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Uterine cavity coring before intra-uterine insemination in patients with unexplained infertility

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Abstract
Introduction: Infertility, a major health problem nowadays, affects around 8-12% of couples worldwide. Unexplained infertility affects up to 15-30% of infertile couples. Management options for unexplained infertility are expectant management, timed intercourse, IUI with or without controlled ovarian stimulation, ART i.e IVF/intracytoplasmic sperm injection (ICSI). Endometrial mechanical injury in order to augment the probability of implantation of embryo and pregnancy rate has been particularly noted in recent years.
Objectives: Evaluation of endometrial scratching on pregnancy rates after IUI.
Material and methods: This interventional study was carried out in SMGS Hospital, GMC Jammu over a period of 18 months from July 2018 to December 2019. A total of 100 infertile women with unexplained infertility were included in the study and were randomly divided into two groups, 50 in each. The IUI procedure was carried out in the first group after the endometrial scratch on day 2-3 of menstrual cycle, while the control group underwent only IUI without any intervention. The pregnancy rates were compared in both the groups.
Results: Among 100 patients who entered this study, 14 (14%) women got pregnant. There were 10 (10%) clinical pregnancies in the study group and 4 (4%) in the control group. Therefore 71% of the pregnant cases in this study were from the case group, showing the two-thirds of the success in treating infertile couple in this study belonged to scratching method. There was a significant difference in between both the groups.
Conclusions: The uterine cavity coring (endometrial scratching) performed on day2-3 of the menstrual cycle, preceding IUI procedure, leads to a significant increase in pregnancy rate. On the other hand, this method can be employed with lower costs in comparison to other fertilisation methods.

Keywords: Pregnancy, infertility, endometrial scratch, IUI, intervention

Introduction
Infertility, affects around 8–12% of couples worldwide, is a major health problem nowdays [1].
Various studies have shown that infertile couples without any treatment have 2% to 4% chance of pregnancy in a monthly cycle, while normal couples have 20%-25% chance of pregnancy in a monthly cycle. Thus, there is 80%-90% less chance of pregnancy in infertile couples. With increasing duration of infertility in young couples, the necessity for intervention rises [2, 3].
Mainstay treatment for these infertile couples are intrauterine insemination (IUI) or *In vitro* fertilization (IVF) [4]. IUI is often the first choice of treatment in patients with unexplained infertility. Unexplained infertility affects up to 15–30% of infertile couples. Various management options for couples with unexplained infertility are expectant management, timed intercourse, IUI with or without controlled ovarian stimulation, ART, i.e. IVF/intracytoplasmic sperm injection (ICSI) [5].
Despite an appropriate follicular growth, confirmed ovulation on transvaginal ultrasonography, satisfactory endometrial thickness and good semen preparation, pregnancy rates with IUI remain a dismal 8–17% per cycle [6-8]. Poor endometrial receptivity could be one of the reason for IUI failure.
Implantation includes apposition, adhesion and invasion phases. For successful implantation there is a complex interaction between maternal endometrium and the conceptus. Receptive endometrium is therefore necessary for successful implantation. In humans, uterus becomes receptive during mid-secretory phase of menstrual cycle (day 19–23) known as window of implantation (WOI) [9, 10]. It is considered that poor endometrial receptivity is responsible for approximately sixty percent of implantation failures [9].
Endometrial scratching (uterine cavity coring) is defined as an intentional damage caused to the

Endometrium [11]. The connection between local injury to endometrium and increased pregnancy rates in IVF cycles was first described in 2003 [12].

Endometrial scratching is a simple, practical, cost- effective procedure which can be done in an OPD (Out Patient Department) setting, if proven effective in improving clinical pregnancy rates, can be offered before more advanced and expensive IVF procedure.

Aims and objectives

To evaluate the effects of scratching from the first to the fifth day of the menstrual cycle, prior to IUI, and compare the pregnancy rates in cycles with and without the intervention.

Material and methods

A randomised case control study was carried out in SMGS Hospital, GMC Jammu over a period of 18 months from July 2018 to December 2019. Infertile couples attending the OPD of SMGS Hospital and requiring IUI as treatment modality were recruited in the study. These patients had prior three or more failed ovulation induction cycles.

Inclusion criteria: couples with unexplained infertility.

A total of 100 patients entered the study based on randomization. Seminal fluid samples were collected in sterile plastic containers after 2 to 3 days of abstinence. Then, the analysis of these fluid samples was carried out based on WHO criteria. The analysis included sperm count, motility and viability.

The patients who met the inclusion criteria were randomly divided into two groups 50 each. Group one named as the 'case group' underwent IUI with endometrial scratch using a pipelle biopsy, between the day 2 and day 3 of menstrual cycle, while sonography was performed simultaneously, while group two, the 'control group', underwent IUI without scratching of the endometrium.

To perform endometrial scratching, the cervix was exposed using a sterile speculum and then the uterine entrance got cleansed using sterile gauze and saline. Then, the lining of the anterior and posterior wall of the uterus was gently scratched by inserting and moving a pipelle up and down.

Ovulation stimulation was done similarly in both groups using 100 mg clomiphene tablets, beginning from the third up to the fifth days of the menstrual cycle for 5 days. In addition, FSH (75 units) was injected for 3 to 5 days, between the seventh and tenth days of the menstrual cycle.

After 10 to 12 days, the patients were visited and sonography was performed in order to evaluate the growth of the follicles and in cases with insufficient growth, more FSH was administered. For the follicles which were big enough (18-20 mm), HCG (5000-10 000 units) was administered intramuscularly, and after 36 hours, IUI was performed.

Moreover, luteal phase was supported by daily administration of 10 mg dydrogesterone (Duphaston) for 14 days. Successful pregnancy after IUI was evaluated by beta human chorionic gonadotropin (β-hCG) titers and sonography.

Statistical analysis

The obtained results were analyzed using SPSS software version 17.0. In order to compare the differences between groups, ANOVA and independent *t* test were used, while chi-square test was used for analyzing nominal data. A *P* value less than 0.05 was considered statistically significant.

Results

A total of 100 couples were included in this study and they were divided into two groups of 50 patients. The mean age of patients in the case group was 28.5± 4.3 while it was 28.4 ±4.8 in the control group. Table 1 shows that age of the patients ranged from 20 to 35 years and about 50% patients belong to 25-29 yrs in both the groups.

Table 1: Baseline characteristics of the Patients in case and control groups

Characteristics	Case group No. (%)	Control group No. (%)
Age (years)		
20-24	15(30%)	14(28%)
25-29	25(50%)	24(48%)
30-35	10(20%)	12(24%)
Parity		
Nulligravida	35(70%)	34(68%)
A1 or >1	4(8%)	5(10%)
Para 1	11(22%)	11(22%)

Among the study population, 68 couples (68%) had primary infertility and 32 (32%) had secondary infertility. In the case group, 35 couples (70%) and in the control group 33 couples (68%) had primary infertility, while secondary infertility was observed in 15 couples (30%) of the case group and 17 couples (34%) of the control group (table 2). The difference between primary and secondary infertility was found statistically significant (p value= 0.029).

Table 2: Type of infertility

Type of infertility	Case group No. (%)	Control group No. (%)	Overall No. (%)	p value
Primary	35(70%)	33(66%)	68(68%)	0.029
Secondary	15(30%)	17(34%)	32(32%)	

Duration of infertility was less than 5 years in approximately 50% patients of both the groups. There was no statistically significant difference between both the groups in terms of duration of infertility (Table 3).

Table 3: Duration of infertility

Duration (yrs)	Case group	Control group	p value
<5	26(52%)	29(58%)	0.283
6-10	21(42%)	17(34%)	
>10	3(6%)	4(8%)	

Among 100 patients who entered this study, 14 couples (14%) got pregnant successfully, 10 of them were in the case group and 4 were in the control group (Table 4). Therefore, 71% of the pregnant cases in this study were from the case group, showing

that two-thirds of the success in treating infertile couples in this study belonged to scratching method and increased pregnancy rates (p value= 0.022).

Table 4: Comparison of clinical pregnancies in both the groups

	Overall	Case group	Control group	p value (fisher's exact test)
Pregnant	14(14%)	10(20%)	4(8%)	0.022
Non pregnant	86(86%)	40(80%)	46(92%)	

The mean no. of dominant follicles were comparable between both the groups. There was no statistical difference found as p value = 0.587 (Table 5). Mean endometrial thickness was comparable in both the cases (9.20± 3.37) and controls (9.16± 3.20). The difference was not statistically significant (p value=0.532).

Table 5: Comparison of dominant follicle and mean endometrial thickness in both the groups

	Case group(n=50) mean ±SD	Control group(n=50) mean±SD	p value (unpaired student t-test)
Mean no. of dominant follicles≥14mm on HCG day	3.4 ±1.5	3.2 ±1.3	0.587
Mean endometrial thickness(mm)	9.20 ±3.37	9.16 ±3.20	0.532

Discussion

Infertility is a serious issue for couples, and despite the advancement of technology, assisted reproduction methods fail to provide successful services with reasonable cost, fewer side-effects, and lower abortion rates.

This study aimed at evaluating the effects of endometrial scratch on pregnancy rates in IUI cycles. The results demonstrated a higher rate of pregnancy in the case group with a significant statistical difference in comparison to the control group. Similar studies in this regard have shown different results. Some were consistent with our study, while others showed that there are no relationships between endometrial injury and pregnancy rate.

In the present study, 100 infertile patients were randomised to 100 each in the case and control group. Case group underwent endometrial scratching in the same cycle on day 2-3. Both the groups underwent ovarian stimulation with clomiphene followed by IUI.

The mean age, age distribution and BMI were comparable between both the case and control groups. Type of infertility in majority of patients in the study and control group was primary infertility (70% in cases and 66% in controls). The difference was statistically significant. Duration of infertility was less than 5 years in approximately 50% patients of both the groups. There was no statistically significant difference between both the groups in terms of duration of infertility.

No. of dominant follicles on the day of HCG was also comparable in both the groups. Mean no. of follicles of size more than 14mm was 3.4± 1.5 in cases and 3.2±1.3 in controls and there was no statistically significant difference. While Gupta *et al.*[13] in their study showed a statistically significant difference between both the groups. No. of dominant follicles were more in cases (1.78± 0.81) as compared to controls (1.54± 0.721). When we compare the endometrial thickness, we observed that mean endometrial thickness was also comparable in both the groups. It was 9.20±3.37 in cases and 9.16±3.20 in controls and the difference was statistically not significant. Similar results were reported by Zarei *et al.* [14], mean endometrial thickness was comparable in both the groups in their study. While study by Hamdi *et al.* [15] showed higher endometrial thickness in control group. Mean endometrial thickness was 8.33± 0.97 in cases and 10.5± 1.37 in controls in their study. On the other hand, Gupta *et al.* [13] found higher endometrial thickness in cases (9.18± 3.35) as compared to controls (8.53 ±1.88).

Pregnancy rate in our study was 14%. Number of clinical pregnancies in the case group and control group was 10 and 4 respectively (p value =0.022). In a study conducted by Hamdi *et al.* [15], pregnancy rate was 21% and it was 19% in study by Gupta *et al.* [13]. On the other hand Zarei *et al.* [14] indicated that local endometrium injury before IUI is not accompanied by increased pregnancy rate.

However, the time for inducing an injury seems to be controversial. For instance, in a study by Hamdi *et al.* [15], the better time considered was day1-5 of the same menstrual cycle. Gupta *et al.* [13] showed that promising results are obtained when the endometrial scratch is carried out on day 20-22 of the cycle preceding IUI. While Zarei *et al.* [14] performed endometrial scratch one month prior to IUI on day 6-8. Therefore, the optimal days for the scratching was evaluated in this study and the first to fifth days of the menstrual cycle in the same IUI cycle showed positive results. On the other hand, this study highlighted the low costs of scratching method, which might be a motivation for couples to undergo this method repeatedly.

Conclusion

Most of the methods used for fertilization are too expensive considering their high rates of failure. However, in this study, using endometrium scratch method, the rate of pregnancy enhanced in infertile patients who used IUI, which is of great importance due to its lower costs.

Thus, endometrial scratching can be offered before more advanced and expensive IVF procedure as it is a simple, practical, cost- effective procedure which can be done in an OPD (Out Patient Department) setting.

Further studies are recommended evaluating effect of endometrial scratching on IUI outcome and endometrial receptivity on a larger sample size in a multicentric design.

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