Short-term copper intrauterine device placement improves the implantation and pregnancy rates in women with repeated implantation failure

Xiaoyan Mao, M.D., Jie Zhang, M.D., Qiuju Chen, Ph.D., Yanping Kuang, M.D., and Shaozhen Zhang, M.S.

Department of Assisted Reproduction, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China

Objective: To study if hysteroscopy and short-term copper intrauterine device placement (Cu-IUD) improves the pregnancy rates of women with repeated implantation failure (RIF) undergoing frozen-thawed embryo transfer (FET).
Design: Retrospective study.
Setting: Medical university hospital.
Patient(s): Infertile women with at least two implantation failures with the use of at least one good-quality embryo.
Intervention(s): All patients received operative hysteroscopy in the follicular cycle, and if endometrial polyps, polypoid endometrium, or intrauterine adhesions were found they were removed. In some patients, a Cu-IUD was inserted immediately after hysteroscopy and removed after two menstrual periods before embryo implantation. All patients underwent in vitro fertilization or intracytoplasmic sperm injection and FET.
Main Outcome Measure(s): Clinical pregnancy and implantation rates.
Result(s): A total of 440 women with a mean age of 33.42 ± 4.45 years (range 23–47 y) were included. There were 382 patients (554 cycles) in the IUD group and 58 patients (87 cycles) in the non-IUD group. The two groups were similar regarding age, body mass index, and infertility factors. The IUD group had a significantly higher implantation rate (29.29% vs. 16.56%), chemical pregnancy rate (53.25 vs. 41.38%), and clinical pregnancy rate (45.13% vs. 26.44%) than the non-IUD group. Multivariable regression analysis indicated that the odds of a chemical pregnancy was significantly increased with IUD usage.
Conclusion(s): Cu-IUD placement for two menstrual cycles at the time of hysteroscopy can improve the implantation and pregnancy rates in women with RIF. (Fertil Steril® 2017;108:55–61. ©2017 by American Society for Reproductive Medicine.)
Key Words: IUD, hysteroscopy, repeated implantation failure

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Repeated implantation failure (RIF; defined as at least two implantation failures with the use of at least one good-quality embryo) remains a significant challenge in patients undergoing assisted reproductive technology (ART) procedures (1, 2). Many different methods have been used to overcome this problem, including increasing the oocyte number and quality, assisted hatching and preimplantation genetic screening to correct embryonic factors, the use of regulatory T cells to regulate maternal-fetal immunotolerance, introduction of maternal peripheral blood monocytes into the uterine cavity to encourage endometrial decidualization and maternal-fetal immunotolerance, endometrial injury to improve poor endometrial response, and Chinese herbal medicine and acupuncture (3). Of all the methods examined, some studies have shown that hysteroscopy can improve pregnancy rates in women with RIF with or without uterine abnormalities (4, 5).

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Reprint requests: Shaozhen Zhang, M.S., Department of Assisted Reproduction, Shanghai Ninth People's Hospital, Zhizaoju Road No. 639, Huangpu District, Shanghai 200011, People's Republic of China (E-mail: 15001867500@163.com).

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Hysteroscopy is a safe minimally invasive technique that can provide a view of the morphology of the uterine cavity. Hysteroscopy can be used to obtain specimens for pathologic examination, and has become the criterion standard for diagnosis of pathologies of the uterine cavity. Studies of hysteroscopy have shown that 25%–50% of patients with RIF have abnormalities of the uterine cavity, such as chronic endometritis, endometrial polyps or polypoid endometrium, and intrauterine adhesions, which can directly affect the success rate of in vitro fertilization and embryo transfer (IVF-ET), and that treatment of these pathologies can increase the success rate (1). Furthermore, a multicenter randomized controlled study of pre-IVF outpatient hysteroscopy in women with recurrent IVF implantation failure found that even if hysteroscopy does not find any abnormalities, the clinical pregnancy rate after a further round of IVF-ET is significantly higher than in the case of patients who had not received hysteroscopy (6). For these reasons, many scholars recommend that RIF patients undergo hysteroscopy.

Although the reasons why hysteroscopy can improve pregnancy rates is not entirely clear, studies suggest that the procedure induces the production of proinflammatory factors in the endometrium, and thus influences embryo adhesion and implantation (7–10). A murine study has shown that the implantation of a copper intrauterine device (Cu-IUD) altered the inflammatory cytokine profile of the endometrium (11).

Therefore, the purpose of the present study was to determine if short-term placement of an IUD would improve the pregnancy rates in women with RIF undergoing hysteroscopy.

MATERIALS AND METHODS

Patients

This study was approved by the hospital Ethics Committee, and because of the retrospective nature requirement of informed consent was waived.

The records of patients receiving care for infertility with RIF in 2014 at the Department of Assisted Reproduction of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine (Shanghai, People's Republic of China) were retrospectively reviewed. RIF was defined as at least two implantation failures with the use of at least one good-quality embryo. Patients with severe intrauterine adhesions (American Fertility Society score ≥ 5), uterine malformations, endometrial lesions, and hysteroscopy surgery history were excluded. All patients included in the study received hysteroscopy, and some received placement of a Cu-IUD at the time of hysteroscopy. The decision to have the IUD placed was up to the patient. For analysis, patients were divided into two groups: those that received an IUD and those that did not receive an IUD.

All patients underwent IVF or intracytoplasmic sperm injection (ICSI) and frozen-thawed embryo transfer (FET).

Hysteroscopy and IUD Insertion

Hysteroscopy was performed by one of two experienced hysteroscopic surgeons with the use of a 2.9-mm rigid hysteroscope (Karl Storz) that was equipped with hysteroscopic scissors (Karl Storz). The procedure was performed under local anesthesia with the use of lidocaine. Saline solution was used to distend the uterine cavity. A 300-W light source with a xenon bulb, a digital camera (Karl Storz), and a 21-inch color video monitor were used. Exploration of the uterine cavity consisted of a panoramic view of the cavity, followed by a thorough evaluation of the endometrial mucosa. The endocervical canal, uterine cavity, tubal orifices, and endometrium were inspected methodically and the findings recorded. During hysteroscopy, both the anterior and posterior uterine walls were thoroughly examined by moving the hysteroscope along the endometrial surface to get a view parallel to the endometrial surface. In this way, any irregularity of the endometrial surface was easily identified. Adhesions, micropolyps, and polypoid endometrium were divided or removed with the use of the hysteroscopic scissors until normal uterine anatomy was achieved. The severity and extent of intrauterine adhesions were scored according to a classification system recommended by the American Fertility Society (AFS; 1988 version). All patients had biopsies of the endometrium that were sent for pathologic examination at the time of initial hysteroscopy. Endometritis was considered during hysteroscopy if the endometrium appeared flushed with densely distributed small red spots or small floccular hyperplasia. In contrast, a normal endometrium appeared pink and loose. Pathologically, endometritis was diagnosed by the presence of plasma cell infiltration.

All hysteroscopies were performed in the follicular phase, and images were recorded in digital format. When the hysteroscopy was completed, a heart-shaped Cu-IUD (Yantai Contraceptive Instrument) was inserted in some patients. All patients received 150 mg tosufloxacin tosilate (Zhuhai Pharmaceutical Co.) orally three times a day for 3 days after the procedure.

Patients who received an IUD had a second-look hysteroscopy two menstrual cycles after IUD placement. At that time the IUD was removed, and recurrent adhesions or endometrial polyps were removed.

Embryo Transfer

Embryo transfer was performed after hysteroscopy in the non-IUD group and after IUD removal in IUD group. Embryo and endometrial synchronization in cryopreserved embryo transfer cycles was performed according to the method described by Kuang et al. (12). In brief, for natural cycles, follicular growth was monitored by measuring serum hormone levels and by means of ultrasound beginning on cycle day 10. When the diameter of the dominant follicle was >16 mm and endometrial thickness was >8 mm, with an E_2 level >150 pg/mL, one of two procedures was carried out depending on the LH and *P* values. If the LH level was <20 IU/L and the P level was <1.0 ng/mL, 5,000 IU hCG was administrated at night (9 p.m.) to trigger ovulation, and transfer of 3-day-old embryos was performed 5 days later. If the LH level was >20 IU/L or the P level was >1.0 ng/mL, 5,000 IU hCG was administered the same afternoon and the transfer of 3-day-old embryos was performed 4 days later. Duphaston (40 mg/d; Abbott Biologicals) was used for luteal support beginning on the 3rd day after hCG injection.