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Original Research Article

Effect of endometrial scratch injury on pregnancy rate after previously failed intrauterine insemination

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ABSTRACT

Background: Endometrial receptivity plays an important role in implantation and successful pregnancy. In literature, various attempts have been made to improve endometrial receptivity. Endometrial scratch injury (ESI) is one such intervention widely offered to improve endometrial receptivity in women with a history of in-vitro-fertilization (IVF) failure. In our present study, this procedure of ESI was performed in cases with previously failed intrauterine insemination (IUI) and its effect on pregnancy rate was assessed.
Methods: A prospective, randomised, controlled study was conducted at Fertility Clinic, Bhabha Atomic Research Centre Hospital, Mumbai. Total 200 women requiring IUI with previously failed one IUI were included in the study. They were randomly divided into 2 groups of 100 each. Both the groups underwent controlled ovarian stimulation with clomiphene citrate and gonadotropins followed by IUI. Study group underwent "endometrial scratching" in mid-proliferative phase of the same cycle preceding IUI. Control group underwent IUI alone. Pregnancy rates (clinical and ongoing) were compared in both the groups.
Results: Endometrial scratching group had significantly higher (<0.0002) (8.4±2.3 mm versus 7.3±1.9 mm) endometrial thickness at the time of ovulation trigger. Clinical pregnancy rate was significantly higher (p<0.0001) (42% versus 16%) in endometrial scratching group with no significant difference in ectopic pregnancy, miscarriage and multiple pregnancy rates in both the groups.
Conclusions: Due to its role in improving pregnancy rates in women with previously failed IUI, clinicians should offer ESI in mid-proliferative phase of the same cycle preceding IUI, before offering advanced IVF treatment.

Keywords: Endometrial scratching, Intrauterine insemination, Pregnancy rate

INTRODUCTION

Unexplained infertility affects up to 15-30% of infertile couples .[1] Intrauterine insemination (IUI) is considered to be the first line of treatment for sub-fertile couples due to its low cost, less psychological burden, and easy access.[1,2]

In spite of ovarian stimulation protocols and luteal phase support, pregnancy rates with IUI are still limited and quite variable, ranging from 10% to 25%.[3]

Investigators have contributed these mixed results to defects in the implantation process.[2,4]

It is assumed that up to two-thirds of implantation failures could be secondary to defects in endometrial receptivity.[5,6] Various attempts have been made to improved endometrial receptivity. "Endometrial scratching" is one such intervention widely offered to enhance endometrial receptivity in women with a history of IVF failure.[7]

This procedure is performed on OPD basis by using common biopsy devices (e.g. pipelle, curette), without analgesia.[8]

At present the procedure is offered in women undergoing IVF cycles and shows promising results, but its role in patients undergoing IUI cycles is less extensively documented.[9-11] Through present study we aimed to study the effect of endometrial scratching on pregnancy rate after previously failed one IUI.

METHODS

A prospective randomized case control study was conducted in the department of obstetrics and gynaecology (fertility clinic), Bhabha Atomic Research Centre Hospital, between December 2018 and November 2019, after obtaining permission from the institutional ethics committee.

Study population included all patients with infertility requiring IUI who were willing to participate in the study as per the formulated inclusion and exclusion criteria and with history of previous one failed IUI. Patients were divided randomly in study and control groups by computer generated table. Study population underwent endometrial scratching once between day 6 and 8 of menstrual cycle (mid-proliferative phase) followed by IUI in the same cycle whereas control group underwent only IUI. Total of 200 women studied with 100 in study group and 100 women in control group.

Women of age ≤40 years with indication for IUI with history of previous failed IUI with following criteria were included: (a) patients with unexplained infertility (documented ovulation, patent tubes and normal semen analysis), (b) normal uterine cavity as assessed by HSG, (c) minimal endometriosis (if diagnosed on hysterolaproscopy) with patent tubes, (d) mild male factor infertility (defined when there was 2 or more semen analysis with 1 or more items below the 5th centile as defined by the WHO, 2010)

Exclusion criteria for the study being: (a) unilateral/bilateral tubal blockage, (b) acute pelvic inflammatory disease and/or vaginal infection, (c) sub mucous myomas/endometrial polyps, (d) anovulation in first or second stimulated cycles.

After an informed written consent, patient details including age, duration of marriage, duration of infertility, menstrual and obstetric history, past and personal history and presence of other co-morbid illness were noted. Detailed physical examination and pelvic examination was performed. Investigations included a baseline day 2-3 transvaginal ultrasound (TVS) and hormone profile (FSH, LH, AMH). Tubal patency was confirmed either by hysterosalpingogram (HSG) or by laparoscopic chromopertubation. At the time of starting the ovarian stimulation, the patients were divided randomly by using computer generated table. Study group (scratching group) underwent ovarian stimulation, endometrial scratching, folliculometry and Intra uterine insemination (IUI) while the control (non- scratching group) was subjected to ovarian stimulation, folliculometry and IUI only. Baseline TVS was performed to exclude residual ovarian cyst on day 3 of the menstrual cycle prior to controlled ovarian stimulation. Controlled ovarian stimulation was done by combined sequential protocol of clomiphene citrate followed by gonadotrophin. Tablet clomiphene citrate (100 mg/day, oral) was administered from day 3 to day 7 of the cycle. Folliculometry was started from day 7 by TVS. In case if follicular growth was inadequate then additional injection gonadotrophin (FSH 75 IU/day, subcutaneous) was given on day 7 and then daily in variable dosage depending upon the ovarian response. Endometrial scratching was performed in study group only. It was done only once any time between day 6 and day 8 as per patient's convenience. Pipelle which is a thin (3.2 mm wide), flexible plastic cannula was used for this purpose (Figure 1). The procedure of endometrial scratching was performed in lithotomy position under all aseptic precautions. Cusco's self-retaining vaginal speculum was gently inserted to expose the cervix which was cleaned with sterile gauze. Pipelle was inserted into the uterus through the cervical canal. The lining of the posterior and anterior wall of the uterus was gently scratched with the Pipelle by back and forth movement once. No analgesic or antibiotic was required post procedure. Once the dominant follicle reached the size of 18-20 mm on TVS, ovulation was triggered by single dose of Injection human chorionic gonadotrophin (hCG) 10,000 IU i.m. In cases where 6-7 growing follicles were noted on TVS with single dominant follicle of 18-20 mm size, ovulation was triggered by injection leuprolide acetate (2 mg subcutaneous, single dose) instead of injection hCG to prevent ovarian hyper-stimulation. If 8 or more dominant follicles were noted no ovarian trigger was given and IUI was cancelled in that cycle.

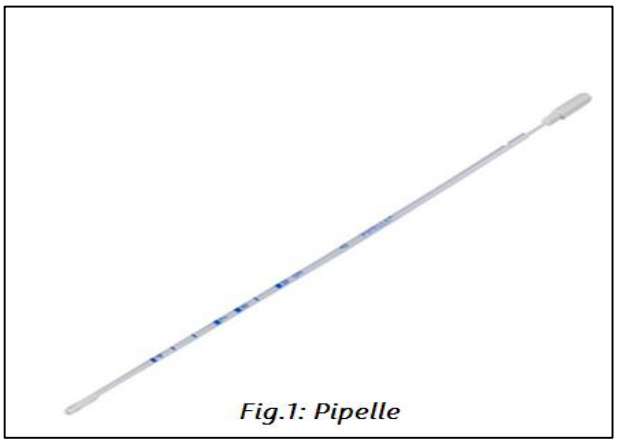

Figure 1: Pipelle.

Single IUI was performed 36 hours after ovulation trigger by using fresh processed semen obtained from the husband. Semen sample was prepared by density gradient

method. Ovulation was confirmed by abdominal ultrasonography documenting disappearance of dominant follicle or regression in size with irregular margins and presence of free fluid in pouch of Douglas. Endometrial thickness was measured on the same day.

Post IUI both the groups received luteal phase support by natural micronized progesterone 200 mg (when ovulation trigger was given by hCG) or 400 mg (when ovulation trigger was given by leuprolide acetate) pessary inserted vaginally twice daily starting from day of IUI for next 2 weeks. Urine pregnancy test was performed after 2 weeks.

IUI was cancelled in both groups for the following reasons: 1) no dominant follicle recruited, 2) ovarian hyper stimulation (8 or more dominant follicle: contraindication to ovarian trigger), 3) non rupture of dominant follicle, 4) failure of husband to provide sample on the day of IUI, 5) pre-wash semen sample of low count or sperm motility (TMSC<5 million/ml) or semen sample <0.5 ml.

Patients with positive pregnancy test were then followed till 20 weeks POG. After every successive cycle, patients who conceived were excluded from the subsequent analysis. 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, ectopic and multiple pregnancy.

All data analysis was done with the help of SPSS (Statistical Product and Service Solution) version 19, Epi InfoTM software version 7. The data collected was analyzed and interpreted according to the type of variables. The continuous variables were analyzed in terms of mean and interpreted by

Student's t test. The discontinuous variables were analyzed in terms of percentages and interpreted by χ^2 (Chi-square) test. The level of significance was fixed as 5% and the p values less than or equal to 0.05 ($p \leq 0.05$) were considered as statistically significant.

RESULTS

Total of 200 women were studied who were divided into cases and control groups randomly by using computer generated table (n=100).

Table 1: Comparison of demographic data of patients in both the groups.

Parameters	Endometrial Scratching group (n=100)	Control group (n=100)	P value
Age (year)	31.23±3.87	31.58±3.75	0.5743
Duration of infertility (year)	5.1±3.2	5.6±3.2	0.2725
FSH (IU/l)	6.2±2.5	6.5±2.6	0.4724
LH (IU/l)	4.3±2.5	4.5±2.5	0.6387
AMH (ng/ml)	4.3±3.1	4.2±3.2	0.61
Basal sperm count (million/ml)	103±58.3	97.99±55.2	0.5371
Basal sperm motility (%)	77.95±13.28	74.15±11.39	0.4729
Endometrial thickness (mm)	10±1	9.9±0.9	0.44
Total number of follicles	2.9±0.8	2.7±0.7	0.09

All the demographic data parameters were matching in both the groups with no statistically significant difference.

Table 2: Comparison of cycle outcome of patients in both the groups.

Parameters	Endometrial Scratching group (n=100)	Control group (n=100)	P value
Endometrial thickness on the day of trigger (mm)	8.4±2.3	7.3±1.9	<0.0002
Clinical pregnancy rate	42	16	0.0001
Ongoing pregnancy rate	38	12	0.000022
Miscarriage rate	2	2	1
Ectopic pregnancy	2	2	1
Multiple pregnancy	1	1	1

Clinical pregnancy rate and ongoing pregnancy rate was compared by applying Chi-square test. $p<0.05$ is considered significant in both the cases. Miscarriage, ectopic pregnancy and multiple pregnancy rates were similar in both the groups.

Demographic data of patients in both the groups were comparable with respect to age, duration of years of infertility, serum FSH, LH and AMH values, cycle characteristics as well as semen analysis parameters (Table 1).

Primary outcome included clinical pregnancy rate and secondary outcomes were measured in terms of overall conception rate, ongoing pregnancy rate (pregnancy beyond 20 weeks POG), abortion, ectopic and multiple pregnancy (Table 2).

Endometrial thickness measured on the day of ovarian trigger was 8.4±2.3 in study group compared to 7.3±1.9 mm in control group. This was significantly more in study group than in control (p<0.0002).

Clinical pregnancy rate was 42% in study group compared to 16% in control group which was significantly higher in study group (p<0.0001).

Chances of conception were 2.65 times higher in study group with significantly higher ongoing pregnancy rate (p-0.000022).

There was no significant difference in ectopic pregnancy rate, miscarriage rate and multiple pregnancy rates in both the groups.

DISCUSSION

In spite of ovarian stimulation protocols and luteal phase support, pregnancy rates with IUI are still limited and vary from 10% to 25%.[3] These mixed results are contributed to defects in the implantation process.[2,4]

Various attempts have been made to improved endometrial receptivity. "Endometrial scratching" is one such intervention widely offered to enhance endometrial receptivity in women with a history of IVF failure.[12]

Endometrial scratching, as a treatment to improve pregnancy rates was first proposed by Barash et al in 2003.[13] They coincidentally, noted a remarkable increase in pregnancy rate in sub-fertile women, who underwent diagnostic endometrial biopsies, performed in a natural cycle a month prior to ovarian stimulation for IVF treatment.

Endometrial scratching is proposed to cause delay in endometrial maturation, corrects asynchrony between endometrium and the conceptus in controlled ovarian stimulation (COS) performed during ART re-establishing the disturbed endocrine and paracrine milieu.

It promotes wound healing by inducing a significant increase in the local secretion of pro-inflammatory cytokines such as macrophage inflammatory protein-1E, tumor necrosis factor-α, osteopontin, interleukins, growth factors, macrophages, and dendritic cells which in turn promotes successful implantation.[14,15]

Cytokines, growth factors, and natural killer cells are responsible for increased angiogenesis, thereby providing adequate blood flow to the tissue and preventing embryo rejection.[16]

Thus, rationale of performing endometrial scratching is to trigger a local acute inflammation, with the release of cytokines and growth factors that could enhance the implantation process.[17,18]

Abdelhamid et al first reported the beneficial effects of endometrial injury in previous failed IUI cycles in 2013 almost a decade after the first report in IVF cycle.[13,19]

In the present study, 200 infertile patients diagnosed with unexplained infertility were randomized to 100 each in the study and control group. Study group underwent "endometrial scratching" in the cycle preceding IUI. Both the groups underwent COS with gonadotropins followed by IUI. Pregnancy rates were compared between both the groups.

Demographic data of patients in both the groups were comparable with respect to age, duration of years of infertility, serum FSH, LH and AMH values, cycle characteristics as well as semen analysis parameters.

Endometrial thickness measured on the day of ovarian trigger was 8.4±2.3 in study group compared to 7.3±1.9 mm in control group. This was significantly more in study group than in control (p<0.0002). Similar findings were seen in the study by Gupta et al, mean endometrial thickness in study and control group was 9.18 mm and 8.53 mm respectively (p=0.018).[20]

In our study, 42% of the cases and 16% of the controls had a clinical pregnancy (p<0.0001) i.e. nearly 2.6 times higher in the cases who underwent IUI with ESI.

In the study by Gupta et al, number of clinical pregnancies in the study and control group was 19 and 8 respectively (p=0.022). There were 4 biochemical pregnancies in the study group compared to nil in control group. Total number of pregnancies in the study group was nearly threefold as compared to control group (23 versus 8, p=0.003).[20]

Doubling of pregnancy rates was reported by Abdelhamid et al in both his study groups one undergoing endometrial scratching in follicular phase of same cycle and the other in the follicular phase of preceding cycle.[19]

Data from other IVF centers showed beneficiary effects of endometrial scratching when scratching was done in follicular, luteal phase of previous cycle or early follicular phase of samecycle.[8] However, endometrial injury even on the day of oocyte retrieval has been evaluated by Karimzadeh et al and they in fact reported a detrimental effect on clinical and ongoing pregnancy rates.[21]

Gnainsky et al suggested that the effect of endometrial scratching is long lived as monocytes recruited to the injured sites are long lived and reside in tissues for a long time.[22] Such beneficial effect even up to 6 months has been reported by Gibreel et al.[23]

Meta-analysis done by Amerigo Vitagliano et al compared different studies for knowing effectivity of ESI timing. The results of ESI done in follicular phase of same cycle were statistically significant compared to ESI done in

previous cycle. Also, there was statistical significance in OPR. CPR (OR 2.27; p<0.00001; data from 1,871 IUI cycles) and OPR (OR 2.04 P<.004; data from 587 IUI cycle.[24]

Various studies compared use of different instruments and concluded that the results of flexible aspiration catheter were promising compared with other instruments used for scratching.

Wadhwa et al mentioned that no patients receiving ESI treatment reported experiencing severe pain or discomfort.[25]

Similarly, Maged et al reported in the methods section that only mild cramping similar to menstrual pain may be felt during the scratch, and mild spotting may occur after withdrawal of the catheter.[26]

Hence, we used a disposable, flexible and atraumatic pipelle with a diameter of 3.2 mm. The procedure of ESI was performed between day 6 to 8 of the same cycle preceding IUI. None of our patients had pain or spotting, pelvic inflammatory disease or vaginitis after the procedure. As the pipelle used was flexible and atraumatic there was no complications of uterine perforation. These observations confirmed the safety of procedure of endometrial scratching.

There are some limitations of this study. Larger sample size in a multicentric design along with molecular biology studies including immunohistochemistry of different molecules, scanning electron microscopy are required to find out the mechanism of increased endometrial receptivity after endometrial scratch injury to further support our clinical findings.

CONCLUSION

This study demonstrated increase in pregnancy rate from 16% to 42% (2.6 times) after endometrial scratch injury and no significant difference in ectopic pregnancy rate, miscarriage rate and multiple pregnancy rates in both the groups.

Endometrial scratching is strongly recommended management option in patients with previous failed IUI cycles before opting for expensive IVF treatment.

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