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Does hysteroscopic resection of polyps require cycle cancellation in women undergoing controlled ovarian hyperstimulation in the ICSI cycle?

ICSI döngüsünde kontrollü over hiperstimülasyonu uygulanan kadınlarda poliplerin histeroskopik rezeksiyonu döngü iptali gerektirir mi?

Serkan Oral

Haliç University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey

Abstract

Objective: Endometrial polyps are one of the most extensive pathologies in the uterus and can be detected incidentally during assisted reproductive therapy in asymptomatic women.

Materials and Methods: In patients planned for in vitro fertilization or intracytoplasmic sperm injection (ICSI) treatment, embryo freezing, or cycle cancelation options are mandatory in many clinics when detected at the beginning of the cycle. In our study, in ICSI treatment, patients with a single endometrial polyp smaller than 1.5 cm, who underwent hysteroscopic polyp resection at the beginning of the cycle and underwent fresh embryo transfer without canceling the treatment (n=31), and patients with the same characteristics of endometrial polyp who underwent hysteroscopic polyp resection before the cycle (n=34) are compared within the pregnancy, abortion and live birth rates.

Results: As a result, no statistical difference was found between the two groups' pregnancy, abortion, and live birth rates.

Conclusion: Hysteroscopic resection of polyps during ovarian stimulation in ICSI treatment does not affect pregnancy and live birth rates and may eliminate the necessity of freezing.

Keywords: Endometrial polyp, ovarian stimulation, hysteroscopy, ICSI

Öz

Amaç: Endometriyal polipler, rahimdeki en yaygın patolojilerden biridir ve asemptomatik kadınlarda yardımcı üreme tedavisi sırasında tesadüfen saptanabilir.

Gereç ve Yöntemler: İn vitro fertilizasyon veya intrasitoplazmik sperm enjeksiyonu (ICSI) tedavisi planlanan hastalarda siklusun başlangıcında tespit edildiğinde birçok klinikte embriyo dondurma veya siklus iptali seçenekleri zorunludur. Çalışmamızda ICSI tedavisinde, siklusun başında histeroskopik polip rezeksiyonu yapılan ve tedavi iptal edilmeden taze embriyo transferi yapılan 1,5 cm'den küçük tek endometriyal polipi olan hastalar (n=31) ve aynı siklus öncesi histeroskopik polip rezeksiyonu (n=34) uygulanan endometriyal poliplerin özellikleri gebelik, abortus ve canlı doğum oranları açısından karşılaştırılmıştır.

Bulgular: Sonuç olarak iki grubun gebelik, abortus ve canlı doğum oranları arasında istatistiksel olarak fark bulunmadı.

Sonuç: ICSI tedavisinde yumurtalık uyarımı sırasında poliplerin histeroskopik rezeksiyonu, gebelik ve canlı doğum oranlarını etkilemez ve dondurma gerekliliğini ortadan kaldırabilir.

Anahtar Kelimeler: Endometriyal polip, over stimülasyonu, histeroskopi, ICSI

PRECIS: There is no significance between pregnancy, abortion, and live birth rates of patients who underwent hysteroscopic polyp resection without cycle cancelation during ovarian stimulation.

Address for Correspondence/Yazışma Adresi: Serkan Oral MD,
Haliç University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkey
Phone: +90 212 345 66 00 **E-mail:** drserkanoral@gmail.com **ORCID ID:** orcid.org/0000-0002-1311-6278
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Introduction

One of the most common structural pathologies that can cause low implantation in the uterine cavity is endometrial polyps[1]. Their number and size may differ. They can be found in the uterine cavity with or without a stalk. These lesions, usually caused by the overgrowth of endometrial glands and stroma, consist of three layers; endometrial glands, stroma, and blood vessels[2]. Polyps can be asymptomatic most of the time[3], but when they are symptomatic, they most commonly present with abnormal uterine bleeding[4], and they may cause infertility at a lesser rate[5].

Endometrial polyps are found in 5-10% of infertility and 15-50% of recurrent miscarriages[6-8]. Endometrial polyps that can be noticed in the evaluation of abnormal bleeding can only be diagnosed during infertility examination[9]. The probability of their transformation into malignancy is low[10,11].

In the hysteroscopic evaluation, endometrial polyps have been found in up to 25% of women with unexplained infertility[9]. In diagnostic hysteroscopy studies performed before in vitro fertilization (IVF) treatment, the incidence of endometrial polyps in asymptomatic women was reported to be 6-30%[12-14]. The appearance of an incidental polyp during ovarian stimulation in IVF or intracytoplasmic sperm injection (ICSI) treatment cycles can put the clinician in a difficult position. In some retrospective studies, polyps have been associated with recurrent miscarriage and infertility[6,8]. Any structural pathology in the uterine cavities, such as fibroids, polyps, intrauterine adhesions, endometritis, or the presence of reduced endometrial thickness, may lead to low pregnancy rates. It has been suggested that endometrial polyps negatively affect implantation by impairing receptivity. In a case-control study, the levels of HOXA 10 and HOXA 11 mRNA, which are markers of endometrial receptivity, were measured, and a decrease in these marker levels was shown in the presence of endometrial polyps[9].

Endometrial polyps are the most common lesions affecting the endometrial cavity[15]. Endometrial polyps have been proven to interfere with fertility with both natural pregnancy[16-18] and intrauterine insemination[19]. In the presence of endometrial polyps during IVF or ICSI: (i) the cycle can be canceled, and polypectomy can be performed; (ii) the cycle can be continued and the resulting embryos scheduled to be frozen for embryo transfer a few months later; (iii) polyp can be ignored (iv) hysteroscopic polypectomy can be performed without cycle cancelation[20,21]. The variety of these treatment options can confuse assisted reproductive clinicians who aim for better implantation and pregnancy rates.

There are a few studies investigating the effect of endometrial polyps on IVF/ICSI cycles. Isikoglu et al.[1] reported that endometrial polyps smaller than 1.5 cm discovered or before IVF/ICSI cycles do not affect implantation and pregnancy rates. Lass et al.[22] found that polyps smaller than 2 cm did not decrease pregnancy rates, but increased miscarriage rates. Therefore, they argued that freezing all embryos after oocyte retrieval followed by hysteroscopic polypectomy produced better baby-to-home rates, and they suggested the possible functional approach of "losing" a few months. Also studies performed hysteroscopic polypectomy with stimulation before oocyte retrieval without cycle cancelation[20,21]. Our study compares the pregnancy, abortion, and live birth rates of patients who underwent hysteroscopic polyp resection without cycle cancelation during ovarian stimulation with those who underwent polyp resection before stimulation. In this way, the necessity of canceling the cycle due to endometrial polyps, which can be seen frequently in women receiving ICSI treatment, will be questioned.

Materials and Methods

Ethics committee approval was obtained for this study by Haliç University Ethics Committee (2022/48). In this retrospective study, electronic data of 65 women who applied for private examination between 2017 and 2020, whose ICSI processes were performed at Haliç Hospital, and whose all follow-up, treatment, and hysteroscopic operations were performed by a single physician were included in the study. Endometrial polyps seen during controlled ovarian stimulation (COS) protocol in 31 patients were resected using cold scissors with a 2.9 mm 30 degree office hysteroscope (Storz, Germany) under general anesthesia at the latest on the 10th day of the cycle. This group is group 1.

In 34 patients, the endometrial polyp detected at the time of application for treatment was resected hysteroscopically with the same method in the cycle before the start of COS treatment. These patients were in group 2. All patients were 38 years of age or younger, ICSI treatment was applied after ovarian stimulation, and the resulting embryos were cultured until the blastocyst stage. All the patients were patients with a normal response, high response patients at risk of ovarian hyperstimulation syndrome (OHSS), patients with low ovarian reserve or low ovarian response were excluded from the study. The study excluded patients with multiple polyps or polyps larger than 1.5 cm. Additionally, those with a uterine anomaly, those with a known chronic disease, those treated for excessive male factor, spouses of azoospermic men, and patients with endometriosis were excluded from the study. The same COS protocol was applied to all patients. A single blastocyst embryo transfer was performed on the fifth day of the same cycle by providing the same luteal phase support to all of them. The pregnancy test was performed with a serum BhCG test on the 12th day after embryo transfer. Clinical pregnancy was recorded as positive with the detection of fetal cardiac activity in transvaginal ultrasonography at the 6th week. Losses up to the 20th week of pregnancy is considered an abortion. Deliveries occurring toward the 37th week of pregnancy were accepted as the term. The data of all pregnant and non-pregnant patients were recorded electronically, and the follow-up of the data continued until delivery. All patients signed the informed

consent form that they read before starting IVF treatment. Within this form, they accepted and approved the use of their medical data in scientific studies. The primary outcome of our study was to compare abortion and live birth rates between the groups. Secondary outcomes are pregnancy, abortion rates, and embryo implantation rates.

Ovarian Stimulation Protocol

After the gynecological examination and transvaginal ultrasonography performed on the second/third day of menstruation in all patients included in the study, the gonadotropin dose was determined on the basis of age, body mass index (BMI), antral follicle count, basal follicle-stimulating hormone (FSH) value, and ovarian response data obtained in previous trials. For this purpose, subcutaneous injection of recombinant FSH (Gonal F, Merck Serono, Switzerland) started with a maximum of 375 IU. The patients were monitored by transvaginal ultrasonography every 2 days after the first 4 days. When the leading follicle reached 13-14 mm, Cetrotide 0.25 (Merck Serono, Switzerland) added to the treatment as a GnRH antagonist. Hysteroscopic polyp operations of the group 1 patients, whose endometrial polyps were detected during the serial evaluations, were performed until the 10th day of the cycle at the latest. When the leading follicle reached 17-18 mm, recombinant hCG (Ovitrelle, Merck Serono, Switzerland) applied subcutaneously for final maturation, and oocyte retrieval (OPU) was performed 36 h later.

OPU and ICSI and Embryo Transfer Procedures

OPU was performed in all patients with a double-lumen 17G needle in the lithotomy position under sedative anesthesia. After denudation, ICSI was applied to the oocytes retrieved after the procedure after 2-3 hours of incubation. Fertilization was confirmed with the pronucleus control performed after 17 h, and the retrieved embryos were cultured until the 5th day. Fresh, single blastocyst transfer was performed in all patients. Anesthesia was not applied in embryo transfer procedures. All transfers were performed in the lithotomy position with the bladder full, accompanied by abdominal ultrasonography.

Hysteroscopic Polypectomy

The patients were covered with sterile drapes after cleaning the vulva and vagina in the lithotomy position under general anesthesia. The cervical os was visualized by placing the speculum. Without dilating the cervical os, the cavity was entered with a 30-degree optical hysteroscope (Storz, Germany) with a shaft thickness of 2.9 mm. Physiological saline was used for cavity expansion. The polyp in the cavity was cut from the stem using cold scissors, gently taken out of the cavity with the help of forceps and sent for pathological examination. Before the procedure was completed, the presence of other lesions or masses, the presence of septum and tubal ostia were checked to ensure a normal anatomical structure. During this process, care was taken to create the least possible contact with the endometrial tissue and not create trauma.

Luteal Phase Support

Vaginal progesterone (Crinone gel 8%, Merk Serono, Switzerland) twice a day was started in all patients for luteal phase support after the OPU procedure. On the same day, 4 mg estradiol (Estrofem TB, Novo Nordisk, Denmark) was added to the treatment. Luteal phase support was continued until the 9th week of pregnancy.

Statistical Analysis

Based on the data of Fatemi et al.'s study[13], it was decided to take 30 patients for each group with 80% power and 5% margin of error. Demographic data and frequency of clinical findings are presented together with frequency and descriptive statistics. In continuous variables, data were given as a median and interquartile range. Comparisons between groups were made with the Mann-Whitney U test. The chi-square test was used to compare categorical variables between the groups. A value of $p<0.05$ was considered statistically significant. IBM SPSS 25.0 was used for statistical analyzes.

Results

The comparison of baseline values such as age, BMI, basal FSH, and treatment indications of group 1 and group 2 is presented in Table 1. Accordingly, no statistical difference was observed between group 1 and group 2 in baseline values. Stimulation time, total FSH dose, serum estradiol, and progesterone values on hCG day and endometrial thickness value data on hCG day obtained during the COS of all patients are presented in Table 2 comparatively. In the same table, the number of oocytes retrieved in OPU, the number of metaphase 2, and the number of fertilized oocytes after ICSI are also compared. Table 2 shows that these values were not statistically different between the groups. When the clinical results were compared, a single embryo transfer was performed in all patients in both groups. There was no significant difference between the groups regarding embryo implantation rates (p=0.457). Pregnancy test positivity did not show a statistical difference in both groups (p=0.457). The clinical pregnancy rate was 58.1% in group 1 and 55.9% in group 2 (p=0.859). When the abortion rates were evaluated, there was no difference between the groups (p=0.924). While the live birth rate was 51.6% in group 1, it was 50% in group 2, and there was no statistical difference between the groups (p=0.897) (Table 3).

Discussion

Endometrial polyps are one of the most common endometrial pathologies, and they may cause interruption of treatment or change of treatment method in infertile patients treated with assisted reproductive methods. According to the Cochrane database, untreated endometrial polyps have been associated infertility and subfertility[24-26].

Table 1. Baseline values

	Group 1 (n=31)	Group 2 (n=34)	p-value
Age	30.0 (25.0-32.5)	31.0 (26.0-33.0)	0.49*
Basal FSH (IU/L)	7.5 (6.1-8.4)	7.15 (5.77-9.13)	0.98*
BMI (kg/m^2)	26.8 (22.7-28.7)	27.1 (24.0-31.03)	0.49*
Indication % (n)			
Male factor	41.9 (13)	26.5 (9)	0.27**
Tubal factor	19.4 (6)	35.2 (12)	
Unexplained infertility	38.7 (12)	38.2 (13)	

Values are median unless otherwise noted (interquartile range). FSH: Follicle-stimulating hormone, BMI: Body mass index. *Mann-Whitney U test, **Chi-square test

Table 2. COS values

	Group 1 (n=31)	Group 2 (n=34)	p-value*
Stimulation time	9 (9-11)	10 (9-11)	0.37
Total FSH dose (IU/L)	1975 (1612-3100)	2901 (1893.3-3381.3)	0.16
hCG day serum estradiol level (pg/mL)	1775 (1278-2244)	1770.5 (1508.3-2402.3)	0.39
hCG day serum progesterone level (ng/mL)	0.8 (0.6-0.9)	0.8 (0.6-0.9)	0.921
hCG day endometrial thickness (mm)	10.0 (9.4-10.7)	9.9 (9.1-11.9)	0.95
Number of oocytes retrieved	12 (8-15)	11 (8-14)	0.57
metaphase II oocyte number	9 (5-13)	7 (5-11)	0.22
Number of 2 PN fertilized oocytes	7 (4-11)	5 (4-8)	0.37

Values are median unless otherwise noted (interquartile range). COS: Controlled ovarian stimulation, FSH: Follicle-stimulating hormone, hCG: Human chorionic gonadotropin. *Mann-Whitney U test

Table 3. Clinical results

	Group 1 (n=31)	Group 2 (n=34)	p-value
Number of embryos transferred*	1 (1-1)	1 (1-1)	1**
Embryo implantation rate* % (n)	67.7 (21)	58.8 (20)	0.457***
Positive pregnancy test % (n)	67.7 (21)	58.8 (20)	0.457***
Clinical pregnancy % (n)	58.1 (18)	55.9 (19)	0.859***
Abortion %(n)	6.4 (2)	5.8 (2)	0,924***
Live birth % (n)	51.6 (16)	50 (17)	0.897***

*Values are average (interquartile range), **Mann-Whitney U test, ***Chi-square test

Polyps can be associated with infertility, blocking the treatment process and causing a negative process for the patient.

It is thought that polyps prevent implantation by narrowing the available space in the endometrial cavity or by triggering inflammatory processes, or impairing receptivity[9]. Many studies in the literature agree on removing polyps before embryo transfer. Scientific evidence shows that 63% of patients reach pregnancy after removing polyps[24-26].

Again, Cochrane data showed that when the polyps detected incidentally during IVF cycles are removed hysteroscopically after the embryos are frozen, pregnancy success is similar to that in the fresh cycle[23,25,27,28].

Few studies have attempted the removal of polyps during COS and embryo transfer in the same cycle. Among them, Batioglu's study[21] presents a single patient, while Madani et al.'s study[23] includes the analysis of 9 patients. Although the numbers in these studies are insufficient, the results show that polyp removal during COS does not affect the pregnancy rate, as in our study.

Our study shows that hysteroscopic polyp resection during COS in patients scheduled for ICSI treatment does not affect pregnancy, abortion, and live birth rates. While other studies in the literature show similarities that pregnancy rates do not change, the study by Tiras et al.[29] also shows that the optimal timing for polyp resection or before COS does not change live birth rates.

In ART cycles, the cancelation of the cycle for any reason creates emotional stress for the patient and her partner[29]. Although studies show the superiority of frozen embryo treatments, there is no clear consensus on this issue[30,31]. The cost of treatment will increase due to the total unnecessary freezing[32].

A good transvaginal ultrasonographic evaluation in a patient with an endometrial polyp may be sufficient to detect endometrial polyps without the need for an additional imaging method[33]. If the polyp is single and smaller than 1.5 cm, hysteroscopic polyp removal is be an approach that should be considered a good alternative while COS treatment continues. When the patient is informed that pregnancy and live birth rates will not be affected by this procedure, total freezing will only be an approach that should be considered in the presence of hyperstimulation (OHSS) risk and high progesterone values. In this way, the cost of treatment and the patient's emotional stress can be reduced.

Study Limitation

The limitations of the study are that it is retrospective, the number of patients is small, and there is no long follow-up period.

Conclusion

Hysteroscopic resection of polyps during ovarian stimulation in ICSI treatment does not affect pregnancy and live birth rates and may eliminate the necessity of freezing.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for this study by Haliç University Ethics Committee (2022/48).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

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