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The effect of local endometrial injury on the success of intrauterine insemination

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Abstract

To determine the effect of local endometrial injury on implantation success in patients diagnosed with unexplained infertility and undergoing intrauterine insemination (IUI) after ovulation induction with gonadotropins. In this prospective randomized controlled trial, 82 infertile patients underwent IUI following ovulation induction with gonadotropin. In the study group (n:40), local endometrial injury (stratch) was performed to the posterior side of the endometrial cavity with a biopsy catheter between the 21-26th days of luteal phase of the cycle preceding ovarian stimulation. There was no statistically significant difference between the study and the control groups in terms of age of female, age of male, duration of infertility, BMI, serum FSH and LH levels, mean dose of gonadotropin and mean duration of ovulation induction ($p>0.05$). Clinical pregnancy was achieved in two patients (4.76%) in control group and four (10%) patients in the study group, with no significant difference between groups ($p=0.18$). All pregnancies achieved in the control and the study groups passed 12th gestational weeks and continued. Ectopic pregnancy, multiple pregnancy and abortion was not observed in any patient in both groups. In the study group, pain level immediately after endometrial biopsy procedure was evaluated with visual analog scale (VAS) and it was established that only one (2.5%) patient experienced severe pain after the procedure. Although local endometrial damage in the menstural period before ovulation induction and IUI cycle increases clinical pregnancy rates in the infertile patients, this increase is not statistically significant. Multi-center randomized controlled studies are needed for local endometrial damage to be recommended routinely in clinical practice.

Keywords: infertility, intrauterine insemination, local endometrial injury, ovulation induction

1. Introduction

If the cause of infertility can not be found in a couple who can not achieve pregnancy despite one year of unprotected sexual relation, this is termed as unexplained infertility and 10-20% of couples are diagnosed with unexplained infertility (1, 2). Of overall infertility cases, in 20-40% ovulatory dysfunction, in 30-40% tubal and peritoneal factors and in 30-40% male factor plays part, while unexplained infertility accounts for 10% (3).

Implantation is the process of attachment of blastocyst produced after fertilization to uterus wall. The period when endometrium is most receptive to implantation is midluteal period, i.e. the period between 19-24. days which is termed as implantation window (4-7). In this period, blastocyst should be implanted on endeometrium successfully by passing the stages of apposition, adhesion and invasion. For a successful implantation, in addition to a receptive endometrium, a functional embryo and synchronous communication between maternal and embryonic tissue are required (8, 9).

75% of pregnancy losses stem from implantation failure (6, 10, 11) and two third of implantation failures results from impairment in endometrial receptivity (12, 13). Although many problems associated with fertility have been overcome with assisted reproductive techniques (ART), mostly embryonal factors have been adressed. Therefore, implantation stage is a problem which still remains to solved (11).

There are many studies in the literature reporting that local endometrial injury caused by endometrial biopsy procedure leads to rise in implantation rate by increasing endometrial receptivity. In these studies, many hypotheses have been put forward regarding the probable impact of endometrial injury, which include proliferation of decidua like cells in endometrium (14, 15), alteration in endometrial gene expression (16, 17), release of various cytokines and growth factors (13) and development of a more synchronous environment between embryo and endometrium (17).

The aim of the present study is to determine the effect of endometrial injury on implantation success in patients diagnosed with unexplained infertility and undergoing intrauterine insemination (IUI) after ovulation induction with gonadotropins.

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2. Materials and methods

2.1. Patients

Overall 96 cases who presented to infertility outpatient clinic of Zeynep Kamil Gynecology and Obtretrics Training and Investigation hospital between 01.02.2013-01.07.2013 were included in the present study. This study was initiated after approval was obtained from Zeynep Kamil Gynecology and Obstretrics Training and Investigation Hospital ethics committee (approval dated 25.01.2013 and numbered 023). All cases were informed about the study and their informed consent was obtained.

Age, BMI, age of spouse, previous history of pregnancy, duration of infertility, menstruation pattern, smoking and drinking habits, history of chronic disease, drug use and history of previous operations were questioned. All patients underwent hysterosalphingography (HSG) examination. All patients were invited to outpatient control visit between 2nd-5th days of their menstrual cycle for antral follicle count and evaluation of pelvic pathology (uterine myoma, endometrial polyp, hydrosalpinx, endometrioma, ovarian mass etc) with transvaginal ultrasonography (TVUSG) and for assessment of FSH, LH, estradiol, TSH and prolactin values. Sperm counts of the spouses of patients were evaluated. Inclusion criteria were as follows:

- Age between 20-40
- BMI <30 kg/m^2
- Primary infertility and at least one year history of infertility
- Patent bilateral tuba in HSG
- FSH value of <10 mIU/ml and LH, estradiol, TSH and prolactin values within normal range
- No history of known systemic disease or of regular use of drugs
- No history of surgical intervention that can play part in the etiology of infertility (endometrial polypectomy, myomectomy, endometriosis surgery, congenital uterine anomaly surgery, ovary cyst surgery, hydrosalpinx surgery etc.)
- Normal pelvic USG
- No endometrial biopsy, endometrial curettage and hysterescopic procedure within the last three months
- Normal spermiogram results according to WHO criteria

All patients who matched these criteria were randomized and classified into two groups: the control group (n:42) and the study group (n:54). 8 patients in the study group were excluded from the study since endometrial biopsy could not be obtained from them because endometrial biopsy catheter could not pass from cervix. Further six patients were excluded from the study, although they underwent biopsy procedure, with the following causes: In two patients, ovulation induction with gonadotropin procedure was cancelled due to the risk of Ovarian Hyperstimulation Syndrome (OHSS). In addition, in four patients, ovarian cyst was detected with TVUSG examination carried out before treatment at the onset of menstrual cycle. Finally, study group included 40 patients and control group 42 patients.

2.2. Treatment protocol

In the study group, patients planned to undergo endometrial biopsy sampling, were invited to infertility outpatient clinic at a date between the 21-26th days of luteal phase of menstrual cycle. The scratch was performed by the same investigator, with a biopsy catheter (Endometrial Sampling cannula, Plastimed, Istanbul, Turkey), on the posterior side of the endometrial cavity under sterile conditions. The internal piston was withdrawn to create negative pressure. Biopsy catheter was moved back and forth four to five times. No medical treatment was administered to the patients after the procedure. The degree of pain experienced by patients after the procedure was evaluated using Visual Analog Scale (VAS). Patients in control group did not undergo endometrial scratching. Following these procedures, on the third day of menstrual cycle, ovulation inducton with gonadotropin was commenced in patients in control and study groups. For induction procedure, follitropin α (Gonal F, rec-FSH, Merck-Serono, Italy) 75 IU/day was administered subcutaneously. The size and number of follicles was measured at certain intervals using TVUSG. Serum estradiol levels were measured and gonadotropin doses adjusted. When at least one follicle reached the size of 18mm or more, 250 μcg recombinant hCG (Ovitrelle 250 μcg, Merck-Serono, Italy) was administered subcutaneously. During follicle monitorization performed with TVUSG, cases with 2 or more follicles larger than 14 mm or who have estradiol values over 1500 pg/ml had their cycle cancelled owing to risk of OHSS and they were excluded from the study. 32-36 hours after ovulation, intrauterine insemination (IUI) was performed by the same investigator under sterile conditions. 15 days after IUI procedure, β-hCG values were evaluated to determine pregnancy. Clinical Pregnancy Rate (CPR), was defined as the detection of intrauterine gestatinal sac and fetus with fetal cardiac activity with TVUSG between 5th-7th weeks of pregnancy and Ongoing Pregnancy Rate (OPR) was defined as pregnancy process which has passed 12th week of gestational pregnancy.

2.3. Statistical analysis

In the present study, for data analysis, IBM SPSS (Statistical Package for Social Sciences) for Windows 20.0 program was used. In data analysis for descriptive statistics, arithmetic mean, standard deviation, minimum, maximum, frequency and percentage were used. Whether the data were normallly distributed was evaluated with Kolmogorov Smirnov test. In the comparison of pregnancy rates in study and control groups, chi-square test was used. Data normally distributed were evaluated with t test in independent groups and with Mann-Whitney U test and Fisher's exact test in others. Results were evaluated with 95% confidence interval and p value of <0.05 was considered statistically significant

3. Results

Overall 82 patients (42 control, 40 study) were included in the present study. There was no statistically significant difference between study and control groups in terms of age of female, age of male, duration of infertility, BMI, serum FSH, LH, levels mean dose of gonadotropin, mean duration of ovulation induction (p>0.05) (Table 1). Clinical pregnancy was achieved in 2 patients (4.76%) in control group and four (10%) patients in study group, with no significant difference between groups (p=0.18). All pregnancies achieved in control and study groups passed 12th gestational weeks and continued (Table 2). Ectopic pregnancy, multiple pregnancy and abortion was not observed in any patient in both groups.

In the study group patients, pain level immediately after endometrial biopsy procedure was evaluated with VAS and it was established that 1 (2.5%) patient experienced severe pain after the procedure (Table 3). In addition, cases in the study group were followed for probable complications such as vaginal bleeding, pain and infection. On the day of procedure, in study group, spotting (mild vaginal bleeding) was detected in 6 (15%) patients and mild abdominal pain in 3 (7.5%) patients.

Table 1. Comparison of demographic and clinical characteristics of control and study groups

	Control group (n=42)	Study group (n=40)	P
Female age (year)	29.57±4.17	28.95±4.43	0.51
Male age (year)	31.81±5.1	32.78±3.79	0.34
Duration of infertility (year)	4.52±3.4	4.39±2.94	0.94
FSH (mIU/mL)	7.55±1.59	7.15±1.6	0.27
E2 (pg/mL)	51.26±25.76	43.29±13.18	0.08
LH (mIU/mL)	4.9±1.74	4.92±1.89	0.97
BMI (kg/m_2)	23.57±3.4	24.35±3.02	0.28
Antral follicle count	12.38±4.4	13.95±4.1	0.106
Total gonadotropin dose (IU)	744.05±259.6	737.19±364.32	0.24
Durataion of ovulation induction (day)	9.64±2.63	9.48±3.37	0.8

Table 2. Comparison of clinical pregnancy rates of control group and study group

	Clinical Pregnancy (-	Clinical Pregnancy (+)	p
Control	40 (95.24%)	2 (4.76%)	0.18
Study	36 (90%)	4 (10%)	

Table 3. VAS scores for study group

	Endometrial Biopsy group
VAS (for pain)	3.29±2.04 (0.1-7.7)
VAS (for pain) >7, n(%)	1 (2.5)

4. Discussion

In the present study, the effect of local endometrial injury exerted in previous cycle in infertile patients undergoing IUI following ovulation induction with gonadotropins on pregnancy outcome was investigated and no significant difference was found between study and control groups with respect to CPR and OPR (p=0.18).

Although endocrinological, immunological, genetic and reproductive physiology factors are considered among probable mechanisms of infertility (2), the most important cause is decrease in endometrial receptivity, associated with impairment in cellular or molecular mechanisms in endometrium, and consequent implantation failure (18). Development of a functional embryo, endometrial receptivity for implantation and complex molecular interactions between them are the required steps for implantation (4, 6, 9, 10, 12).

Some investigators have stressed that COH cycle exerts negative impact on implantation and reported that in COH cycle endometrial stromal development and pinopod development are at more advanced stage compared to natural cycle, which produces an environment without developmental synchrony between embryo and endometrium and influences implantation unfavourably (19, 20). In the study of Zou et al, it was stated that the most likely cause of the positive effect of local endometrial injury on implantation success may be that this advanced development process in COH cycle becomes slower during wound healing after endometrial injury and hence a more balanced environment is produced between embryonal development and endometrial development (17). Another mechanism known to be inducive to endometrial implantation is the release of cytokines and other growth factors during wound healing period following endometrial injury. With all these autocrine and paracrine effects, the release of sex stroids is regulated and uterus becomes receptive to embryo which will be implanted. (21). It is also known that cytokines such as IL-6, LIF, (TNF-α) and growth factors relaeased from immune system cells and endometrial cells after endometrial injury increases receptivity (13).

In literature review, it can be observed that the effect of local endometrial injury on pregnancy outcomes has mostly been investigated in ART (assisted reproductive technology) cycles. In the meta-analysis of Nahshon C. et al including 3016 cases from 17 randomized controlled studies (RCT), in women with at least one previous failed cycle, the effect of local endometrial injury on IVF outcomes was evaluated and CPR (RR 1.19 [95% CI 1.06–1.32]) and LBR (live birth rate) (RR 1.18 [95%CI 1.04–1.34]) were found to be significantly improved after local endometrial injury (22). However, in the meta-nalysis of Van Hoogenhuijze et al. including 14 RCT with 2537 participants, the effect of local endometrial injury in patient groups with a previous failed full IVF/ICSI cycle was evaluated and no difference was found between study and control groups with regard to LBR (RR 1.01 [95%CI 0.68–1.51]) and CPR (RR 1.04 [95%CI 0.74–1.45]) (23). Similarly, in the meta-analysis of Vitagliano et al, after local endometrial injury prior to first IVF cycle, nonsignificant difference was found between control and study groups with respect to LBR

(RR 0.99 [95% CI 0.57–1.73]) and CPR (RR 1.12 [95% CI 0.79–1.59]) (24). In the meta-analysis of Nastri et al, it was stated that local endometrial injury prior to IVF cycle had no significant effect on pregnancy in the groups which has not undergone IVF before or has undergone IVF once with failure while in the group with two or more failed IVF attempts CPR (RR 1.63 [95%CI 1.12–2.38]) and LBR (RR 1.96 [95%CI 1.21–3.16]) were significantly higher (25). The cause of discrepant results reported by meta-analyses is that different inclusion criteria are used in studies with different designs (randomized or nonrandomized studies, the number of previous IVF attempts, whether local endometrial injury is exerted before or during cycle). In conclusion, all of these meta-nalyses emphasized that well designed randomized controlled multicenter studies are warranted in order that the effect of local endometrial injury prior to IVF cycle on pregnancy outcomes can be determined more accurately.

In the meta-analysis performed by Vitagliano A. et al including 8 RCTs with 1523 participants, the effect of local endometrial injury on the outcome of intrauterine insemination (IUI) stimulated was evaluated (26). In included studies, local endometrial scratch injury was carried out either during the course of IUI stimulated cycle (C-ESI) or during the menstrual cycle preceding IUI treatment (P-ESI). In local endometrial injury group, higher rates of CPR (OR 2.27; P<.00001) and OPR (OR 2.04; P=.004) were found. Nevertheless, these findings were supported by moderate level evidence for CRP and low level of evidence for OPR. In subgroup analysis based upon the timing of endometrial injury, in the subgroup undergoing C-ESI, CPR (OR 2.57; P<.00001) and OPR rates (OR 2.27; P=.004) were higher. In addition, in patients with endometrial injury, even though the quality of evidence was low, the risk of multiple pregnancy (OR 1.09), induced abortion (OR 0.80) and ectopic pregnancy (OR 0.82) was not found to be increased. In the present study, although clinical pregnany rate was found to be higher in the study group, the difference between groups was not significant, which may be due to low number of patients. In the present study, multiple pregnancy, abortion and ectopic pregnancy was not observed. In the above mentioned meta-analysis, pain status after local endometrial injury was not evaluated in any study, except for the study of Wadha et al, who reported without using any pain scale that no patients had severe pain (27). In a study, patients were evaluated for pain with VAS and when number 4 karman cannula was used in the procedure, pain at the mean rate of 6/10 was experienced (28). In the present study, pain level after endometrial biopsy procedure was evaluated using VAS and it was established that only one (2.5%) patient experienced severe pain following procedure. In the studies evaluated in the aforementioned meta-analyses, there is no data on short and long term complications. In the present study, on the day of procedure, spotting (vaginal bleeding) was detected in in 6 (15%) patients and mild abdominal pain in 3 (7,5%) patients. Especially probable intrauterine adhesions that may develop after local endometrial injury are cause for concern. Therefore, long term studies which will clarify this tissue are required.

In an international survey performed in England, New Zealand and Australia, it was established that 92% of physicians recommend local endometrial injury (scratching) before IVF cycles used after repeated implantation failure while before IUI, it is recommended by only 3.2% of clinicians (29).

In conclusion, whether local endometrial injury exerts favorable effect on pregnancy outcome in patients administered ART is still debated at present. To reach definitive conclusions, well designed larger randomized controlled multicenter studies are required.

Conflict of interest

There is no conflict of interest to declare.

Acknowledgments

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