



The Value of Hysteroscopy before the First IVF/ICSI Treatment Cycle in Patients with Endometrial Polyp

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Abstract

Objective: To evaluate the value of hysteroscopy in patients with endometrial polyp(s) before starting the first IVF/ICSI treatment.

Materials and Methods: A total of 141 infertile women were divided into 2 groups according to whether they had already had IVF/ICSI treatment before hysteroscopy. 78 patients in group I didn't have IVF/ICSI Embryo Transfer (ET) before hysteroscopic removal of polyps while another 63 patients group II already had IVF/ICSI ET at least once. General information and pregnancy outcomes were compared and studied retrospectively.

Results: In group I, more oocytes were retrieved (13.46 ± 6.48 vs. 10.63 ± 4.72 ; $P < 0.05$) and more embryos were cryopreserved (4.38 ± 4.05 vs. 3.06 ± 2.63 ; $P < 0.05$), with statistical significance. Both clinical pregnancy rate (87.2% vs. 71.4%; $P < 0.05$) and ongoing pregnancy (73.1% vs. 55.6%, $P < 0.05$) rate in group I were significantly higher than group II.

Conclusion: EPs do have some negative effects on pregnancy and hysteroscopic removal of polyps before starting the first IVF/ICSI treatment could help relieve some unnecessary burdens of recurrent failure caused by IVF/ICSI ET.

Keywords: Endometrial polyps; Hysteroscopy; Infertility; TCRP; First cycle

Introduction

Endometrial Polyps (EP) is a mass in the inner lining of the uterus presented with the symptoms of irregular menstrual bleeding such as menorrhagia, menostaxis and menstrual disorder. Besides, young patients are often complicated with infertility. It has been reported that the incidence rate of EP in infertile females was about 14.89% [1]. In recent years, with the rapid development of hysteroscopy, the detection rate of EP has been greatly improved [2]. However, Check JH et al. [3] indicated that EP actually had no influence on pregnancy rate [4]. Thus, whether hysteroscopy should be recommended as a routine examination in patients with EP and infertility still remains to be discussed. The aim of this prospective study was to evaluate clinical and ongoing pregnancy rate in patients who had already underwent IVF/ICSI Embryo Transfer (ET) before Transcervical of Endometrial Polyps Resection (TCRP) with those who had never had IVF/ICSI ET. After removing of the polyps, IVF/ICSI ET or frozen Embryo Transfer was followed a few months later.

Materials and Methods

Study objects

141 patients diagnosed with infertility and endometrial polyp(s) receiving IVF/ICSI Embryo Transfer treatment from June 2016 to June 2017 were analyzed prospectively in the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. 78 patients (Group I) didn't have IVF/ICSI Embryo Transfer before TCRP while another 63 patients (Group II) already had IVF/ICSI ET at least once. This study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (Ethic Reference No: L-2018-08). All patients completed informed written consent in accordance with the ethics committee protocol.

Inclusive criteria: 1) married women 2) Premenopausal women between the ages of 25 and 42 years. 3) Had regular unprotected intercourse and failed to get pregnant for over 1 year 4) Infertile women diagnosed with EP under hysteroscopy complicated with tubal infertility, unexplained infertility or with partners diagnosed with male factor infertility, eligible for IVF and/or Intra Cytoplasmic Sperm Injection (ICSI) using fresh or frozen ejaculated sperm from male partner

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5) Removal of EP once detected and confirmed by pathological examination 6) Negative serum hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus antibody tests within 2 years.

Exclusive criteria: 1) Combined with other diseases in uterus cavity such as intrauterine adhesion, submucous myoma, uterus septum or related malformation 2) Combined with endometriosis or ovarian tumor 3) abnormality of basal hormone level 4) Any known clinically significant systemic disease (e.g., insulin-dependent diabetes).

Method

Hysteroscopy: All patients were admitted in gynecological minimal invasive center in our hospital. Rigid hysteroscope produced by Olympus Corporation was used during the operation. Surgical procedure: 1) Patients were placed in the dorsal lithotomy position after voiding the bladder. 2) General anaesthesia was administered and anaesthetic depth was in no consciousness and no feeling when dilated cervix. 3) Thoroughly assess uterine cavity under hysteroscopy. 4) Remove EP for pathological examination.

Ovulation induction protocol: All the patients were given subcutaneous injection of 3.75 mg GnRH-a (Leuprorelin Acetate Microspheres for injection, a product of Livzon Pharmaceutical Group Inc.) on the first or second days of menstruation cycle and were informed about the potential effects of GnRH-a, including vaginal dryness, depression, hot flushes, and slight but reversible bone loss. Successful pituitary down-regulation was confirmed via finding: no antral follicles large than 8 mm, E2<50 pg/ml, serum LH levels less than 5 IU/L and the thickness of endometrium less than 5 mm. Patients who meet this criterion started ovarian stimulation with human menopausal gonadotropin (HMG, Menotropin, a product of Shandong Baxter Beauty Medical Equipment Co., Ltd.) of 75 IU to 300 IU daily for the first several days. The dose could be adjusted according to individual follicular response, patient's age and BMI. Triggering of final follicular maturation was performed with Chorionic Gonadotrophin for Injection (HCG, a product of Livzon Pharmaceutical Group Inc.) when at least two follicles reached diameters of 17 mm or one dominant follicle reached 18 mm. Oocytes were retrieved 34 h to 36 h after triggering of final follicular maturation. No more than two embryos were transferred into the uterine cavity 3 to 5 days after oocyte pickup. Extra embryos remaining after the Embryo Transfer may be cryopreserved (frozen) for future transfer. When endometrial thickness is less than 8 mm, Embryo Transfer should not be considered in this cycle. The luteal phase support was started on the day of Embryo Transfer by intramuscular progesterone and hypodermic heparin sodium daily for two weeks.

Definition of pregnancy: Clinical pregnancy was defined as the presence of a gestational sac with fetal heart activity under ultrasound examination 4 weeks after ET. The pregnancy that can only be detected by a urine or blood test and cannot be seen on an ultrasound is called biochemical pregnancy. Ongoing pregnancy can be diagnosed when the gestational age is over 12 weeks with at least one embryonic heartbeat. The termination of a pregnancy before 28th week of gestation is diagnosed as abortion.

Appraised goals

The primary assessments for this study were clinical pregnancy rate and ongoing pregnancy rate. The secondary assessments included

Table 1: The comparison of general information.

| | I | II | P |
|------------------------------|---------------|---------------|-------|
| Age (y) | 32.89 ± 4.34 | 31.99 ± 3.90 | 0.203 |
| Duration of infertility (y) | 4.23 ± 3.54 | 4.21 ± 3.15 | 0.966 |
| BMI (kg/m ²) | 21.84 ± 3.16 | 21.66 ± 3.40 | 0.741 |
| Previous IVF failures, n (%) | 0 | 2.63 ± 0.90 | 0 |
| AFC | 13.64 ± 5.48 | 12.94 ± 7.56 | 0.537 |
| Fasting glucose level | 5.08 ± 0.46 | 4.96 ± 0.40 | 0.124 |
| TSH level | 2.10 ± 1.15 | 2.35 ± 1.62 | 0.274 |
| Basal hormone level | | | |
| LH (IU/L) | 3.79 ± 2.90 | 3.15 ± 2.34 | 0.163 |
| E2 (pg/mL) | 46.17 ± 14.52 | 47.21 ± 12.25 | 0.647 |
| P(ng/ml) | 0.82 ± 1.44 | 0.60 ± 0.34 | 0.181 |
| FSH(IU/L) | 6.24 ± 2.00 | 6.94 ± 3.64 | 0.175 |
| Primary infertility, n (%) | 39 (50.0) | 30 (48) | 0.78 |

the number of retrieved oocytes and frozen embryos, hormone levels (LH, E2) on triggering day, Gn duration, Gn dose, HCG dose and endometrial thickness on transfer day.

Statistical methods

SPSS20.0 software was used for all statistical analysis in the study. Results were presented as mean ± standard deviation or percentage (%). Measured data were compared with analysis of variance. Enumeration data were performed with chi-square test. P<0.05 was considered statistically significant.

Results

General information

141 patients aging from 24 years to 42 years were divided into two groups. 78 patients in group I had not had IVF/ICSI ET before hysteroscopic removal of polyps while another 63 patients group II already had IVF/ICSI ET at least once (2.63 ± 0.90) before hysteroscopic operation. The general information of the patients in the study is shown in Table 1. Patient age, duration of infertility, Body Mass Index (BMI), fasting glucose level, Thyroid Stimulating Hormone (TSH) level, basal levels of LH, E2, P and FSH, and the percentage of primary infertility were comparable between the two groups.

Ovulation induction

The comparison of ovulation induction between two groups was shown in Table 2. The mean Gn duration and Gn dose had no statistical significance between the two groups. The number of oocytes retrieved (13.46 ± 6.48 vs. 10.63 ± 4.72; P<0.05) and cryopreserved embryos (4.38 ± 4.05 vs. 3.06 ± 2.63; P<0.05) in the group I was significantly higher than in group II. The LH level on trigger day in group I was slightly higher but did not reach significant difference compared with the group II (0.71 ± 0.54 vs. 0.66 ± 0.63 IU/L; P>0.05) while the E2 level in group I was significantly higher than those in the group II (2281.77 ± 1109.67 vs. 1654.59 ± 986.89 pmol/L; P<0.05), which indicated a significant lower dose of HCG in the former group (6987.18 ± 2586.14 vs. 7894.13 ± 3016.7 IU; P<0.05). Also, although the endometrial thickness on Embryo Transfer day in both groups had reached the standard thickness (≥ 8 mm) for embryo transfer, group I had a significantly thicker endometrial thickness compared with group II (11.43 ± 2.19 vs. 10.5 ± 2.23 mm; P<0.05),

Table 2: The comparison of ovulation induction.

| | I | II | P |
|--------------------------------------|-------------------|-------------------|-------|
| Gn duration (d) | 11.83 ± 2.80 | 11.24 ± 3.13 | 0.236 |
| Gn dose (IU) | 2452.91 ± 1059.00 | 2316.27 ± 1043.55 | 0.445 |
| Oocytes retrieved (n) | 13.46 ± 6.48 | 10.63 ± 4.72 | 0.004 |
| All cryopreserved embryos(n) | 4.38 ± 4.05 | 3.06 ± 2.63 | 0.021 |
| hormone levels on trigger day | | | |
| LH(IU/L) | 0.71 ± 0.54 | 0.66 ± 0.63 | 0.57 |
| E2(pg/mL) | 2281.77 ± 1109.7 | 1654.59 ± 986.9 | 0.001 |
| HCG dose | 6987.18 ± 2586.1 | 7894.13 ± 3016.7 | 0.036 |
| Endometrial thickness (mm) | 11.43 ± 2.19 | 10.5 ± 2.23 | 0.028 |

Table 3: The comparison of pregnancy outcomes.

| | 1 | 2 | P |
|---|--------------|--------------|-------|
| Patients (n) | 78 | 63 | |
| Pregnancy outcome (%) | | | |
| Biochemical pregnancy rate | 6/78 (7.7) | 4/63 (6.3) | 0.759 |
| Clinical pregnancy rate per transfer | 68/78 (87.2) | 45/63 (71.4) | 0.024 |
| Ongoing pregnant rate | 57/78 (73.1) | 35/63 (55.6) | 0.032 |

which might provide a better endometrial environment for embryo transplantation.

Pregnancy outcomes

The pregnancy outcomes were presented in Table 3. Both clinical pregnancy rate (87.2% vs.71.4%; $P<0.05$) and ongoing pregnancy rate (73.1% vs. 55.6%, $P<0.05$) in group I were comparatively higher than in group II, with statistical significance. Although biochemical pregnancy rate in group I was slightly higher than group II, no statistical significance could be found between two groups (7.7% vs. 6.3%; $P>0.05$).

Discussion

EP is localized overgrowth of uterine mucosa leading to abnormal uterine bleeding. Inflammation and abnormal hormone levels, especially high estrogen levels are considered risk factors of EP. How polyps contribute to infertility is still uncertain and possible mechanisms are poorly understood. It may be related to the risk of jeopardizing implantation due to endometrial bleeding, mechanical interference with sperm transport, embryo implantation or through intrauterine inflammation or altered production of endometrial receptivity factors [3]. Usually, no positive results could be found in a normal gynecological examination and, hence, EP is apt to be misdiagnosed as dysfunctional uterine bleeding. Transvaginal sonography is a diagnostic method most commonly employed nowadays while hysteroscopy still remains the gold standard for diagnosis since there could be false positive results ultrasonographically [5]. EPs have the lowest incidence of malignant transformation as compared to colon, urinary bladder, oropharyngeal, nasal and laryngeal carcinomas [6]. Malignant change rate of EP in childbearing age was only 4.18% while in postmenopausal women; the malignant rate could increase to 10.10% [7]. Early polypectomy could not only promote fertility but also decrease malignant change rate. Previous treatment for EPs including dilation and curettage (D&C), with the disadvantage of operative blindness and high recurrence rate, has been gradually abandoned clinically. Due to the possible effect of EP on fertility,

TCRP prior to IVF/ICSI ET is widely practiced in people who suffer from infertility over 1 year. Currently, there is evidence showing that performing hysteroscopy before IVF treatment could increase pregnancy rate in the subsequent IVF cycle in women who had failed IVF cycles at least once [8]. However, the routine use of hysteroscopy prior to starting the first IVF treatment cycle has not been widely recommended and there is no robust evidence to support it since the procedure has risks of bleeding, uterine perforation, and infection together with associated anaesthetic risks [9,10]. Some studies [3,11] suggested EP actually had no negative influence on pregnancy rate and they tend to start IVF/ICSI treatment despite the existence of EP. Only after several pregnancy failures will they consider hysteroscopy for further treatment, which could add both economic burdens as well as psychological burdens to infertile families.

In this study, more oocytes were retrieved and more embryos were cryopreserved in group I. E2 levels on trigger day in group I were also significantly higher than those in group II, which indicated a lower dose of HCG in the former group. Thus, it could be inferred that increased cycles may reduce ovarian response to superovulation in some way. Endometrial Thickness on ET day is one of the most crucial factors for successful pregnancy in ART and endometrial thickness <8 mm is considered an unfavorable factor [12,13]. Although the average endometrial thickness is over 8 mm in both groups, the patients in group I had a slightly thicker endometrium than in group II, with significant difference. Furthermore, the ovulation induction protocol we chosen in this study was mostly applied in our center, with a clinical pregnancy rate of over 70% in all groups of infertile female patients.

In conclusion, TCRP before the first cycle of IVF/ICSI ET seems to be a more feasible method compared with IVF/ICSI ET regardless of EPs, which could mitigate patients' burden when confronted with several pregnancy failures. In this study, there are still some limitations, including the method of regression analysis, limited samples and remained cryopreserved embryos that are left to be transferred. In addition, a majority of the patients are still in the process of pregnancy. Thus, the complete information of live birth rate cannot be obtained. Next, enlargement of sample size, further follow-up study about pregnancy outcomes, refined experimental design, control for potential confounding factors are needed to substantiate the effectiveness of the hysteroscopic removal of EPs in infertile women prior to IVF or ICSI.

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This study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (Ethic Reference No: L-2018-08). All patients completed informed written consent in accordance with the ethics committee protocol.

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