Does endometrial injury enhances implantation in recurrent *in-vitro* fertilization failures? A prospective randomized control study from tertiary care center

Neeta Singh, Varnit Toshyan, Sunesh Kumar, Perumal Vanamail, Malti Madhu
Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence:
Dr. Neeta Singh, Room No. 3090A, Academic Block, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: drneetasingh@yahoo.com

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ABSTRACT

BACKGROUND: Though Assisted Reproductive Techniques have overcome many fertility disorders, implantation is still considered, the rate-limiting step for the success of IVF. **AIM:** The aim of this study was to evaluate the role of endometrial scratching in improving the implantation rate in patients undergoing IVF-ET cycles. **DESIGN:** Prospective randomized control trial. **METHODS:** Sixty infertile women with a history of >1 previous failed IVF-ET cycles were randomizedinto two groups of 30 each. The patients in group 1 underwent endometrial scratching once between days 14-21 of menstrual cycle in the cycle prior to embryo transfer (ET), while in group 2scratching were not done. Implantation rate, ongoing pregnancy rate, abortion rate and live birth rate were comparedbetween both groups. **STATISTICAL ANALYSIS:** Mean values were compared between two groups using Student's't' independent test. Frequency distributions of categorical variables were compared using Chi-Square/ Fisher's exact test as appropriate. **RESULTS:** Implantation rate in group 1 was 19.4% whereas in group 2 it was 8.1%. Difference between two groups was statistically significant (P =0.028). The live birth rate was higher in the group 2 compared to group 1, however this difference was not statistically significant (3.3% vs 10%, P =0.612). No significant difference was observed between the two groups regarding the ongoing pregnancy rate (16.7% vs 0.0%; P =0.052), abortion rate (10.0% vs 3.3%, P =0.612) and miscarriage rate (6.7% vs 3.3%, P =0.99). **CONCLUSIONS:** Implantation rate increases significantly after endometrial scratching in patients with previous failed IVF-ET.

KEY WORDS: Embryo implantation, endometrial injury, *in-vitro* fertilization, repeated implantation failure

INTRODUCTION

Assisted reproductive techniques (ART's) have become the treatment of choice in indicated cases of male and female infertility. Despite advances in *in-vitro*-fertilization (IVF) technology, success rates of these procedures are relatively low. ART's have overcome many fertility disorders, but implantation is still considered the rate-limiting step for the success of IVF. Embryo implantation starts with apposition of blastocyst to the uterine endometrium, after which it gets attached to the surface epithelium of endometrial. A receptive uterus is necessary for implantation to takes place. In humans, the uterus becomes receptive during the mid-secretory phase (days 19–23) of the menstrual cycle, known as the window of implantation.[1] For implantation to occur, a genetically normal blastocyst should be able to hatch, appose, adhere, penetrate, and finally invade a well-synchronized endometrium, under the influence of estrogens and progesterone.[2] Lot of brainstorming research is happening to overcome the hurdle of implantation and lately scratching of endometrium before

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embryo transfer (ET) is being investigated as a possible technique to increase implantation rate. Endometrial injury and its effect on implantation were first studied by Barash *et al*. in 2003. They demonstrated that endometrial biopsy performed on days 8, 12, 21, and 26 of the menstrual cycle is associated with higher pregnancy rate after IVF.[3] They also hypothesized that injury to the endometrium could lead to secretion of growth factors and cytokines during the process of wound healing, which could help in implantation. There are three possible mechanism by which endometrial scratching may increase uterine receptivity and improve clinical pregnancy rate of IVF-ET. First, local injury to the endometrium induces endometrial decidualization, which increases the probability of implantation of the replaced embryo.[4] Second, endometrial healing following injury is associated with a significant increase in the secretion of cytokines, interleukins, growth factors, macrophages, and dendritic cells, all of which are beneficial to embryo implantation.[5,4] Third, endometrial maturation is abnormally advanced when controlled ovarian stimulation is performed during ART,[6,7] endometrial injury performed in the previous cycle might retard endometrial maturation leading to better synchronicity between the endometrium and the transferred embryo.[4] This randomized clinical trial aimed to evaluate the role of endometrial scratching in improving the implantation rate in patients undergoing IVF-ET cycles.

MATERIALS AND METHODS

This study was conducted at a Tertiary Care Center from April 2013 to July 2014. Ethical approval for the study was obtained from the Institute Ethics Committee before commencement of the study. Sixty patients with a history of >1 previous failed IVF attempts, who fulfilled the inclusion criteria, were recruited after obtaining written informed consent. The inclusion criteria were age <35 years, women with good ovarian reserve (antral follicle count [AFC] >8, anti-mullerian hormone [AMH] 2–6 ng/ml, follicle-stimulating hormone [FSH] level <8 m IU/ml), no uterine manipulation within last 3 months (e.g., hysteroscopy, myomectomy etc.,), and willingness to participate in the trial. The exclusion criteria were age >35 years with confounding factors (e.g. poor ovarian reserve), Grade III and IV endometriosis, history of septal resection, adhesiolysis and abnormal uterine cavity, presence of possible causes for failure of implantation such as diabetes mellitus, hypertension, and autoimmune diseases. These patients were evaluated with detailed history, examination, and investigations for infertility. The patients were divided into two groups randomly: An experimental Group 1 ($n = 30$) and a control Group 2 ($n = 30$). The random allocation of patients into two groups was carried out using random allocation software. The study was not blinded. The patients in Group 1 underwent endometrial scratching once between days 14 and 21 of menstrual cycle in the cycle prior to ET. Anterior and posterior walls of endometrium were scratched gently by a 4 mm disposable Karman's cannula inserted through the cervical os. Oral antibiotic ciprofloxacin 500 mg was given for 5 days after the procedure. To avoid the possible confounding effect of antibiotic on IVF success, subjects in the control group was also administered the same antibiotics. Each patient recruited in the trial received injection GnRH analog (Leupride; Bayers, Zydus) 1 mg daily sc starting from day 21, according to long protocol for 14 days. Ovarian stimulation was started after 14 days with injection recombinant gonadotrophin (Gonal F; Merc serono) in doses varying from 150 U to 375U daily sc and monitoring was done by follicular tracking by transvaginal (TVS) ultrasound, using Siemens EV9F4 model-07481968, with 8 MHz frequency TVS probe injection human chorionic gonadotropin (HCG) (ovitrel 250 mcg) was administered when 2–3 follicles reached >18 mm size. Endometrial thickness and blood flow were measured by TVS ultrasonography on the day of HCG administration. Endometrial blood flow was graded into zone I, II, and III depending upon vascularity in both the groups (as shown in Images 1–3). Oocyte retrieval was performed 34–36 h after the HCG injection using cook's ovum pick up needle (17 Fr) by TVS route under ultrasound guidance under general anaesthesia. Retrieved oocytes were inseminated or injected with sperms intracytoplasmic sperm injection. Fertilization check was done after 18 h of insemination and embryos were cultured in sequential medium (Vitrolife, Sweden). ET was done on day 2–5 using ET catheter (Cook, Ecotip), depending on the number, and quality of embryos. Luteal phase support in the form of injection progesterone 100 mg intramuscular daily or vaginal pessary 300 mg BD (Susten, Sun pharma) was administered to both the groups. Serum beta HCG was checked in all women on the day 16 after the transfer. Those with positive beta HCG were confirmed for clinical pregnancy by sonography 2 weeks after ET. Implantation rate was defined as number of gestational sacs as seen on TVS sonography divided by the number of embryos transferred.

Statistical analysis

Data was computerized using excel sheet. All data analysis was carried out using Statistical Package for the Social SPSS IBM version 19.0. Descriptive statistics, such as mean, median, standard deviation, and range value were calculated for continuous variables. After testing for normality assumptions, using appropriate statistics, mean value were compared between two groups using Student's *t*-independent test. Frequency distributions of categorical variables were compared using Chi-Square/Fisher's exact test as appropriate. For all statistical tests, the probability of $P < 0.05$ was considered for statistical significance.

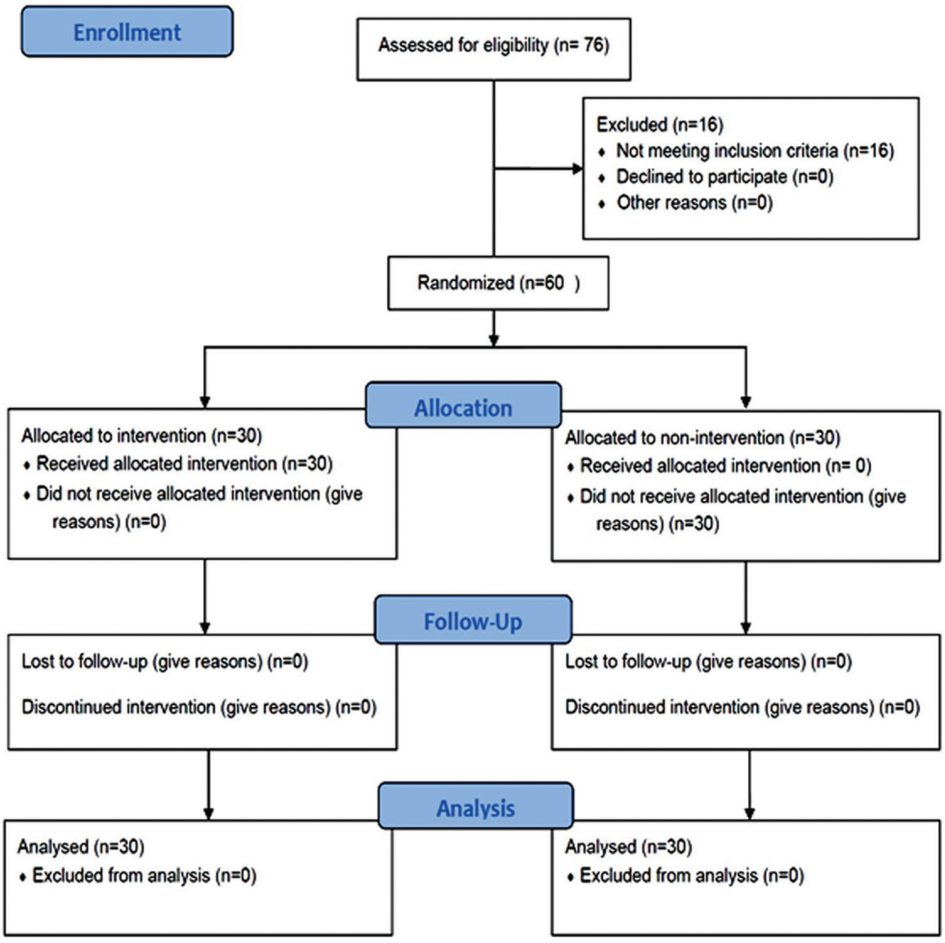

Figure 1: Consort flowchart of the trial

RESULTS

Figure 1 shows the consort flowchart of the trial. A total of 76 patients were initially recruited for the study. Of these, 16 were excluded for not meeting the inclusion criteria and refusal to participate.

The baseline characteristics of patients in two groups were comparable and are summarized in Table 1. There were no statistically significant differences between the two groups regarding the age, body mass index, basal FSH, AMH, luteinizing hormone, B/L AFC, duration hormone stimulation, number of oocytes retrieved, and number and day of ET.

As Shown in Table 2, implantation rate in Group 1 was 19.4% whereas in Group 2, it was 8.1%. Difference between two groups was statistically significant ($P = 0.028$). The live birth rate was higher in the Group 2 compared to Group 1, however this difference was not statistically significant (3.3% vs. 10%, $P = 0.612$). No significant difference was observed between the two groups regarding the ongoing pregnancy rate (16.7% vs. 0.0%; $P = 0.052$), abortion rate (10.0% vs. 3.3%, $P = 0.612$), and miscarriage rate (6.7% vs. 3.3%, $P = 0.99$).

DISCUSSION

The results of the present study suggest that implantation rate is significantly increased after local injury to the endometrium. Several strategies have been suggested to improve implantation rates in cases with recurrent implantation failure (RIF) after IVF-ET cycle. Recently, local injury to the endometrium has been postulated as a method to improve implantation rate by many investigators. Barash *et al*. in 2003[3] were first to report that IVF treatment that is preceded by endometrial biopsy doubles the chance for a take-home baby. A total of 134 patients were divided into two groups: An experimental group ($n = 45$) that included patients from whom endometrial samples were collected and a control group ($n = 89$). The implantation rate in the biopsy-treated patients was 27.7%, which is significantly higher than that in the control group (14.2%, $P = 0.00011$). Moreover, 30 of the 45 patients in the

Table 1: Summary of baseline characteristics between the study groups

Characteristics	Group 1 (*n*=30)		Group 2 (*n*=30)		*P*
	Mean	SD	Mean	SD	
Age (years)	31.73	2.5	32.10	2.2	0.547
BMI (kg/m^2)	26.17	4.2	26.10	3.9	0.924
AMH (ng/ml)	3.57	1.2	3.40	0.9	0.555
D2LH (mIU/ml)	4.87	2.6	4.90	2.2	0.958
D2FSH (mIU/ml)	5.37	1.5	6.00	1.2	0.076
B/L AFC	11.43	3.2	12.90	3.6	0.099
Days of stimulation	11.73	1.4	11.37	1.3	0.300
Oocytes retrieved	9.73	4.5	10.93	5.1	0.339
Number of embryo transferred	3.1	0.80	2.9	0.89	0.363
Day of transfer	4.07	1.2	4.33	1.2	0.384

SD= Standard deviation, AFC= Antral follicle count, AMH= Anti-mullerian hormone, LH= Luteinizing hormone, FSH= Follicle-stimulating hormone, BMI= Body mass index

Table 2: Comparison of the outcome measures in the two groups

Parameter	Group 1 (%)	Group 2 (%)	*P*
Implantation rate	19.4	8.1	0.028
Live birth	3.3	10.0	0.612
Ongoing pregnancy (>24 weeks)	16.7	0.0	0.052
Abortion	10.0	3.3	0.612
Miscarriage rate	6.7	3.3	0.99

biopsy-treated group conceived, exhibiting a doubled rate of pregnancy as compared to that of the control group (66.7% and 30.3%, respectively, P = 0.00009). Live births rate in the biopsy-treated patients was more than twofold higher than that in the controls (48.9% and 23.6%, respectively, P = 0.016). Raziel *et al*. in 2007[8] prospectively studied 120 couples with high-order implantation failure of >4 unsuccessful ET of fresh embryos. Intervention group (n = 60) underwent endometrial biopsy twice on days 21 and 26 of the preceding ovarian stimulation cycle; control group had no intervention (n = 57). Implantation rate was significantly higher for the biopsy group, whereas no statistically significant difference was observed for the ongoing pregnancy and miscarriage rates. Compared with that of the controls: The respective rates were 11% versus 4% (P = 0.02) for implantation, 30% versus 12% (P = 0.02) for pregnancy, and 2% versus 8% (P = 0.07) for ongoing pregnancies. The abortion rate was 28% for each group.

Zhou *et al*. in 2008[9] found similar results in their study. A group of 121 patients were divided into two groups: The experimental group whose endometrial samples were collected (n = 60) and the control group (n = 61). The implantation rate in the biopsy-treated patients was 33.33%, which was statistically significantly higher than that of the control group (17.78%, P < 0.05). Moreover, 29 of the 60 patients in the biopsy-treated group conceived, exhibiting a higher rate of clinical pregnancy compared with that of the control group (48.33% and 27.86%, respectively, P < 0.05). Live births rate in the biopsy-treated patients was higher than that of the controls (41.67% and 22.96%, respectively, P < 0.05). Erlik *et al*. in 2008[10] did a study to determine if a single endometrial biopsy taken during a routine diagnostic hysteroscopy improves the success rate of IVF treatments for women who failed IVF treatment at least 3 times. Their results showed a higher implantation rate in the study group compared to the control group (12.5% vs. 6.8%, P = 0.16), a higher chemical pregnancies rate of the study group (41.7% vs. 30.6%, P = 0.33), and a higher clinical pregnancies rate of the study group (36.1% vs. 19.4%, P = 0.11). The live birth rate was higher in the study group and was statistically significant (27.8 vs. 8.3%, P = 0.032).

Karimzadeh *et al*. in 2009[11] in a randomized controlled trial (RCT) evaluated the influence of endometrial biopsy on increasing implantation rate in patients with RIFs. The patients were divided into two groups randomly: An experimental group (n = 58) and a control group (n = 57). Endometrial biopsy was performed in the experimental group at the luteal phase on the days 21–26 of spontaneous menstrual cycles, when gonadotropin-releasing hormone agonist use began. Implantation rate was found to be 10.9% in the biopsy group compared to 3.38% in the controls, and the difference was statistically significant (P = 0.039). Clinical pregnancy rate was significantly higher in the women experiencing endometrial biopsy than in the control group, 27.1% and 8.9%, respectively, with a statistical value of 0.023. The patients in both the groups have been followed after ET and there was no significant difference in miscarriage rate among women in the endometrial injury group and controls (P > 0.05). Narvekar *et al*. in 2010[2] did a randomized controlled trial to determine whether endometrial injury in the nontransfer cycle could improve the probability of pregnancy in the subsequent IVF cycle in patients who had previous failed IVF outcome. One hundred patients were randomized to the two groups with 49 women in the intervention group and 51 in the control group. The live birth rate was significantly higher in the intervention group compared to control group (22.4% and 9.8% P = 0.04). The clinical pregnancy rate in the intervention group was 32.7%, while that in the control group was 13.7%, which was statistically significant (P = 0.01). The implantation rate was significantly higher in the intervention group as compared to controls (13.07% vs. 7.1%). Shohayeb and El-Khayat in 2012[12] found that the single endometrial biopsy regimen performed during hysteroscopy has statistically significant higher implantation rate, clinical pregnancy rate, and live birth rate than hysteroscopy without endometrial scraping. The study included two hundred cases with a history of previous implantation failure, divided into two groups. Group A included one hundred cases who underwent hysteroscopy with endometrial curettage of the fundus and posterior wall once in the follicular phase (D4–D7),

and Group B included one hundred cases who underwent diagnostic hysteroscopy only. There were statistically significant differences regarding the implantation rate, the clinical pregnancy rate, and live birth rate. The implantation rate in Group A was 12% while in Group B it was 7% ($P = 0.015$), the clinical pregnancy rate was 32% in Group A while it was only 18% in Group B ($P = 0.034$), and the live birth rate was 28% in Group A while it was 14% in Group B ($P = 0.024$). The abortion rate was 12.5% in Group A while it was 22% in Group B, with no statistically significant difference ($P = 0.618$). In a RCT done by Nastri C *et al*., in 2013,[13] they concluded that endometrial scratching performed once, during oral contraceptive pill pretreatment 7–14 days before starting COS, increases the chance of live birth and clinical pregnancy, but might cause considerable pain. Among the 158 women included, COS was initiated in 74 women in the endometrial scratch group and in 75 women in the control group. Endometrial scratching was associated with higher rates of live birth (41.8% vs. 22.8%, $P = 0.01$) and clinical pregnancy (49.4% vs. 29.1%, $P = 0.01$), higher pain score (6.42 ± 2.35 cm vs. 1.82 ± 1.52 cm, $P < 0.001$), endometrial vascularization index (3.71 ± 1.77 vs. 2.95 ± 1.56, $P < 0.01$), and vascularization flow index (0.97 ± 0.51 vs. 0.76 ± 0.40, $P < 0.01$). There was no significant effect of endometrial scratching on rate of miscarriage (15.4% vs. 21.7%, $P = 0.53$) or multiple pregnancy (22.5% vs. 25.0%, $P = 0.79$), or on endometrial thickness (10.12 ± 1.55 mm vs. 9.98 ± 1.62 mm, $P = 0.59$), endometrial volume (6.18 ± 1.63 cm3 vs. 6.01 ± 1.48 cm3, $P = 0.51$), or flow index (26.12 ± 2.82 vs. 25.91 ± 2.72, P = 0.65). The implantation rate was significantly higher in women submitted to endometrial scratching (35.82% vs. 21.32%) compared to control group ($P = 0.01$). In a RCT conducted in 2014, Kumbak *et al*.[14] investigated whether office hysteroscopy and concurrent endometrial biopsy performed in the luteal phase improves subsequent IVF outcome. In the study group, comprising 70 patients, office HS was performed on the 21st day of the cycle preceding ET cycle and an endometrial sample was obtained using a biopsy catheter and sent for histopathological examination at the end of HS procedure. In the control group, comprised 58 patients, GnRH agonist was initiated on the 21st day of the cycle without performing HS or endometrial biopsy. Fertilization rate was higher (82 vs. 73%; $P = 0.009$) in the study group compared to the control group. Although the number of transferred grade I embryos was similar, implantation rate (38 vs. 25%; $P = 0.04$) and the pregnancy rate per ET (67 vs. 45%; $P = 0.01$) were found to be significantly higher in the study group compared to the control group. However, no significant difference was noticed between the two groups with regard to miscarriage rate or ongoing pregnancy/live birth rate. However, Karimzade *et al*. in 2010[15] evaluated the effect of local injury to the endometrium on the day of oocyte retrieval on implantation and pregnancy rates in assisted reproductive cycles. They concluded that local injury to the endometrium on the day of oocyte retrieval disrupts the receptive endometrium and has a negative impact on implantation and IVF outcomes. Significantly lower implantation rate (7.9 vs. 22.9%, $P = 0.002$) was noted in the experimental group compared with the controls. Similarly, Safdarian *et al*. in 2011[16] also found that endometrial biopsy did not increase the chances to conceive at the following cycle of treatment. Patients were divided to control groups ($n = 50$) and experimental group ($n = 50$), who underwent endometrial biopsy. Endometrial biopsy in these patients was taken by biopsy catheter on day 21 of their previous menstrual cycle with use of contraceptive pill before the IVF-ET treatment. The rates of implantation, chemical pregnancy, and clinical pregnancy in the operation group were 4.9% 18.2%, 12.1%, and in the control group 6.7%, 19.5%, 17.1%, respectively, that were not significant differences. Baum *et al*. in 2012,[17] performed a RCT which did not find any benefit from local injury to the endometrium in women with a high number of RIFs. Thirty-six women with RIF undergoing IVF were randomly allocated into two groups: An experimental group ($n = 18$) and a control group ($n = 18$) using a table of random numbers. Endometrial biopsy was performed in the experimental group on days 9–12 and 21–24 of the spontaneous menstrual cycle proceeding the IVF treatment cycle. The implantation rate was found to be 2.08% in the biopsy group compared to 11.11% in the control group. Live births rate was 0% in the biopsy group compared to 25% in the controls. The differences were not statistically significant ($P = 0.1$ and $P = 0.1$, respectively). Clinical pregnancy rate (0 vs. 31.25%, $P < 0.05$) was significantly lower in the experimental group.

CONCLUSION

Implantation rate increases significantly after endometrial scratching in patients with previous failed IVF-ET. Endometrial scratching causes changes within the endometrium, gene expression, and the immune system, leading to enhanced endometrial receptivity and better implantation environment. Performing injury in preceding cycle is more effective as all these processes require time and are controlled by the hormones. This is a simple and inexpensive procedure with lot of benefits as compared to risks of infection and potential of future subfertility. However large, multicenter randomized studies are needed to investigate role of local endometrial injury and pregnancy outcomes, as regarding the timing of the procedure, number of scratching to be done, and to find out benefit of repeating the procedure in women, who failed to conceive after undergoing endometrial scratching once.

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Conflicts of interest

There are no conflicts of interest.

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