

Endometrial injury and fertility outcome on the day of oocyte retrieval

Mechanical injury on OPU day

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Abstract

Aim: In this study, we aimed to investigate the effect of mechanical endometrial injury, performed on the day of egg retrieval, on pregnancy rates in patients who underwent IVF/ICSI due to PCOS and planned total embryo freezing.

Material and Methods: Sixty women with PCOS scheduled for total embryo freezing due to the risk of ovarian hyperstimulation syndrome were included in the study. The participants were randomly divided into two groups as treatment and control, with 30 patients in each group. For patients in both groups, standard antagonist protocol for controlled ovarian stimulation was applied. The patients in the treatment group underwent endometrial scratching with a Pipelle cannula after egg collection. The patients in the control group (sham) were reached up to the fundus with a Pipelle catheter, but scratching was not performed. The primary outcome measures of the study were beta-hCG, clinical pregnancy rates (CPR), live birth rates (LBR), and miscarriage rates.

Results: There was no significant difference between the two groups in terms of the percentage of beta-hCG positive patients, clinical pregnancy and live births ($p>0.05$). Clinical pregnancy and live birth rates of both groups were recorded as similar. No significant difference was found between the injury group and the control group in terms of miscarriages rates. All of the pregnancies in the scratching group and control group were intrauterine localized and no ectopic pregnancy was encountered.

Discussion: Injury to the endometrium on the day of egg collection does not cause a significant increase in clinical pregnancy and live birth rates.

Keywords

Mechanical Endometrial Injury, Oocyte Retrieval Day, Clinical Pregnancy, Live Birth, Miscarriage

DOI: 10.4328/ACAM.20856 Received: 2021-09-14 Accepted: 2021-10-10 Published Online: 2021-10-13 Printed: 2022-01-01 Ann Clin Anal Med 2022;13(1):89-92

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Introduction

Intentional endometrial injury (i.e. endometrial scratching) during ART in patients with recurrent implantation failure results in an approximately two-fold increase in both implantation and pregnancy rates [1,2]. However, many studies and reviews reported that the effects of injury on fertility outcome are not clear, thus there is not enough scientific data to recommend its routine use [3,4]. In connection with this, it has been reported that injury is not beneficial in patients with first IVF/ICSI trials and in unselected infertile patient groups [5,6]. Despite all these moderate quality study results, approximately 80% of infertility practitioners apply injury to their patients [7]. In many studies, mechanical injury is performed in the midluteal phase of the cycle, and IVF/ICSI is performed in the next cycle. However, in addition to studies that apply injury in the follicular phase, there are studies that have injury in both phases and achieve successful results [7]. There are a limited number of studies investigating the effects of injury on the day of egg collection on fertility outcome. In all but one of these studies, it was reported that the injury on the day of egg collection did not have an additional effect on implantation and pregnancy rates. In one study, the devastating effect of mechanical endometrial injury on implantation and clinical pregnancy rates on the day of egg retrieval was mentioned [8].

Although it varies according to the patient's phenotype, PCOS is the most common endocrine disorder with subfertility. The mechanisms leading to subfertility in PCOS are phenotypic features such as hyperandrogenemia, ovarian morphology, or ovulatory dysfunction. In addition, the endometrium of PCOS patients is more resistant to embryo invasion and placentation than healthy individuals [9,10]. In PCOS cases, it may be possible to make the endometrium receptive by mechanical endometrial injury. Ovarian hyperstimulation syndrome (OHSS) is a life-threatening complication in patients undergoing IVF/ICSI for PCOS. To prevent the development of OHSS in this patient group, total embryo freezing is one of the most important preventive measures [11]. Patients planned for total freezing due to the risk of OHSS are an ideal study group to investigate the effect of mechanical injury in PCOS. Therefore, this study was aimed to investigate the effect of mechanical endometrial injury, performed on the day of egg retrieval, on pregnancy rates in patients who underwent IVF/ICSI due to PCOS and planned total embryo freezing due to the risk of OHSS.

Material and Methods

Sixty women with PCOS scheduled for total embryo freezing due to the risk of ovarian hyperstimulation syndrome were included in the study. The two groups did not differ significantly in age and BMI. Patients were diagnosed with PCOS based on the revised Rotterdam criteria, which require two of the following three manifestations: (1) oligo and/or anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) polycystic ovaries determined with ultrasonography. Participants were selected among patients who applied to our IVF-Center for infertility treatment between 2019-2021. The study was started after obtaining patient consent and approval from the local ethics committee. Participants were randomly divided into two groups: treatment and control groups, with 30 patients in

each group. For patients in both groups, a standard antagonist protocol for controlled ovarian stimulation was applied. rFSH treatment was started on the 2nd or 3rd day of the cycle. The gonadotrophin-releasing hormone antagonist was started on the 5th or 6th day of stimulation. Recombinant hCG (Ovitrelle, Merck-Serono, 250 mg, Modugno, BA, Italy) treatment was initiated when at least three follicles with a diameter of 18-20 mm were detected on ultrasonographic evaluation. Oocyte pick-up was performed 35 to 36 hours after hCG administration, guided by trans-vaginal ultrasonography. All embryos were vitrified as previously described. The patients in the treatment group underwent endometrial scratching with a Pipelle cannula after egg collection. The patients in the control group (sham) were reached up to the fundus with a Pipelle catheter, but scratching was not performed. Women with Asherman's syndrome, endometrial polyp, submucous fibroids, uterine septum or other congenital uterine anomalies, hydrosalpinx, or endometrioma were excluded. Participants with a history of hormonal medication or intrauterine contraception use within the past 12 months and those with a history of habitual abortion or endocrine disorders were also excluded.

Following the OPU procedure, the injury procedure was performed while the patient was still under anesthesia. The injury procedure was performed in accordance with the previous studies. The Pipelle catheter was introduced through the cervix into the uterine fundus. The piston of the Pipelle cannula was withdrawn to create negative pressure and suction. Then the catheter was pushed back and forth in the cavity and withdrawn. The procedure was repeated until most of the cavity was injured and the procedure was terminated by removing the catheter from the cavity. In the control (sham) group, the Pipelle catheter was advanced through the cervix to the fundus and then removed from the cavity, but no injury was made. Following artificial endometrial preparation, the embryos were thawed and their qualities were examined. One or two good quality embryo transfer was performed to the patients in both groups in the following cycle after mechanical endometrial injury. Micronized progesterone was initiated vaginally for luteal support. Three patients in the treatment group and 4 patients in the control group were not transferred because they had clinical and laboratory findings of OHSS. The primary outcome measures of the study were to evaluate beta-hCG, clinical pregnancy rate (CPR), live birth rate (LBR), and miscarriage rate. The clinical pregnancy rate is defined as evidence of a gestational sac, confirmed by ultrasound examination at the 4th week of transfer. The live birth rate is defined as delivery of a live fetus after 24 completed weeks of gestational age. Serum beta-hCG levels were measured in all patients on the 12th day of embryo transfer. The loss of fetus before 20 weeks of gestation was defined as miscarriage.

Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences software 21.0 for Windows package software (SPSS, Inc., Chicago, IL, USA). All parameters studied in the treatment and sham groups showed normal distributions, which were confirmed by the one-sample Kolmogorov-Smirnov test. During the statistical evaluation, ANOVA tests for continuous variables and Pearson's chi-square tests for categorical variables were

used. If the frequencies were less than we expected, Fischer's exact test was used. Data were presented as mean \pm SD. CPR, LBR, miscarriage rates and beta-hCG positive cases were given as percentages. $P < 0.05$ was used for determining statistical significance.

Results

Demographic and cycle characteristics of the patients are shown in Table 1. Baseline characteristics of both groups were similar. There was no significant difference between the groups in terms of age, BMI, basal FSH and LH levels, endometrial thickness, and infertility duration in the participants. Both the number of oocytes collected from patients in both groups and the number of transferred embryos were recorded as similar. Mechanical endometrial injury was successfully performed in all patients in the treatment group. No complications were detected, except for pain and short-term spotting. A single dose of antibiotic prophylaxis was administered to the participants before the procedure. All cases in the control group successfully underwent the sham procedure, and no complications developed. As shown in Table 1, there was no significant difference between the two groups in terms of the percentage of beta-hCG positive patients, clinical pregnancy and live births. Clinical pregnancy and live birth rates in both groups were recorded as similar. Similarly, no significant difference was found between the injury group and the control group in terms of miscarriages rates. All pregnancies in the scratching group and control group were intrauterine localized, and no ectopic pregnancy was encountered.

Table 1. Demographic and laboratory findings of both groups

	Scratching Group (n=27)	Control (sham) Group (n=26)	*p-value
Age (y)	27.8 \pm 0.87	28.3 \pm 1.33	0.66
BMI (kg/m ²)	24.9 \pm 1.50	25.1 \pm 2.30	0.30
Infertility duration (y)	3.93 \pm 2.01	4.02 \pm 2.48	0.07
Endometrial thickness (mm)	9.67 \pm 2.11	10.6 \pm 2.44	0.32
FSH (mIU/mL)	5.01 \pm 2.03	5.40 \pm 3.55	0.09
LH (mIU/mL)	9.33 \pm 2.09	10.1 \pm 1.90	0.30
No of retrieved oocytes	18.6 \pm 3.22	16.7 \pm 2.87	0.06
No of frozen embryos	11.08 \pm 2.90	10.1 \pm 3.76	0.40
No of transferred embryos	2.11 \pm 0.33	2.08 \pm 1.64	0.08
Beta-hCG (%)	11 (40.7%)	10 (38.4%)	0.20
Clinical pregnancy (%)	10 (37.0%)	10 (38.4%)	0.44
Miscarriage (%)	1/10 (10.0%)	1/10 (10.0%)	0.50
Live birth (%)	8 (29.6%)	8 (30.7%)	0.10

Data presented as mean \pm SD. BMI; body mass index, FSH; follicle-stimulating hormone LH; luteinizing hormone, * $p < 0.05$.

Discussion

Implantation failure remains on the agenda as a rate-limiting step in the follow-up of infertile patients. For infertile patient groups suffering from this problem, the most effective method currently available is to expose the endometrium to controlled injury. However, there is no consensus in studies on the effects of endometrial injury on clinical pregnancy rates. While most of the studies have reported a significant increase in pregnancy rates in the post-injury period [1,2], some studies have reported

that endometrial injury does not have a positive effect on pregnancy rates [5,6] and may even have detrimental effects on reproductive outcomes if the wrong cycle is applied [8]. We can list the main reasons for the inconsistency between injury studies as follows: (i) the participants are not homogeneous, (ii) the phase in which the injury is applied is different in each study, (iii) the injury method is different, (iv) the injury is done once in some studies and more than one in some studies. In addition to all these disadvantages, routine use of the method is not recommended since it has not been clearly demonstrated by which biological mechanisms injury increases pregnancy rates. However, it continues to be widely used by many infertility practitioners despite the mysteries of its mechanism of action and the possible harmful consequences of the described method [2,7]. In most of the injury studies, the method was applied either in the follicular phase or the luteal phase, or in both phases. The method can be performed either as an outpatient with a Pipelle cannula or with a hysteroscopy-guided Novak curette or electro cautery [1,2,8]. It has been reported that the effect on the fertility outcome does not change significantly depending on the phase of the cycle or the method applied. However, at one stage of ART practice, an important opportunity arises to apply injury to the patient. There are four studies designed to determine whether causing endometrial injury to a patient under anesthesia on the day of egg retrieval is beneficial [8,12-14]. In three of them, the injury was performed during egg collection, and the remaining one was on the day of embryo transfer.

Our study is the fourth study in the literature investigating the effects of endometrial injury on fertility outcome on the day of egg collection. In the present study, unlike other studies, the participants consisted of a homogeneous patient group diagnosed with PCOS, and total embryo freezing was performed in all of our patients. All patients underwent frozen embryo transfer in the next cycle. The patients in our control group consisted of patients diagnosed with PCOS without endometrial injury. Since the participants in both groups were similar in terms of demographic characteristics and age, the results obtained were homogeneous and more objective when compared. Our study clearly showed that there was no significant difference between the two groups in terms of the percentage of beta-hCG positive patients, clinical pregnancy rates and live birth rates. Similarly, there was no significant difference between the two groups in terms of miscarriage rates.

Our results are consistent with three of the four studies when compared with other studies with egg total day injury. In all these three studies, beta-hCG positivity and pregnancy rates after injury on egg collection day and/or transfer day were reported similar to patients without injury. [12-14]. Only one study reported that ovarian total day injury significantly reduced implantation, clinical pregnancy, and ongoing pregnancy rates. However, in that study, embryo freezing could not be performed after injury, and fresh embryo transfer was applied on the second day [8]. In our study, total freezing was performed after egg collection, and frozen embryo transfer was performed in the next cycle. Therefore, it is not correct to compare the results of these two studies with each other.

When the previous three studies and our study are evaluated together, damage to the endometrium on the day of egg collection does not cause a significant increase in pregnancy rates and does not have a harmful effect [8,12-14]. As a result, the patient's being under anesthesia or being a candidate for total freezing is not an opportunity for injury after egg collection. Since the injury to be done will not be beneficial to the patient in terms of fertility, it should not be processed. In light of these results, we can perhaps suggest that since interventions such as endometrial biopsy or polyp removal during egg collection do not affect pregnancy rates in the next cycle, such procedures can be performed if necessary.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Nurettin Turktekin, Cemil Karakus, Ramazan Ozyurt. Endometrial injury and fertility outcome on the day of oocyte retrieval. *Ann Clin Anal Med* 2022;13(1):89-92