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Effect of Hysteroscopic Surgery Before Frozen Embryo Transfer on Patients with Previous Implantation Failure

İmplantasyon Başarısızlığı Olan Hastalarda Donmuş Embriyo Transferi Öncesi Histeroskopik Cerrahinin Etkisi

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ABSTRACT

Aim: The aim of this study was to evaluate the benefit of hysteroscopy (HS) before single frozen-thawed embryo transfer (sFET) on patients with previous implantation failure.
Material and Methods: A total of 1352 infertile women with a previous implantation failure who underwent their first sFET treatment between January 2015 and December 2017 were included in this study. The patients were classified into two main groups in which HS was omitted (Group 1), and who underwent HS (Group 2). Furthermore, Group 2 was classified into two subgroups as patients without any intrauterine pathology (Group 2a), and those with intrauterine pathology (Group 2b). sFET was performed on all patients within 50 days of hysteroscopy. The major outcome measure was the clinical pregnancy rate.
Results: The mean number of mature oocytes and fertilization rates were similar between groups. The clinical pregnancy rate was found to be 33.3% (n=70) in Group 1. Comparatively this rate was statistically significantly higher in patients in Group 2. The clinical pregnancy rate was 44.2% (n=378) in Group 2a, and 44.4% (n=127) in Group 2b (p=0.014). There was a significant difference between Group 1 and Group 2a (OR: 1.58, 95% CI: 1.15-2.17, p=0.004), and also Group 2b (OR: 1.59, 95% CI: 1.10-2.31, p=0.013). However, no significant difference was observed between Group 2a and Group 2b (p=0.896).
Conclusion: Our findings demonstrate that HS surgery increases the probability of pregnancy rate at least by 1.58 times in patients having previous implantation failure when the hysteroscopic procedure is followed by sFET.
Keywords: Hysteroscopy; infertility; sFET; blast; implantation failure.

ÖZ

Amaç: Bu çalışmanın amacı, daha önce implantasyon başarısızlığı olan hastalarda tek donmuş çözülmüş embriyo transferi (single frozen-thawed embryo transfer, sFET) öncesi histeroskopinin faydasını değerlendirmektir.
Gereç ve Yöntemler: Bu çalışmaya, Ocak 2015 ile Aralık 2017 tarihleri arasında daha önce bir implantasyon başarısızlığı olan ve ilk kez sFET tedavisi yapılan toplam 1352 infertil kadın dahil edildi. Hastalar HS yapılmayanlar (Grup 1) ve HS uygulananlar (Grup 2) olmak üzere iki ana gruba ayrıldı. Ayrıca, Grup 2, intrauterin patolojisi olmayan hastalar (Grup 2a) ve intrauterin patolojisi olanlar (Grup 2b) olmak üzere iki alt gruba ayrıldı. Tüm hastalara histeroskopi prosedüründen sonraki 50 gün içinde sFET uygulandı. Ana sonuç ölçütü klinik gebelik oranları idi.
Bulgular: Ortalama olgun oosit sayısı ve fertilizasyon oranları gruplar arasında benzerdi. Grup 1'de klinik gebelik oranı %33,3 (n=70) olarak bulundu. Karşılaştırıldığında bu oran Grup 2'deki hastalarda istatistiksel olarak anlamlı şekilde daha yüksekti. Klinik gebelik oranı, Grup 2a'da %44,2 (n=378) ve Grup 2b'de ise %44,4 (n=127) idi (p=0,014). Grup 1 ile Grup 2a arasında (OR: 1,58; %95 GA: 1,15-2,17; p=0,004) ve aynı zamanda Grup 1 ile Grup 2b arasında (OR: 1,59; %95 GA: 1,10-2,31; p=0,013) istatistiksel olarak anlamlı fark vardı. Ancak Grup 2a ve Grup 2b arasında anlamlı bir fark gözlenmedi (p=0,896).
Sonuç: Bulgularımız, histeroskopik prosedürü sFET ile takip edildiğinde, daha önce implantasyon başarısızlığı olan hastalarda HS cerrahisinin gebelik olasılığını en az 1,58 kat artırdığını göstermektedir.
Anahtar kelimeler: Histeroskopi; infertilite; sFET; blast; implantasyon başarısızlığı.

INTRODUCTION

Hysteroscopy (HS) is a surgical procedure for diagnosing and simultaneously treating intrauterine pathologies. In order to increase pregnancy rates, HS can be utilized either before the embryo transfer or after a failed embryo transfer attempt. Recent advances in reproductive medicine have propagated higher pregnancy rates, however, many women still suffer from recurrent implantation failure (1). For these individuals, treatment approaches vary according to the patient and the individual clinical protocols. Many factors may contribute to implantation failure such as endometrial receptivity disorders, low embryo quality, intrauterine pathologies, anatomical uterine abnormalities, thrombophilias, endometritis, male and female reproductive cell problems, and immunological and chromosomal anomalies (2,3). When we evaluate these causes, it is important to choose the most appropriate action; in order to lower the economic costs and increase the success of future treatments. Currently, 2D transvaginal ultrasonography (2D-TVUSG) and hysterosalpingography (HSG) are recommended as first-line management steps in the detection of intrauterine pathologies (4). However, HS is the gold standard for the assessment of the uterine cavity. It provides an opportunity for concomitant treatment of intrauterine pathologies (5). In patients with recurrent in vitro fertilization (IVF) failure, intrauterine pathology has been identified in 25-50% of cases (6). Furthermore; published studies have reported that office HS including endometrial scratching (ES) increases pregnancy success while other randomized controlled studies have not found a beneficial effect of local endometrial injury before IVF (7-9).

There is a Cochrane review published in 2019 (10). One of the key results of this Cochrane review is that in women undergoing IVF, performing an HS first, improved the chances of live birth or clinical pregnancy (10). We conducted this study, prior to the publication of this review and we wanted to evaluate the effectiveness of HS before the second embryo transfer in order to increase pregnancy rates. The aim of this study was to evaluate the effectiveness of HS in increasing pregnancy rates before single frozen-thawed embryo transfer (sFET) in patients with previous implantation failure.

MATERIAL AND METHODS

Study Groups

This is a retrospective study conducted between January 2015 and December 2017 at Private Prof. Dr. Mehmet Turan Çetin IVF Center. During this period, 2012 patients underwent their first sFET treatment. Among these, 1430 who had first implantation failure were evaluated. Seventy-eight patients who were lost to follow-up were excluded. A total of 1352 infertile women were included in the study. The patients were classified into two groups: Group 1 consisted of 210 patients who did not undergo HS and group 2 consisted of 1142 patients who underwent HS. Group 2 was further classified into 2 subgroups: Group 2a consisted of 856 patients without any diagnosed intrauterine pathology. In Group 2a bilateral vertical incision was performed on the lateral walls of the uterus during HS until tubal ostiums were observed. Group 2b consisted of 286 patients with intrauterine pathology diagnosed and/or treated during HS (Figure 1).

Most patients had normal findings on 2D-TVUSG and HSG with the exception of 48 patients who had an arcuate uterus and 32 patients with uterine subseptus. After giving detailed information about the potential benefits of HS, all patients with subseptus and arcuate uterus and no suspicion of uterine pathology decided to undergo HS. The rest proceeded directly to the second transfer treatment. HS was performed within 50 days before the beginning of the second sFET treatment.

Endometrial polyps, filmy adhesions, chronic endometritis, and arcuate and subseptate uterus were considered as intrauterine pathologies. Operative intervention was performed when pathology was detected. Chronic endometritis was suspected by the appearance of the endometrial lining, the presence of stromal edema, focal or diffuse periglandular hyperemia, and micropolyps of <1 mm in size as described previously (11). Endometritis diagnosis was confirmed by histological examination of the punch biopsies taken during the procedure, using hysteroscopic instruments. When chronic endometritis was diagnosed, patients were treated with estrogen and progesterone for 21 days together with 14 days of doxycycline 100 mg twice daily before the initiation of the second sFET cycle.

Hysteroscopy Procedure

Outpatient HS was done in the early follicular phase of the cycle (cycle days 6-11) under intravenous sedation with midazolam. The operating device was a 5 mm office hysteroscope with a 30-degree angle and 1.5 mm operative channel (Bettocchi Office Hysteroscope, Karl Storz GmbH & Co Tuttlingen, Germany). Uterine distention was performed with 0.9% normal saline using an electronic

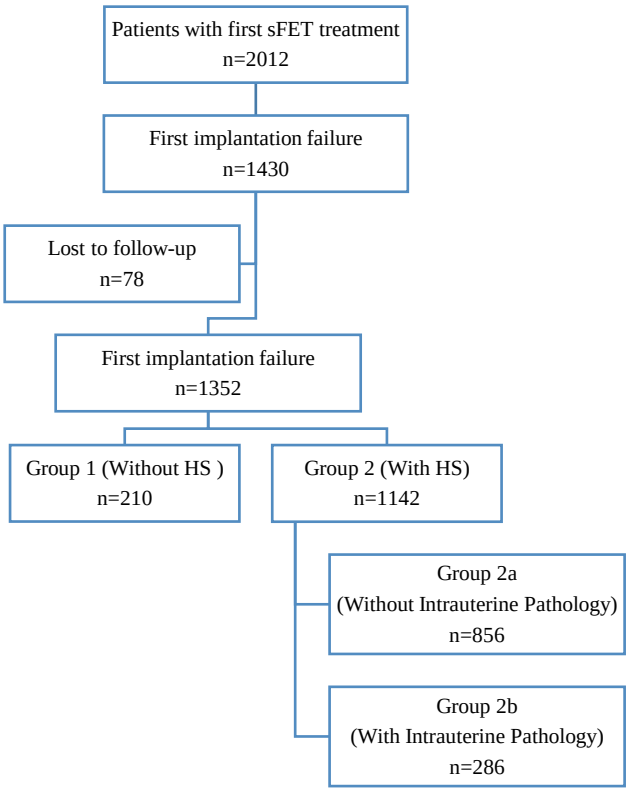

Figure 1. Flow chart of the study

pump (Hysteromat, Karl Storz GmbH & Co Tuttlingen, Germany). Uterine cavity pressure during the operation was between 80-100 mmHg. Standard gynecologic surgical procedures were used to treat the recognized pathologies. Scissors were used for filmy adhesiolysis. Grasping forceps and Twizzle tip of Versapoint bipolar electrosurgical system (Versapoint Electro-Surgical System; Gynecare Inc, Menlo Park, CA, USA) were used for the removal of polyps and for the incision of the arcuate uterus and uterine subseptum. A highly experienced single physician (MTÇ) performed all the procedures and each procedure was digitally recorded. If no pathology was detected during the procedure, a vertical incision was made on the lateral uterine walls until the internal os by Twizzle tip of Versapoint.

ICSI-sFET Protocol

An antagonist protocol with follitropin alfa (GONAL-f, Merck, Germany) and cetrorelix (Cetrotide, Merck, Germany) were used in all of the patients for ovulation stimulation. Vitrification was used for the cryopreservation of all embryos. Endometrium was prepared with estradiol (Estrofem, Novo Nordisk) 2 mg orally, 3 times a day starting from day 3 of the menstrual cycle. Patients who had an endometrial thickness of more than 8 mm started to receive vaginal progesterone (Crinone vaginal gel, Merck Serono) twice a day (days 17-20) for 6 days. All cycles were frozen-thawed cycles. Day 5 single frozen-thawed grade 1 quality embryo transfers were performed on days 17-20 of menstruation. After the transfer, estrogen and progesterone administration was continued for 12 days until the beta-hCG test. If the beta-hCG test was positive, treatments were continued until the 10^{th} week of pregnancy. Clinical pregnancy was defined as the visualization of an intrauterine fetus plus fetal heart activity with TVUSG at 7 weeks of pregnancy.

Ethical committee approval was obtained from the Ethics Committee of Çukurova University (Report no: 76/26 date: 13.04.2018) and all subjects provided informed consent for the utilization of their clinical data.

Statistical Analysis

The descriptive statistics of the qualitative variables in the study were given as numbers and percentages, and the descriptive statistics of the quantitative variables were given as mean and standard deviation. Relationships between qualitative variables were examined by Pearson chi-square analysis. In post hoc evaluations, Bonferroni corrections were made and group differences were determined in detail. The conformity of the quantitative variables to the normal distribution was examined with the Kolmogorov-Smirnov test. An independent sample t-test was used to compare the mean of quantitative variables. A one-way analysis of variance was used to compare the mean of more than two groups. Tukey test was used as a post hoc test in pairwise comparisons of the groups with differences. The level of statistical significance was defined as $p<0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0.

RESULTS

There were 1352 patients with one failed implantation. Among these, 210 (15.5%) of the participants did not undergo HS (Group 1), and the other 1142 (84.5%) underwent HS (Group 2a+Group 2b). The mean age of the patients in groups 1, 2a, and 2b were 33.02±4.40, 32.51±4.90, and 33.01±4.12 years, retrospectively. The duration of infertility and causes of infertility were demonstrated in Table 1. There were no statistically significant differences between the groups with regard to demographics, infertility etiology, or duration of infertility. Following HS surgery, 25% (n=286) of the patients in Group 2 were discovered to have an intrauterine pathology (Group 2b), which was surgically or medically treated. The most frequently diagnosed intrauterine pathology was a single endometrial polyp at 8.1% (n=93). The median polyp size was 7 mm (range, 5-10 mm). Chronic endometritis was diagnosed in 5.3% (n=61) of patients. There were 5.8% (n=66) patients with an arcuate uterus and 2.8% (n=32) uterine subseptum (Table 2). No complications occurred during any procedure.

The mean number of mature oocytes, fertilization rates, and sFET quality were similar between groups (Table 3). There was a significant difference in clinical pregnancy rate between the three groups (p=0.014). The clinical pregnancy rate was found to be 33.3% (n=70) in patients without HS (Group 1), 44.2% (n=378) in patients without intrauterine pathology (Group 2a), and 44.4% (n=127) in patients with intrauterine pathology (Group 2b). When subgroup analysis was performed, a statistically significant difference was found between Group 1 and Group 2a (OR: 1.58, 95% CI: 1.15-2.17, p=0.004), and also Group 2b (OR: 1.59, 95% CI: 1.10-2.31, p=0.013). However, no significant difference was observed between Group 2a and Group 2b (p=0.896).

Table 2. Findings of hysteroscopy (n=1142)

Without Intrauterine Pathology, n (%)	**856 (75)**
With Intrauterine Pathology, n (%)	**286 (25)**
Endometrial polyp	93 (8.1)
Uterus arcuatus	66 (5.8)
Endometritis	61 (5.3)
Filmy Adhesions	34 (3.0)
Uterine subseptum	32 (2.8)

Table 1. Clinical characteristics and infertility causes of patients

	Group 1 (n=210)	Group 2a (n=856)	Group 2b (n=286)	p
Age (years), mean±SD	33.02±4.40	32.51±4.90	33.01±4.12	0.160
Duration of infertility (years), mean±SD	5.15±0.92	5.30±0.97	5.20±0.95	0.070
Causes of infertility, n (%)				
Male	63 (30.0)	274 (32.0)	89 (31.1)	
Tubal-Ovulatory	59 (28.1)	248 (29.0)	77 (26.9)	0.874
Unexplained	88 (41.9)	334 (39.0)	120 (42.0)	

Group 1: without hysteroscopy, Group 2a: hysteroscopy without intrauterine pathology, Group 2b: hysteroscopy with intrauterine pathology, SD: standard deviation

Table 3. Results of intracytoplasmic sperm injection-embryo transfer cycle and clinical pregnancy rates

	Group 1 (n=210)	Group 2a (n=856)	Group 2b (n=286)	p
Number of mature oocytes, mean±SD	7.9±1.3	8.0±2.0	7.5±1.5	0.278
Fertilization rate, n (%)	149 (70.9)	645 (75.4)	210 (73.4)	0.653
Clinical pregnancy rate, n (%)*	70 (33.3)	378 (44.2)	127 (44.4)	**0.014**

Group 1: without hysteroscopy, Group 2a: hysteroscopy without intrauterine pathology, Group 2b: hysteroscopy with intrauterine pathology, SD: standard deviation

DISCUSSION

The major finding in this study was that HS increased the probability of pregnancy rate at least by 1.58 times in patients with or without intrauterine pathology. In the literature, when HS was performed in asymptomatic patients in whom no intrauterine pathology was detected with 2D-TVUSG and/ or HSG, intrauterine pathologies were identified in 11-22.9% of the cases (12,13). Even higher rates (51.2%) were reported in patients with previous IVF failure (14). The most important causes of implantation failure are poor embryo quality, problems with embryo transfer techniques, and chromosomal and intrauterine pathologies. The first step during infertility evaluation for intrauterine pathology is 2D-TVUSG in many centers. However, the gold standard for the detection of intrauterine pathology is HS. HSG has a lower positive predictive value (PPV) and specificity than HS for intrauterine pathology (5). In a study with routine HS before IVF 26% of patients were shown to have common intrauterine pathologies including endometrial polyp, arcuate and subseptus uterus (15,16). In this study, intrauterine pathology was detected in 286 (25%) patients. Therefore we can strongly argue that HS is of upmost importance prior to IVF trials. In this study, a vertical incision was performed to the sidewalls of the uterus. A vertical incision was preferred because we wanted to avoid intrauterine adhesions and we did not want to decrease the chances of embryo implantation.

The most common hysteroscopic pathology in this study group was endometrial polyps in 8.1% (n=93) of the cases. We demonstrated improved clinical pregnancy rates after the polyp resection, which is consistent with prior literature (17). In addition, the pregnancy rate was increased by 10% with the HS procedure in patients with or without intrauterine pathology. Hysteroscopic injury may also increase the pregnancy rate, even in cases with a normal uterine cavity (18). Likewise, we performed vertical incisions on 856 patients who had no intrauterine pathology (Group 2a). When subgroup analysis was performed, there was a statistically significant difference between Group 1 and Group 2a. Several explanations have been suggested to explore the benefit of HS in patients without any intrauterine pathology (19). First, washing of the cavity with saline may provide mechanical cleaning and removal of harmful anti-adhesive glycoprotein molecules on the endometrial surface (20). Second, office HS can aid the clinician as "try-on transfer" and improve the results of easy embryo transfer. In addition to all the aforementioned mechanisms, endometrial injury (EI) may induce a change in the endometrial ultrastructure by the following mechanisms: i) facilitating regulation of the inflammatory reactions of macrophages, ii) decidualization and preparation of the endometrium to receive the transferred embryo (21,22). In a meta-analysis, it was reported that EI intervention is 70% more likely to achieve clinical pregnancy compared to no intervention (23). Nastri et al. (24) reported that if 30% of women become pregnant without EI, 33-48% will conceive if the hysteroscopic intervention takes place. On the other hand, anti-biotherapy was used in all HS groups in the present study. This may also have added accessive benefits by healing undiagnosed endometritis of uterobiata. Cicinelli et al. (25) demonstrated that women who received adequate antibiotic treatment for endometritis had a significantly higher rate of successful pregnancy compared with women who were not treated with persistent disease. In a randomized controlled study involving 171 patients, Ben Abid et al. (26) compared the groups who underwent HS before the first IVF with those who did not. The authors did not detect a statistically significant difference between the groups in pregnancy rate and live birth rate (LBR) at 12-month follow-up. In a retrospective cohort study by Eserol et al. (27) in which 765 patients were included, it was shown that performing HS before IVF had no effect on pregnancy rates in both groups who underwent fresh cycle and FET cycle.

There is still controversy about the efficacy and the optimal timing of HS in sFET cycles. In this study, a consecutive approach was preferred. Although a systematic review and meta-analysis showed that HS prior to the first IVF cycle may improve treatment outcomes, some prospective randomized studies concluded that it does not improve the results (12,18,28). The TROPHY study, a multicenter, randomized controlled trial reported that, especially for women with recurrent, unsuccessful implantation following IVF, HS had no effect on the LBR (16). However, this contrasts with the results of a prior systematic review suggesting that routine HS improved the LBR for women with recurrent unsuccessful IVF cycles (29). The problem with large multicenter trials such as the TROPHY or SCRATCH trial is that the techniques are not consistent and the laboratory performance of embryologists differ. Consequently, multicenter trial results should be interpreted with caution. Marking our point in a single-center randomized controlled trial Gurgan et al. (18) showed that endometrial injury is beneficial in recurrent implantation failure. In conclusion, consistent with prior other studies, we demonstrated that HS with a 5 mm office hysteroscope can be done with sedation in the office environment for diagnostic and operative procedures utilizing electrosurgery in experienced hands with no complications.

Strengths and Limitations

The major limitation of this study was the retrospective design. The strengths of this study were embryo transfer was with a frozen-thawed single blast in all cases, and

there was a large sample size. Additionally, all the hysteroscopies were performed by a single, experienced surgeon.

CONCLUSION

HS after the first failed embryo transfer may improve the pregnancy rates regardless of intrauterine pathology. In conclusion, our findings clearly show that HS surgery increases the probability of pregnancy rate at least by 1.58 times compared to the cases when hysteroscopic surgery was omitted.

Ethics Committee Approval: The study was approved by the Non-invasive Clinical Research Ethics Committee of Çukurova University (13.04.2018, 76/26).

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