction and IUI over 6 months. After each failed cycle, couple was advised to try for natural conception for one cycle. Those who conceived were excluded from further analysis. Primary outcome was clinical pregnancy rate. Secondary outcome measures included conception rate, ongoing pregnancy, abortion and ectopic rate.

Results Baseline characteristics were comparable in both groups. Clinical pregnancy rate was significantly higher in intervention group (31.9%; 23/72) as compared to control group (16.7%; 12/72) (p value 0.030). On per cycle analysis, first IUI cycle had significantly high pregnancy rate (18.1%; 13/72) as compared to control group (5.6%; 4/72). Three

patients in intervention group and one in control group conceived in wash out cycle. Ongoing pregnancy rate was significantly higher in scratching group (30.0%; 21/70) as compared to control group (15.7%; 11/70) (p value 0.044).

Conclusions Endometrial scratching can be used as a low cost-effective tool to improve clinical pregnancy and ongoing pregnancy rate in IUI cycles. Further large number studies are required to document its role in improving live birth rate.

Trial registration number CTRI/2015/12/006419

Keywords Infertility · Implantation · Endometrial receptivity · Endometrial scratching

Introduction

Implantation is the rate-limiting step in all infertility treatments. It is considered to be a complex and multifactorial process involving several growth factors and cytokines, which regulate the interaction between the embryo and endometrium. About 75% embryos are lost at the time of implantation leading to implantation failure, and the couple presents as unexplained infertility [1]. Intrauterine insemination (IUI) with the partner's semen is the first-line treatment for unexplained infertility, mild male factor infertility and minimal or mild endometriosis. The success of IUI improves when combined with controlled ovarian stimulation (COS) with ovulation induction agents and/or gonadotropins, especially in unexplained infertility [2].

The process of implantation involves two main components: a healthy embryo that should have the potential to implant and a receptive endometrium that enables implantation. The “cross-talk” between the embryo and the endometrium finally leads to apposition, attachment and invasion of embryo which is mandatory for successful implantation and subsequently normal

✉ Reeta Mahey
reetamahey52@gmail.com

¹ Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi 110049, India

² Department of Statistics, All India Institute of Medical Sciences, New Delhi 110049, India

placentation. Any abnormality of the embryo, endometrium or the immune system will result in implantation failure [3].

Mechanical manipulation of the endometrium has been proposed to improve receptivity by modulating gene expression of factors needed for implantation like laminin alpha 4, integrin alpha 6, matrix metalloproteinase 1 and glycodefin A [4]. The mechanism proposed for improving implantation is perhaps endometrial regeneration, which could slow down the disproportionate endometrial development often associated with ovarian stimulation cycles thereby restoring embryonic-endometrial synchrony. Another mechanism is due to the increased production of growth factors and proinflammatory cytokines locally [5].

Endometrial injury is a cost-effective, cheap and well-tolerated procedure that can be used in patients undergoing IUI/IVF to increase the probability of pregnancy and live birth rate. Its role in improving implantation was first studied by Barash et al. in a prospective study, and the authors concluded that women allocated to endometrial biopsy in the preceding cycle were twice more likely to get pregnant as compared to controls [6].

Following this, several studies have been done to evaluate the role of endometrial injury in IVF. The data on its role in IUI cycles is sparse. Also, amongst all the studies involving endometrial injury in IVF/IUI cycles, there is a wide diversity about time of injury, method of scratching and number of scratches required.

The present study was done to evaluate the role of endometrial scratching in infertile couples undergoing ovulation induction and IUI cycles in terms of clinical pregnancy rate.

Materials and methods

This was a prospective open-labelled randomized controlled clinical trial (RCT) conducted in the outpatient Department of Obstetrics and Gynaecology, AIIMS, New Delhi (July 2014 till July 2016). Ethical clearance was obtained from the Institute's Ethics Committee (Institute Review Board). After an informed written consent from infertile women willing to participate in the study, a detailed workup was done that included age, duration of marriage, duration of infertility, menstrual and obstetric history, past and personal history and presence of other co-morbid illness. Detailed physical examination including height, weight, BMI, and pelvic examination was done. Investigations included a baseline day 2–3 transvaginal ultrasound (TVS) and hormone profile (FSH, LH, TSH, Prolactin). Tubal patency was confirmed either by hysterosalpingogram (HSG) or laparoscopy.

Women with primary or secondary infertility due to unexplained or mild male factor infertility were included in the study. The age group of these women was 21–35 years, BMI 18.5–29.9 kg/m², normal hormone profile (FSH <10 mIU/ml on day 2–3), euthyroid state, bilateral free spill on HSG or laparoscopy, and no adnexal mass on TVS (GE Voluson S6 5–9 MHz,

Wauwatosa, USA). Patients with severe male factor infertility, stage III or IV endometriosis, tubal factor infertility, baseline FSH >10 mIU/mL, abnormal thyroid /prolactin levels, fibroid uterus and systemic diseases were excluded from the study.

Both intervention group and control group received ovulation induction with clomiphene citrate (day 2–6) 50 mg/day and 75 IU human menopausal gonadotrophin (HMG) on days 6 and 7. After ovulation induction, follicle monitoring was started from day 8 of the cycle. Women recruited in the intervention group underwent endometrial scratching on D8 using Karman's cannula no. 4 as an OPD procedure. Patient was placed in lithotomy position and under strict asepsis; Karman's cannula no. 4 was introduced into the uterine cavity with its bevelled edge facing posteriorly. A single scratch was made on the posterior uterine wall.

Patients were then followed up with serial transvaginal scans till a mature follicle (≥ 18 mm) was reached. The dose and number of HMG injections were administered depending upon the size of the follicle. Injection HCG 5000 IU was given intramuscular when 1–3 follicles of diameter ≥ 18 mm were reached. IUI was done 36–38 h following the hCG trigger. Urine pregnancy test was done 15 days after IUI. Luteal phase support was given with vaginal micronized progesterone 200 mg BD for 15 days, and periconceptional folic acid was continued.

Patients with positive pregnancy test were then followed till 20 weeks POG. Those with negative pregnancy test were allowed to try for spontaneous conception for one cycle and then received treatment according to the intervention or control group that they had been randomized into for a maximum of three cycles over a period of 6 months. Patients in the intervention group underwent endometrial scratching on day 8 of each stimulation cycle if they did not conceive. Following each stimulation cycle, the couple was advised to try naturally for one cycle (wash out cycle) before proceeding for the next OVI+ IUI cycle. After every successive cycle, patients who conceived were excluded from the subsequent analysis. Record was also kept of the conceptions happening in the wash out cycles and was included in the final analysis at the end of 6 months.

No drugs other than those mentioned in the protocol were given to the patient. Any adverse reaction to any drug or procedure were noted. A record of dropouts including premature terminations from the study was maintained.

Primary outcome included clinical pregnancy rate (viable intrauterine pregnancy), and secondary outcomes were measured in terms of overall conception rate, ongoing pregnancy rate (pregnancy beyond 20 weeks POG), abortion and ectopic pregnancy.

Statistical analysis

A total of 284 infertile patients with primary or secondary infertility were screened and only 144 out of 284 were eligible to participate in the study. These 144 were either unexplained

or mild male factor infertility patients studied over a period 2 years (July 2014 till July 2016).

Statistical analysis was carried out using Stata 11.0 (College station, Texas, USA). Data were presented as number (%) or mean $\pm$ SD/median (min-max) as appropriate. Baseline categorical and continuous variables were analyzed using chi-square test and *t* test for independent samples/Wilcoxon rank-sum test, respectively. The primary outcome clinical pregnancy rate was analyzed by both intention-to-treat and per-protocol analysis whereas secondary outcomes were analyzed by only per-protocol analysis. The difference in clinical pregnancy rate, conception rate, ongoing pregnancy rate, rate of abortion and ectopic pregnancy were compared between the groups using *Z* test or Fisher's exact test as appropriate. The relative risk (95% confidence interval) was also calculated and

reported. The *p* value less than 0.05 was considered as statistically significant.

Results

A total of 284 patients presenting with primary or secondary infertility (unexplained infertility and mild male factor) were screened and assessed for eligibility criteria. Of these, 100 did not meet the inclusion criteria, 28 declined to participate and 12 were excluded due to other reasons. A total of 144 patients were recruited in the study and were randomized into intervention group (*n* = 72) and control group (*n* = 72) (Fig. 1).

Fig. 1 Consort diagramme

The participants in the two groups were comparable with respect to age, height, weight, body mass index and other baseline parameters (Table 1).

Cycle characteristics

There was no difference in the mean follicle size, day of trigger and endometrial thickness (millimetre) measured on the day of trigger and median dose of HMG requirement between the intervention and control groups (Table 2).

Outcomes

Primary outcome

Clinical pregnancy rate (CPR)

The overall clinical pregnancy rate in the intervention group was 23/72 (31.9%) and in the control group was 12/72 (16.7%), and the difference was statistically significant ($p = 0.033$) (Table 3). A woman who received the intervention (endometrial scratching) had 1.92 times (95% CI 1.03, 3.55) higher chance of becoming pregnant than a woman in the control group (Fig. 2). On per cycle analysis, clinical pregnancy rate was significantly higher in the first IUI cycle in the intervention group (13/72; 18.1%) as compared to the control group (4/72; 5.6%) ($p = 0.020$). Three patients in the

Table 1 Baseline characteristics in two groups

Characteristic	Intervention group ($n = 72$)	Control group ($n = 72$)	p value
Age (years)	28.1 ± 3.4	28.1 ± 3.0	1.00
Height (cm)	158.5 ± 3.9	158.8 ± 4.3	0.763
Weight (kg)	60.9 ± 5.1	60.0 ± 5.5	0.322
BMI (kg/m^2)	24.2 ± 2.1	23.8 ± 1.8	0.205
Type of infertility			
Primary	27 (37.5%)	24 (33.3%)	0.728
Secondary	45 (62.5%)	48 (66.6%)	
Duration of infertility (years)	5.1 ± 2.9	4.9 ± 2.4	0.596
Baseline hormone profile			
FSH(mIU/ml)	6.68 ± 1.3	6.79 ± 1.9	0.605
LH (mIU/ml)	4.56 ± 1.2	4.64 ± 1.2	0.679
TSH(mIU/ml)	2.72 ± 0.8	2.73 ± 0.8	0.965
PRL(mIU/ml)	13.56 ± 4.3	13.52 ± 4.8	0.952
Husband semen parameters			
Total sperm count (million/ml)	78.4 ± 25.4	72.9 ± 18.6	0.135
Motility (%)	70.3 ± 25.4	71.3 ± 22.7	0.798
Morphology (%)	50.1 ± 22.3	56.5 ± 24.3	0.103

Data presented as mean $\pm$ SD and number (%)

Table 2 Cycle characteristics of two groups

Cycle	Intervention group ($n = 72$)	Control group ($n = 72$)	P value
Mean day of trigger			
Cycle 1	14.8 ± 2.1	14.6 ± 2.2	0.696
Cycle 2	14.1 ± 2.3	14.1 ± 2.2	0.928
Cycle 3	13.8 ± 2.4	14.1 ± 2.3	0.525
Mean follicle size(millimetre) on day of trigger			
Cycle 1	19.5 ± 0.8	19.5 ± 1.0	0.851
Cycle 2	19.6 ± 0.7	19.5 ± 0.7	0.694
Cycle 3	19.5 ± 0.8	19.6 ± 0.8	0.443
Mean endometrial thickness (millimetre) on day of trigger			
Cycle 1	8.5 ± 0.9	8.4 ± 0.9	0.438
Cycle 2	8.6 ± 0.9	8.7 ± 0.9	0.549
Cycle 3	8.8 ± 0.9	8.6 ± 0.7	0.273
Median HMG requirement (no. of 75 IU injections)			
Cycle 1	4(2–8)	2(2–8)	0.078
Cycle 2	2(2–6)	2(2–8)	0.852
Cycle 3	2(2–8)	2(2–6)	0.229

Data presented as mean $\pm$ SD and median (minimum-maximum)

intervention group and one patient in the control group conceived in wash out cycles.

II. Secondary outcome

Overall conception rate (total number of patients with positive urine pregnancy test) and ongoing pregnancy rate were significantly higher in intervention group as compared to control group (Table 4). Abortion and ectopic pregnancies were comparable in both groups.

Discussion

The present study was conducted to evaluate the role of endometrial scratching in infertile couples undergoing ovulation induction and IUI cycles. Our results showed significantly higher clinical pregnancy rate and ongoing pregnancy rate in patients undergoing endometrial scratching in mid proliferative phase during the stimulation cycle.

Possible explanation for the effect of scratching was suggested by Gnainsky et al. [7]. The authors observed that endometrial biopsy induced an inflammatory response that perhaps facilitates the preparation of the endometrium for implantation by increasing interleukin-15 (IL-15), tumour necrosis factor (TNF- α) and macrophage inflammatory protein 1 B (MIP-1B) expression. Several other studies have been published on the role of scratching in ART/IUI cycles. On reviewing the literature, there is no exact standardization on the timing of endometrial scratching and instrument used for

Table 3 Primary outcome

Clinical pregnancy rate	Intervention (%)	Control (%)	<i>p</i> value	Relative risk (95% CI)
Intention to treat analysis				
Cycle 1	13/72 (18.1)	4/72 (5.6)	0.020*	3.25 (1.11, 9.49)
Cycle 2	5/54 (9.3)	3/68 (4.4)	0.464	2.10 (0.52, 8.39)
Cycle 3	2/46 (4.4)	4/60 (6.7)	0.695	0.65 (0.12, 3.41)
Overall	23 ^a /72 (31.9)	12 ^a /72 (16.7)	0.033*	1.92 (1.03, 3.55)
Per-protocol analysis				
Cycle 1	13/72 (18.1)	4/72 (5.6)	0.020*	3.25 (1.11, 9.49)
Cycle 2	5/53 (9.4)	3/66 (4.6)	0.464	2.08 (0.52, 8.29)
Cycle 3	2/45 (4.4)	4/60 (6.7)	0.698	0.67 (0.13, 3.48)
Overall	23 ^a /70 (32.9)	12 ^a /70 (17.1)	0.032*	1.92 (1.04, 3.54)

**p* value <0.05, statistically significant^a Three patients in intervention group and 1 in control group conceived in wash out cycles which were included in final analysis

causing endometrial injury. Table 5 shows the time and the instruments used for endometrial scratching in various studies in ART cycles.

The first study on the role of endometrial scratching in IUI cycles was conducted by Abdelhamid et al. The authors compared the pregnancy rate after endometrial injury in the cycle preceding IUI (group 1) versus endometrial injury in the stimulated cycle (group 2) versus patients undergoing IUI without endometrial scratching (group 3). Their study concluded that performing endometrial injury significantly increases pregnancy rates whether it is done in the proliferative phase of the IUI cycle, or in the cycle preceding IUI, than pregnancy rates with IUI alone (36 vs. 38 vs. 18%, respectively) [17]. Additional advantages of performing endometrial scratching in the same cycle include convenience to the patient and practical advantage of recent inflammatory response that may help in better implantation.

Wadhwa et al. studied the effect of endometrial biopsy (EB) on IUI outcome in controlled ovarian stimulation (COS) cycles. The results showed a significantly higher clinical pregnancy rates (CPR) in the group that underwent endometrial scratching either in the preceding cycle or in the same stimulation cycle. The difference in CPR was maximum after first cycle of ovulation induction and IUI [21].

The results of the present study are comparable with studies done by Abdelhamid et al. and Wadhwa et al. Scratching group had significantly higher clinical pregnancy and ongoing pregnancy rate in our study. We further observed that the first stimulation cycle had significantly high pregnancy rate in the intervention group as compared to the control group. This may be explained by failure to implant due to poor endometrial receptivity as the sole cause of infertility in these patients, which probably improved by endometrial scratching.

Fig. 2 Forest plot showing the primary and secondary outcomes in intervention and control group

Table 4 Secondary outcomes

S. no.	Secondary outcomes	Intervention (%)	Control (%)	<i>p</i> value	Relative risk (95% CI)
A.	Overall conception rate				
1.	Cycle 1	16/72 (22.2)	4/72 (5.6)	0.007	4.0 (1.41, 11.4)
2.	Cycle 2	6/53 (11.3)	5/66 (7.6)	0.433	1.49 (0.48, 4.63)
3.	Cycle 3	2/45 (4.4)	4/60 (6.7)	0.698	0.67 (0.13, 3.48)
4.	Overall	27/70 ^a (38.6)	14/70 ^a (20.0)	0.016*	1.93 (1.11, 3.36)
B.	Ongoing preg. rate	21/70 (30.0)	11/70 (15.7)	0.044	1.91 (0.99, 3.66)
C.	Abortion	2/27 (7.4)	1/14 (7.1)	1.000	
D.	Ectopic pregnancy	4/27 (14.8)	2/14 (14.3)	1.000	

**p* value <0.05 significant^a Includes wash out cycles pregnancies also. (Analysis done according to per protocol analysis)

In a similar study by Soliman B et al., patients with either unexplained infertility or mild male factor infertility were recruited to study the effect of endometrial scratching on pregnancy rate after failed previous IUI. Intervention group underwent USG-guided endometrial scratching in the mid proliferative phase of the IUI cycle. They reported significantly higher biochemical, clinical and ongoing pregnancy rate in the scratching group and concluded that endometrial scratching can be used in patients with previous failed IUI cycles before referring them for ART [18].

In another study by Maged et al., 154 women with unexplained infertility were recruited for IUI and were

divided into two groups: study group underwent endometrial scratch injury (ESI) before IUI and control group underwent IUI only. The results were in favour of endometrial injury in terms of improved clinical pregnancy rate [22].

Parsanezhad et al. studied the role of endometrial injury in 217 women with unexplained infertility. Local endometrial injury was induced by pipelle endometrial sampling after COS, which was performed during the pre-ovulatory days then followed by regularly timed intercourse. They concluded that local endometrial injury increased pregnancy rate compared to the control group (17.5 vs. 6.7%, *p* = 0.027) [23].

Table 5 Endometrial scratching devices in various studies

S. no.	Study	Time of intervention	Method of intervention
IVF cycles			
1.	Barash et al.[6]	8, 12, 21, 26 (4 times) preceding cycle	Pipelle
2.	Raziel et al. [8]	D21 and D26; 2 times in preceding cycle	Pipelle
3.	Karimzadeh et al. [9]	Luteal phase of preceding cycle (21–26)	Pipelle
4.	Tiboni et al. [10]	Day 21 of preceding Cycle	NA
5.	Zepnep et al. [11]	Luteal phase; 2 times with 1-week interval	Pipelle
6.	Zhou et al. [12]	Day 10 preceding Cycle	Endometrial biopsy catheter
7.	Li et al. [13]	Once 2–3 weeks prior to ET, same cycle	Endometrial biopsy catheter
8.	Bonavita et al. [14]	Between D5 and D26 of preceding cycle	Pipelle
9.	Guven et al. [15]	D3 of the menstrual cycle following downregulation	Endometrial biopsy catheter
10.	Nastri et al. [16]	7–14 before starting COS	Pipelle
IUI cycles			
11 a	Abdelhamid et al. (Group 2)[17]	D 8–9 in the preceding cycle	Tao Brush
11. b	(Group 3)	D8–9 in the same cycle	Tao Brush
12.	Soliman B et al. [18]	Day 7 of IUI cycle	embryo mucus aspiration catheter
13	Zarei et al. [19]	D6–8 of the previous cycle	Novak biopsy catheter
14.	El-Khayat W et al.[20]	Follicular phase at D4–7 in the preceding cycle	With office hysteroscopy using grasping forceps with teeth
15.a.	Wadhwa L et al. (group A) [21]	Luteal phase (D19–24) of the preceding cycle	Endocell
15.b.	(Group B)	Follicular phase (D2–6) of the same cycle	Endocell
16.	Present study	Follicular phase (D8) of the same cycle	Karman's cannula no. 4

There are some studies which have shown no benefit of endometrial injury in improving implantation. In a study by Zarei et al., 144 women with either mild male factor or unexplained infertility were randomly divided into two groups: study group underwent endometrial biopsy on 6–8 days in the cycle preceding IUI and control group received no biopsy. They concluded that performing endometrial injury in the preceding cycle is not associated with increase in pregnancy rate or a decrease in abortion rate [19]. The possible explanation may be longer time between scratching and IUI leading to limited benefit of endometrial injury. In the remaining studies, scratching has been done in either the luteal phase of previous cycle or proliferative phase of the IUI cycle. Further data is required to explain this disparity.

El-Khayat et al. conducted a randomized controlled trial in 332 patients, which were divided into two groups. Intervention group ($n = 166$) underwent office hysteroscopy with endometrial injury using grasping forceps, while the control group ($n = 166$) subjects underwent office hysteroscopy alone without endometrial injury in the cycle preceding IUI. Their study did not find any difference in clinical pregnancy rate and live birth rate amongst the study and control group [20]. But hysteroscopy itself is a type of mechanical trauma to the endometrium so whether the results of this study can be generalized or not is the question. Further data is required to answer this question.

Till date, the evidence is still not clear regarding the benefits of endometrial scratching in IUI and ART cycles because the sample size is less and quality of the studies are poor. The low quality of the available evidence questions the presence of any real beneficial effect, and the applicability of the intervention in different populations remains unclear. To answer these questions, multi-center, randomized controlled trials are ongoing. The required sample size for the PIP studies has been estimated at 840 (PIP-IVF), 350 (PIP-UE) and 280 (PIP-PCOS), and the results of these trials are awaited [24]. With dearth of available information, our study may add to literature regarding benefits of endometrial scratching in IUI cycles. However, the main limitation of the study is the small size.

Pregnancies in wash out cycles can be explained based on the effect of scratching in the preceding cycle though difference was not statistically significant. This hypothesis is supported by Barash et al. who first demonstrated that endometrial biopsy performed during a natural cycle dramatically increases the chances to conceive in the IVF treatment performed in the subsequent cycle [6]. The study by Kalma et al. demonstrated a sustained effect of endometrial biopsy on the endometrial gene expression, which continued in the subsequent cycle also [25].

Endometrial scratching can be considered as a low-cost and minimally invasive procedure to improve endometrial receptivity in IUI cycles. The advantage of

performing this procedure in the same stimulation cycle is as follows:

- (a) Patient friendly (less visits)
- (b) Practical advantage of recent inflammatory reaction
- (c) Cheap and cost effective (can be used as a tool to improve implantation before referring the couple to IVF)

Conclusion

Endometrial scratching done in mid proliferative phase of the IUI cycle is a low-cost, cheap procedure and is beneficial in improving clinical pregnancy rate and ongoing pregnancy rate. Further multicenter randomized controlled trials are required to document its role in IUI cycles and the effect on live birth rate. Also, we need to generate more evidence on the best time, method, mode of scratching and number of scratches required to improve implantation rate.

Authors' contribution RM and TG have drafted the manuscript. MK has done the statistical analysis. SP has helped in keeping the USG and data of all the patients. AK and NB have given their valuable inputs to finalize the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal studies No animals were used.

Informed consent Informed consent was taken from all the patients participating in the study.

References

1. Dekel N, Gnainsky Y, Granot I, Mor G. Inflammation and implantation. *Am J Reprod Immunol*. 2010;63:17–21.
2. Quaas A, Dokras A. Diagnosis and treatment of unexplained infertility. *Rev Obstet Gynecol*. 2008;1(2):69–76.
3. Finn CA, Martin L. Endocrine control of the timing of endometrial sensitivity to a decidual stimulus. *Biol Reprod*. 1972;7(1):82–6.
4. Mirkin S, Arslan M, Churikov D, Corica A, Diaz J, Williams S, Bocca S, Oehninger S. In search of candidate genes critically expressed in the human endometrium during the window of implantation. *Hum Reprod*. 2005;20:2104–17.
5. Zhou L, Li R, Wang R, Huang H, Zhong K. Local injury to the endometrium in controlled ovarian hyper stimulation cycles improves implantation rates. *Fertil Steril*. 2008;89:1166–76.
6. 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. *Fertil Steril*. 2003;79:1317–22.
7. Gnainsky Y, Granot I, Aldo PB, Barash A, Or Y, Schechtman E, et al. Local injury of the endometrium induces an inflammatory

- response that promotes successful implantation. *Fertil Steril*. 2010;94:2030–6.
8. Raziel A, Schachter M, Strassburger D, Berno O, Ron-El R, Friedler S. Favorable influence of local injury to the endometrium in intracytoplasmic sperm injection in patients with high-order implantation failure. *Fertil Steril*. 2007;87:198–201.
 9. Karimzadeh MA, Ayazi Rozbahani M, Tabibnejad N. Endometrial local injury improves the pregnancy rate among recurrent implantation failure patients undergoing in vitro fertilisation/intra cytoplasmic sperm injection: a randomised clinical trial. *Aust N Z J Obstet Gynaecol*. 2009;49:677–80.
 10. Tiboni GM, Giampietro F, Gabriele E, Di Donato V, Impicciatore GG. Impact of a single endometrial injury on assisted reproductive technology outcome: a preliminary observational study. *J Reprod Med*. 2011;56:504–6.
 11. Zepnep IO, Gorkemli H, Hasan IA. The effect of local injury to the endometrium for implantation and pregnancy rates in ICSI-ET cycles with implantation failure. *Eur J Gen Med*. 2012;9:223–9.
 12. Zhou L, Li R, Wang R, Huang HX, Zhong K. Local injury to the endometrium in controlled ovarian hyperstimulation cycles improves implantation rates. *Fertil Steril*. 2008;89:1166–76.
 13. Li R, Gui Y, Lu L, Hao G, Cai Z. Local injury to the endometrium improves the pregnancy rate in patients undergoing in vitro fertilisation. *Int Cong Ser*. 2004;1271:73–6.
 14. Bonavita M, Mattila M, Ferreira F, Maia-Filho V, Rocha A, Serafini P, et al. Local endometrial injury/healing increases embryo implantation and pregnancy rates of *in vitro* fertilization treatments. *Hum Reprod*. 2011;26:205–6.
 15. Guven S, Kart C, Unsal M, Yildirim O, Odaci E, Yulug E. Endometrial injury may increase the clinical pregnancy rate in normoresponders who underwent long agonist protocol intracytoplasmic sperm injection cycles with single embryo transfer. *Eur J Obstet Gynecol Reprod Biol*. 2014;173:58–62.
 16. Nastri CO, Ferriani RA, Raine-Fenning N, Martins WP. Endometrial scratching performed in the non-transfer cycle and outcome of assisted reproduction: a randomized controlled trial. *Ultrasound Obstet Gynecol*. 2013;42:375–82.
 17. Abdelhamid AM. The success rate of pregnancy in IUI cycles following endometrial sampling. A randomized controlled study: endometrial sampling and pregnancy rates. *Arch Gynecol Obstet*. 2013;288:673–8.
 18. Soliman B, Harira M. Local endometrial scratching under ultrasound guidance after failed intrauterine insemination and cycle outcome: a randomized controlled trial. *Middle East Fertility Society Journal*. 2017;22:60–6.
 19. Zarei A, Alborzi S, Dadras N, Azadi G. The effects of endometrial injury on intrauterine insemination outcome: a randomized clinical trial. *Iran J Reprod Med*. 2014;12:649–52.
 20. El-Khayat W, Elsadek M, Saber W. Comparing the effect of office hysteroscopy with endometrial scratch versus office hysteroscopy on intrauterine insemination outcome: a randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol*. 2015;194:96–100.
 21. Wadhwa L, Pritam A, Gupta T, Gupta S, Arora S, Chandoke R. Effect of endometrial biopsy on intrauterine insemination outcome in controlled ovarian stimulation cycle. *J Hum Reprod Sci*. 2015;8:151–8.
 22. Maged AM, Al-Inany H, Salama KM, Souidan II, Abo Ragab HM, Elnassery N. Endometrial scratch injury induces higher pregnancy rate for women with unexplained infertility undergoing IUI with ovarian stimulation: a randomized controlled trial. *Reprod Sci*. 2016;23(2):239–43.
 23. Parsanezhad ME, Dadras N, Maharlouei N, Neghabban L, Keramati P, Amini M. Pregnancy rate after endometrial injury in couples with unexplained infertility: a randomized clinical trial. *Iran J Reprod Med*. 2013;11:869–74.
 24. Lensen S, Martins W, Nastri C, Sadler L, Farquhar C. Pipelle for pregnancy (PIP): study protocols for three randomised controlled trials. *Trials*. 2016;17:216.
 25. Kalma Y, Granot I, Gnainsky Y, Or Y, Czernobilsky B, Dekel N, et al. Endometrial biopsy-induced gene modulation: first evidence for the expression of bladder-transmembranal uroplakin Ib in human endometrium. *Fertil Steril*. 2009;91:1042–9.