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Comparing the effect of office hysteroscopy with endometrial injury versus office hysteroscopy in gonadotropin-induced cycles before intrauterine insemination: A randomized controlled trial

Serhat Ege[a,*], Numan Cim[b]

[a] *Dicle University, Faculty of Medicine, Department of Obstetrics and Gynecology, Diyarbakır, Türkiye*
[b] *Istanbul Haseki Training and Research Hospital, Department of Obstetrics and Gynecology, Istanbul, Türkiye*

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Abstract

Aim: Our aim in this study was to evaluate the implantation success in local endometrial injury in patients undergoing intrauterine insemination following induction of ovulation with gonadotropins.

Materials and Methods: In this prospective randomized controlled study, 62 patients undergoing gonadotropin-assisted ovulation induction after intrauterine insemination were included. Thirty patients with hysteroscopy-related injuries were included in Group 1 and 32 control patients who underwent hysteroscopy alone were included in Group 2.

Results: The rates of clinical pregnancy (16.6% [5/30] vs. 18.7% [6/32]; p = 0.8), abortion (3.3% [1/30] vs. 3.1% [1/32]; p = 0.9), and multiple pregnancy (3.3% [1/30] vs. 3.1% [1/32]; p = 0.9) were similar between the two groups.

Conclusion: There were no significant differences in clinical pregnancy, multiple pregnancy, or abortion rates between the groups. The intervention group underwent hysteroscopic injury in the follicular phase before gonadotropin-induced intrauterine insemination, while the control group underwent hysteroscopy only.

Introduction

Creating mature follicles, ensuring ovulation, and eliminating cervical factors can increase pregnancy rates in intrauterine insemination (IUI) performed with ovulation induction. Since IUI is cheap, easy, and noninvasive, it is the first method that should be used in cases of unexplained infertility [1,2]. Implantation failure is a possible cause of unexplained infertility [3]. Blastocyst invasion of the endometrium occurs during the implantation window [4]. During this period, there is a reciprocal interaction between the embryo and the endometrium.. If the uterus can not become receptive, this reciprocation is impaired, and implantation fails [5]. Many different methods are mentioned to increase the success of insemination [6,7].

Endometrial injury (EI) has attracted much attention for improving implantation success. This method aims to increase pregnancy rates by causing injury in a patient's IUI cycles before initiating assisted reproductive techniques. Interfering with the endometrium may increase the secretion of cytokines, growth factors, and adhesive molecules by modulating gene expression, hence providing the basis for implantation [7-11].

The current study aims to investigate the local implantation success of EI in patients having IUI after gonadotropin-induced ovulation.

Materials and Methods

Sixty-two infertile patients admitted to the infertility polyclinic in a tertiary center hospital, Gynaecology and Obstetrics department participated in this prospective randomized controlled trial (RCT).

According to World Health Organization (WHO) rules [12], male factor infertility was defined as sperm count less than 15×10^6/mL, overall motility less than 40%, or normal forms less than 4%. Aberrant semen parameters with >5% normal morphology and $>5\times10^6$/mL motile spermatozoa recovered following sperm preparation were characterized as mild male factor infertility [13].

The following patients were excluded from the study:

*Corresponding author:
Email address: serhatege782@gmail.com (Serhat Ege)

Table 1. The demographic and clinical characteristics of the patients in the study groups.

	Group 1 (n = 30)	Group 2 (n = 32)	P-value
Age (years) (mean ± SD)	26.5±3.6	26.15±4.4	0.463
Duration of infertility (years)	3.08±1.04	3.22±1.05	0.313
BMI (kg/m^2)	24.51±1.71	24.29±1.88	0.353
Basal FSH (mIU/mL)	4.63±1.16	4.63±1.25	0.974
Basal LH (mIU/mL)	4.85±0.89	4.65±1.12	0.13
E2 (pg/mL)	47.92±5.89	47.21±5.21	0.7078
TSH (ng/dL)	2.8±1.1	3.08±1.47	0.107
PRL (ng/mL)	14.46±2.63	14.35±1.68	0.709
Sperm count ×10^6/mL	24.33±6.48	25.32±3.48	0.151
Follicles >18 mm(milimeter) on hCG administration	1.23±0.5	1.51±0.5	0.862
Endometrium thickness on day of hCG (mm)	11.48±1.52	11.61±1.61	0.538
Total gonadotropin (IU/L)	524.77±68.32	527.11±52.96	0.771

Values presented as mean ± SD. BMI: body mass index, LH: luteinizing hormone, FSH: follicle stimulating hormone, TSH: thyroid stimulating hormone, PRL: prolactin, E2: estradiol.

Table 2. Summary of the outcome and success of both intervention groups in the study.

	Hysteroscopy with injury (n = 30)	Hysteroscopy (n = 32)	P-value
Clinical pregnancy	5/30 (16.6%)	6/32 (18.7%)	0.8
Multiple pregnancy	1/30 (3.3%)	1/32 (3.1%)	0.9
First-trimester abortion	1/30 (3.3%)	1/32 (3.1%)	0.9

Values are presented as mean ± SD or n (%).

those with male factor infertility, those with anovulatory cycles, those over 39 or under 18 years of age, smokers, women with a history of chronic medication or disease, and those who had not undergone IUI or canceled their appointment.

Patients who met these criteria and applied to the outpatient clinic were assigned to the intervention, the clinic nurse assigned participants to two groups: the intervention group (Group 1) and the control group (Group 2). Group 1 included 30 patients who received hysteroscopic endometrial injury, while Group 2 consisted of 32 patients who underwent hysteroscopy without injury. Patients who met the criteria but had no follicle development during follow-up were also excluded from the study.

Treatment protocol

On the third day of the menstrual cycle, ovulation induction was started in both groups with 75 IU gonadotropins (Gonal-F pen, follitropin alfa, Merck & Co., Inc.). In all patients, hysteroscopic scissors (Karl Storz Endoscopy) were used to create an injury on the posterior endometrial wall during the follicular phase, specifically 5 to 7 days before the IUI cycle.

EI was conducted by filling the uterine cavity with normal saline solution at 100–120 mmHg of pressure without using a speculum or tenaculum and without anesthesia or analgesia. In the control group, only office hysteroscopy was performed, and no EI was carried out.

Transvaginal ultrasonography was used to measure the number and size of follicles at 3- to 5-day intervals after ovulation induction. Afterwards, serum estradiol levels were assessed, and gonadotropin dosage adjustments were made periodically. In the absence of ovarian hyperstimulation (E2 $>$ 3000) or multiple pregnancy (follicular count $>$4) risk, a single dosage (250 mcg/0.5 mL) of human chorionic gonadotropin (hCG) (Ovitrelle, Merck & Co., Inc.) was given subcutaneously when a dominant follicle (18 mm and above) was produced.

The same researcher used sterile procedures to do IUI 36 hours following ovulation. Vaginal progesterone (Crinone 8%, Merck & Co., Inc.) was used to support the luteal phase following IUI. Fourteen days following IUI, serum beta-hCG levels were assessed to identify pregnancies. Transvaginal ultrasonography was used to diagnose pregnancy by detecting the presence of the fetal heartbeat and gestational sac during 5th and seventh week of gestation. A clinical diagnosis of pregnancy was made if both were present. Early loss of pregnancy occurring before 12 weeks of gestation was considered an abortion.

All volunteers signed informed consent and also gave verbal consent to participate in our study. The Declaration of Helsinki's ethical guidelines for medical research involving human participants were followed (ethics committee no. 147).

Statistical analysis

The statistical data was analyzed using Statistical software Package for Social Sciences version 18 (SPSS ve 18.0) (IBM,USA), $>$ Contiuous (mean ± SD). When comparing quantitative data, normally distributed variables were compared using the Student's t-test, while the data that showed non-normal distribution were compared using the

Mann-Whitney U test. The qualitative data were compared using a chi-square test. Any p value less than 0.05 was considered to be statistical significant.

Results

Sixty-two patients undergoing intrauterine insemination (IUI) were enrolled in this study and randomly assigned to two groups: an intervention group receiving office hysteroscopy (OH) with endometrial injury (EI) (n = 30) and a control group undergoing OH only (n = 32). Baseline characteristics, including age, BMI (kg/m^2), duration of infertility, basal LH (mIU/mL), basal E2 (pg/mL), basal FSH (mIU/mL), and sperm count, were similar between the groups. No statistically significant differences were found between groups regarding the day of hCG administration, total gonadotropin dose per cycle (IU/L), the number of mature follicles (≥18 mm), and endometrial thickness on the day of hCG administration (Table 1).

As shown in Table 2, there were no significant differences between groups in the rates of multiple pregnancies (3.3% [1/30] vs. 3.1% [1/32]; p = 0.9), clinical pregnancies (16.6% [5/30] vs. 18.7% [6/32]; p = 0.8), and abortions (3.3% [1/30] vs. 3.1% [1/32]; p = 0.9).

Discussion

In our study, no significant difference was found in the clinical pregnancy, live pregnancy and abortion rates among the study groups.

IUI with ovulation induction should be the first choice in cases of unexplained infertility [1]. Pregnancy rates have been reported to be 7% for each cycle in IUI conducted with clomiphene citrate (CC) and 12% for IUI conducted with gonadotropins [14].

Many studies have been performed to increase the pregnancy rates slightly using EI. Soliman et al. [15] concluded that EI performed with CC and human menopausal gonadotropin (Merional) in the follicular phase increased the pregnancy rate after an IUI deficiency. Wadhwa et al. [16] evaluated the effect of EI on IUI outcome, they concluded that EI in the follicular phase was associated with a better clinical pregnancy rate compared to injury in the luteal phase of the previous menstrual cycle. Bahaa Eldin et al. [17] assessed EI performed with a Pipelle catheter in the follicular phase of the stimulation cycle combined with IUI and found that the results were significantly bettwe. In a study conducted by Zarei et al. [18], EI performed in the follicular phase showed no significant difference in the live pregnancy and abortion rates of the control groups. We studied hysteroscopic injury with gonadotropins, and we found no statistical difference in the treatment group compared with the control group in terms of the outcomes of insemination.

A systematic review on EI with IUI stated that 8 RCTs [15–22] with total of 1,871 IUI cycles (and 1,523 participants) were included . Patients got EI in 998 IUI cycles, while no intervention was carried out in 873 IUI cycles the EI had significantly superior results over the control groups in terms of . In terms of clinical pregnancy rate (CPR),[ongoing pregnancy rate (OR) = 2.27; p <.00001; data from 1,871 IUI cycles)]. In addition, follicular-EI was associated with a statistically significantly higher CPR (OR = 2.57; p < .00001) in comparison with the controls.

Various studies report superior results in patients who were injured in the follicular phase and the controls [15, 17, 20]. Our results did not support these observations. We believe that the number of studies ragrding this area of research are insufficient and that more comprehensive studies are needed in future. Furthermore, studies vary in the type of patients included, the type and timing of intervention, and the number of IUI cycles. Therefore, comparing and drawing conclusions is problematic due to the large number of confounding factors.

The reviews published on yhis subject have no definitive results on whether the endometrial injury improves CPR, LBR, or ongoing pregnancy rates in women undergoing IUI or having sexual intercourse. The quality of evidence was rated as low or very low [23]. Furtyhermore, another review stated that that endometrial injury improved CPR (odds ratio (OR) 2.27, P < 0.00001) and ongoing pregnancy rates (OR 2.04, P = 0.004) in patients undergoing IUI. Endometrial injury did not increase the risk of multiple pregnancy, miscarriage, or ectopic pregnancy [24].

Key advantages of this study include the use of hysteroscopy in both groups, allowing for the detection of intrauterine pathologies potentially missed by ultrasound (USG) and enabling intervention for minor pathologies such as polyps. A limitation is that hysteroscopic scissor injury may cause greater pain than injuries induced by other devices (e.g., pipelle, Karman cannula, aspiration catheter, or endometrial brush).

Conclusion

Clinical pregnancy, multiple pregnancy, and abortion rates did not differ significantly between the intervention group (hysteroscopic injury in the follicular phase before gonadotropin-induced IUI) and the control group (hysteroscopy only).

Conflict of interest

All of the authors declare that they do not have any conflicts of interest.

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Ethical approval

Ethical approval was obtained for this study from the Diyarbakır Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee (Date: 05.10.2018, Number: 147).

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