Fertility Preserved Hysteroscopic Approach for the Treatment of Stage Ia Endometrioid Carcinoma

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**Objective:** This study aims to explore the feasibility of a hysteroscopic procedure combined with progestin therapy in young patients with stage Ia endometrioid carcinoma (EC) to avoid sterilization.

**Materials and Methods:** Eleven young women with stage Ia EC (International Federation of Gynecology and Obstetrics grade 1) who were treated with a hysteroscopic approach combined with progestin from July 2004 to June 2016 were retrospectively analyzed and followed up to monitor their general recovery and pregnancy outcome.

**Results:** The patients’ median age was 27.3 years (range, 25–39 years). Comorbidities consisted of primary infertility in 8 patients, polycystic ovary syndrome in 4, uterine fibroids in 2, and diabetes in 1. The results of immunohistochemical analysis were positive for all estrogen and progestin receptors. After treatment, 9 patients attained complete remission, and 2 patients achieved partial remission. The results of peritoneal cytology in 4 patients were negative. As of this writing, 6 of the 11 patients have given birth to 7 infants, and 1 patient had an ectopic pregnancy. Two patients ultimately underwent radical resection. The average follow-up time was 82.3 months (range, 15 to 152 months), and all patients remain disease-free.

**Conclusions:** Hysteroscopic surgery combined with progestin treatment for stage Ia EC in young patients to avoid sterilization was practical and may represent a new option for patients with stage Ia EC who wish to preserve their fertility.

**Key Words:** Endometrioid carcinoma, Fertility preservation, Hysteroscopy, Progestin
an obvious advantage over dilatation and curettage (D&C) in localizing lesions in the uterus, avoiding endometrial damage and minimizing disturbance to implantation.\textsuperscript{10-13} We investigated the effect of hysteroscopic resection combined with progestin therapy in a series of young women with early-stage EC who wished to preserve their fertility.

MATERIALS AND METHODS

Research Subjects

The study was approved by the institutional review board of Zhejiang University Women's Hospital and Zhejiang Cancer Hospital. All participants signed an informed-consent form after thorough counseling. The clinical information was collected in these hospitals from July 2004 to June 2016 including patient presentation, diagnostic method, pathological results, peritoneal cytology (PC), treatment, and follow-up results for survival rate and pregnancy outcome. These data were then analyzed retrospectively.

The inclusion criteria were as follows. (1) Patients had undergone hysteroscopic resection for lesion biopsy as the initial treatment. (2) Patients met the following conditions for the treatment of fertility preservation\textsuperscript{3,4,14}: (a) nulliparity, age less than 40 years, and a desire to retain fertility; (b) histologic classification of cancerous tissue as well-differentiated endometrioid adenocarcinoma (International Federation of Gynecology and Obstetrics [FIGO] grade 1) and confirmation of progestin receptor positivity; (c) an absence of myometrium invasion, cervical involvement, or extrauterine lesions on transvaginal ultrasound and magnetic resonance imaging (MRI) studies, in accordance with FIGO stage Ia; and (d) normal liver and kidney function. (3) Patients had undergone regular hysteroscopic examination and electrosurgery, combined with conservative treatment with progestin.

Hysteroscopy Procedure

After epidural anesthesia and cervical dilatation, the uterus was distended with 5% glucose solution or mannitol solution, at 80 to 100 mm Hg perfusion pressure. The patient first underwent hysteroscopy (Richard Wolf GmbH, Germany) to observe the cervical canal, uterine cavity, and endometrial tissue and to localize lesions. Using the loop electrode, the lesions and the endometrium underlying the lesion were completely resected and sent for pathological assessment. The operation time was controlled at about 30 min.

Evaluation Criteria

The evaluation criteria of this study were as follows\textsuperscript{15}: (1) complete remission (CR): complete removal of lesions, no cancerous tissues or atypical hyperplasia tissue discernible by hysteroscopy and biopsy; (2) partial remission (PR): pathological classification downgraded from cancer to atypical hyperplasia; (3) no change: lesion remained stable; (4) progression: results of pathology trending toward a higher histological grade, or myometrium and a wider range of invasion, cervical involvement, and extrauterine lesions newly identified; and (5) relapse: emergence of cancer tissue after CR.

Drug Therapy

Five patients were treated with medroxyprogesterone acetate (MPA) of 250 to 500 mg and 4 with megestrol acetate (MGA) of 160 to 320 mg regularly after diagnosis. One patient received MPA of 500 mg (intramuscular) twice weekly, and 1 developed abnormal liver function and was switched to a different regimen after 3 months (see Results section). If patients had not attained CR or PR after progestin treatment for 3 months, they were asked to undergo traditional surgery and were excluded from the study. Indications for withdrawal were either (1) no sign of relapse 3 months after the patient had reached CR or (2) pathological findings that had not worsened after at least 1 year of continuous medication and the desire to become pregnant.

Follow-Up and Surveillance

Follow-up began in the first discharge month, as of March 2017. Observed for surveillance were symptoms, gynecological examination, fertility, pelvic imaging (ultrasound or MRI), and the blood tumor markers (carbohydrate antigen-125 and -199). Hysteroscopy or hysteroscopic electrosurgery were assessed every 3 months until CR. After progestin treatment, all patients were referred to a reproductive specialist. The patients were surveilled every 3 months during the first 2 years after CR and every 6 months thereafter for the next 3 years; all received the medical tests mentioned above, except hysteroscopy. Once tumor relapse was verified, patients underwent surgical resection and were excluded from the study.

RESULTS

General Clinical Features

The median age of the 11 patients was 27.3 years (range, 25–39 years). Irregular menses were the initial complaint in 7 patients; the other 4 had no symptoms and were diagnosed by an incidental imaging examination. Concomitant diseases were primary infertility (PI) in 8 patients, polycystic ovary syndrome (PCOS) in 4, uterine fibroids in 2, and diabetes in 1. No other patients had any history of diabetes or hypertension. All patients were married and had no previous successful delivery. One patient had 2 miscarriages; the others had no pregnancy history. The median body mass index was 23.6 kg/m\textsuperscript{2} (range, 18.1–28.6 kg/m\textsuperscript{2}).

Uterine enlargement was found by pelvic examination in 1 patient; there were no remarkable findings in the other patients. Transvaginal ultrasound examination revealed 1.0 to 2.5 cm endometrial polyps in 8 patients, 5 of whom had increased vascularity within the endometrium; echo guidance found heterogeneous endometrial tissue in 3 patients (Table 1). No myometrial invasion, cervical or lymph node involvement, or extrauterine infiltration were revealed on MRI scans. Also, serum tumor marker levels of all patients were under the limit.

Clinical Observation of Hysteroscopy

We performed cavitary exploration in hysteroscopic surgery in all patients. Nine patients had a uterine cavity length of 8.0 cm or less (6.5 to 8.0 cm), and 2 patients, between 8.5 and 9.0 cm. On hysteroscopy, we observed smooth endometrial polypoid lesions that were soft in texture and locally...
hypervascular in 8 patients; 1 patient showed small, white, brittle cauliflower excrescences, and the other 2 patients had floating pink endometrioid tissue.

Pathological Results

Well-differentiated endometrioid adenocarcinoma (FIGO grade 1) was diagnosed in all patients. Nine patients had complex endometrial hyperplasia with atypia and local carcinogenesis, 1 had malignant transformation of endometrial polyps, and 1 had endometrial adenocarcinoma with squamous differentiation (Table 2). All resected tissue below the lesion showed no tumor. Immunohistochemical analysis confirmed that both estrogen and progestin receptors were positive.

PC Examination

Four of the 11 patients underwent PC by combined laparoscopy and hysteroscopy (3) or posterior fornix aspiration (1). The former procedure included collection of a 20- to 30-mL peritoneal washing sample after irrigation of the peritoneal and pelvic cavities with 200 mL of normal saline solution. The latter procedure consisted of collection of 20 mL of peritoneal washing liquid via posterior fornix aspiration after percutaneous peritoneal injection of 50 mL of normal saline solution. No tumor cells were found in the peritoneal lavage fluid (Table 3).

Treatment Outcome and Pregnancy

Five patients received MPA 250 to 500 mg daily, 4 patients received MGA 160 to 320 mg daily, and one patient received MPA 500 mg twice per week by intramuscular injection. One patient developed abnormal liver function after receiving MPA 500 mg/d for 3 months and instead began receiving MGA 320 mg/d and never had any complications. Nine patients had achieved CR after 3 to 12 months of fertility-sparing treatment, and all patients had achieved at least PR within 3 months (Table 2). The average response time was 6 months.

At the end of follow-up, 6 patients had successful pregnancies with 7 infants, and 1 patient had an ectopic pregnancy after ovulation induction. The other 4 patients failed to become pregnant after 1 to 4 attempts at in vitro fertilization and embryo

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**TABLE 1. General clinical features of all cases**

| Number | Age, y | BMI  | Menarche, y | PI | PCOS | Myoma | Symptom       | Transvaginal Ultrasound       |
|--------|--------|------|-------------|----|------|-------|---------------|-----------------------------|-------------------------------|
| 1      | 27     | 19.6 | 12          | Yes| Yes  | No    | Irregular menses | Uterine neoplasm            |
| 2      | 30     | 19.6 | 15          | Yes| Yes  | No    | Irregular menses | Uterine neoplasm            |
| 3      | 31     | 24   | 16          | Yes| No   | Yes   | No            | Uterine neoplasm            |
| 4      | 39     | 22.7 | 11          | No | No   | Yes   | Irregular menses | Uterine neoplasm            |
| 5      | 31     | 23.7 | 12          | Yes| Yes  | No    | Irregular menses | Heterogeneous                |
| 6      | 28     | 25.6 | 13          | No | No   | No    | No            | Uterine neoplasm            |
| 7      | 25     | 20.5 | 13          | Yes| No   | No    | Irregular menses | Hyperplasia                  |
| 8      | 26     | 24.6 | 15          | Yes| No   | No    | No            | Uterine neoplasm            |
| 9      | 26     | 24.7 | 12          | Yes| No   | No    | No            | Hyperplasia                  |
| 10     | 26     | 18.1 | 13          | No | No   | No    | No            | No                           |
| 11     | 27     | 28.6 | 12          | Yes| Yes  | No    | No            | Uterine neoplasm            |

BMI, body mass index.

**TABLE 2. Pathological diagnosis by hysteroscopy**

| Number | Initial Tumor Differentiation | 3 mo Later | 6 mo Later | 9 mo Later | 12 mo Later | 15 mo Later |
|--------|-------------------------------|------------|------------|------------|-------------|-------------|
| 1      | Well differentiated            | CR         |            |            |             |             |
| 2      | Well differentiated            | PR         | PR         | PR         | CR          |
| 3      | Well differentiated            | CR         |            |            |             |             |
| 4      | Well differentiated            | PR         | PR         | CR         |
| 5      | Well differentiated            | CR         |            |            |             |             |
| 6      | Well differentiated            | PR         | PR         | CR         |
| 7      | Well differentiated            | PR         | PR         | PR         | PR          |
| 8      | Well differentiated            | PR         | PR         | PR         | PR          |
| 9      | Well differentiated            | PR         | PR         | PR         |
| 10     | Well differentiated            | CR         |            |            |             |             |
| 11     | Well differentiated            | PR         | PR         | CR         |

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transfer or controlled ovarian hyperstimulation and intrauterine insemination (Table 3).

**Prognosis**

The average follow-up was 82.3 months (range, 15–152 months), and no patients were lost to follow-up. Two patients underwent radical hysterectomy after successful delivery, and the postoperative pathological examination showed no recurrence of the disease. As of March 2017, all 11 patients were disease-free survivors (Table 3).

| Number | Treatment | Time, mo | PR, mo | CR, mo | PC | Method of Pregnancy | Pregnancy Outcome |
|--------|-----------|----------|--------|--------|----|---------------------|-------------------|
| 1      | 6         | 3        | 3      | 3      | Negative | COH + IUI | 1 Term infant by C-sect |
| 2      | 12        | 3        | 12     | 3      | Negative | IVF-ET | 1 Term infant by C-sect |
| 3      | 3         | 3        | 3      | 3      | Negative | IVF-ET | 1 Term infant by C-sect |
| 4      | 9         | 3        | 9      | N/A    | IVF-ET | 1 Term infant by C-sect |
| 5      | 3         | 3        | 3      | N/A    | COH + IUI | Ectopic pregnancy |
| 6      | 9         | 3        | 9      | N/A    | IVF-ET | 1 Term infant by C-sect |
| 7      | 15        | 3        | N/A    | N/A    | IVF-ET | Not conceived |
| 8      | 15        | 3        | N/A    | N/A    | COH | 1 Term infant by eutocia |
| 9      | 6         | 3        | 3      | N/A    | COH | 1 Term infant by C-sect |
| 10     | 12        | 3        | 9      | N/A    | COH | Not conceived |
| 11     | 6         | 3        | 3      | N/A    | COH | Not conceived |

COH, controlled ovarian hyperstimulation; IUI, intrauterine insemination; C-sect, Caesarean section; IVF-ET, in vitro fertilization and embryo transfer; N/A, not applicable.

**DISCUSSION**

The estrogen dependency of most ECs in young patients may be owing to the long-term lack of counteracting progestin. The pathology of this type of tumor is mainly endometrioid adenocarcinoma with a high expression rate of both estrogen and progestin receptors. The general prognosis of this disease is good, even though many patients have concomitant PI, irregular menstruation, polycystic ovaries, and endometrial hyperplasia. The 11 patients in this study were younger than 40 years of age and had well-differentiated endometrioid adenocarcinomas. Also, immunohistochemical analysis confirmed positivity for both estrogen and progestin receptors. Among the patients studied, 7 had a history of irregular vaginal bleeding, 8 had PI, and 4 had PCOS.

Soliman et al. reported that 70% of young patients with EC were childless at their initial diagnosis. The European Society of Gynecological Oncology has published a clinical recommendation for a conservative approach to EC, considering that progestins can offer very good results in treating early-stage EC in nulliparous women who have a strong desire to maintain their fertility. However, repeated D&C to obtain histology and monitor the disease may cause endometrial impairment and failure of implantation. Hysteroscopy is a means to view directly the cervical canal and uterine cavity and the extent of tumor invasion, thus greatly improving the accuracy of preoperative staging. Some large-sample and multicenter clinical research studies have shown the sensitivity of EC diagnosed by hysteroscopy to be 60.9% to 72.4%; the specificity was 94.7% to 99.9%, and the accuracy was 97.1%. In addition, excision of focus by hysteroscopy can reduce tumor load and improve the treatment effect. These studies have led to the acceptance of hysteroscopy as the criterion standard for the diagnosis of endometrial lesions. All patients in our study underwent hysteroscopy, and all received treatment with progestins after EC was confirmed. We found that 81.8% patients achieved CR after 3 to 12 months of treatment.

Pregnancy is the ultimate goal of fertility-sparing treatment. Gunderson et al. reported that the pregnancy rate in the group receiving progestins was 35.7% (78/218). In this study, 6 patients had successful delivery of seven infants, with a pregnancy rate of 54.5%, consistent with the result of a prospective study reported by Mazzon et al. However, because our sample size was too small to provide valid evidence for evidence-based medicine, we still need more multicenter, large population studies to evaluate the advantages of combined hysteroscopy and progestin in stage Ia EC over progestin treatment alone.

Because the uterus must be filled with fluid to maintain intrauterine pressure in the procedure of hysteroscopy, whether it would increase the PC positive rate and thus affect prognosis is controversial. Zerbe et al. and Bradley et al. performed retrospective analysis on the PC-positive rate of EC patients with a history of preoperative hysteroscopy and compared with the patients without preoperative hysteroscopy, and they found that the hysteroscopy group had a higher PC-positive rate than the control group. Arikan et al. used surgical specimens from EC patients to simulate the process of hysteroscopy in vitro and observed that perfusate leaked from tubes in 83% of the uterine specimens. They found tumor cells in 71% of the leakage fluid samples, and 42% of the cells showed viability. In contrast, some reports have stated that hysteroscopy does not increase the PC-positive rate or affect the prognosis. Obermair et al. conducted a multicenter study to compare the PC results of patients with and without hysteroscopy;
their results showed no statistical difference between the 2 groups. Moreover, throughout the follow-up, they also found no significant difference in the mortality rate from EC. Some scholars considered that the prognosis was unaffected by PC positivity if the patient had no other metastases.37,38 Revel et al29 reviewed the literature on Medline about the risk of hysteroscopy in EC patients from 1980 to 2001 and concluded that there was as yet no confirmation that the endometrial cells in the peritoneum are washed by the uterine lavage fluid, and no prospective randomized trial has confirmed that hysteroscopy causes cancer spread. In addition, Revel et al29 found it difficult to determine any difference in EC patients’ prognosis between those who underwent hysteroscopy and those who underwent other traditional examinations such as D&C. We summarized recent studies on the abdominal dissemination of EC that might be caused by hysteroscopy and found that, in general, PC positivity had a prognostic significance only in EC patients with extraterine metastases; otherwise, it would not affect patient survival.25,35–39

Because of the potential risk of tumor spread, the surgeon should not only be gentle and quick in the process of hysteroscopy for EC patients but also should attempt as much as possible to reduce intrauterine pressure without affecting the operative field. Evidence-based medicine has provided no data to recommend that intrauterine pressure should be lower than a certain value to avoid the spread of endometrial cells. Chang et al40 concluded from a meta-analysis that, at intrauterine pressures of 100 mm Hg or lower, there would be no increase in the risk of cancer cells spreading into the abdominal cavity. Baeskø et al41 reported that, at intrauterine pressures of greater than 80 mm Hg, the perfusion fluid would flow through the fallopian tubes into the abdominopelvic cavity. In our study, all patients underwent successful hysteroscopy when the intrauterine pressure was maintained at 80 to 100 mm Hg, the procedure time was controlled in 30 minutes, and the PC results were negative for the 4 patients who underwent the procedure.

The ideal result of fertility preservation in EC patients should be both a successful pregnancy and a good outcome. However, whether conservative treatment would worsen the prognosis is dubious. Because young women’s ECs are well differentiated and restricted to the uterus, the disease progresses slowly. Hence, we emphasize the importance of monitoring the process of treatment. Patients whose endometrial biopsy reveals a poor response to conservative treatment should expeditiously undergo hysterectomy. Indeed, most reports have discovered that patients with a poor response to conservative treatment or with relapse after treatment rarely had extraterine metastases.12,42 Other studies reported on patients with well-differentiated EC for whom conservative treatment had been unsuccessful and who had promptly undergone hysterectomy; on long-term follow-up, none of these patients had died from tumor.5,43,44 Nevertheless, because of the small sample sizes of these studies, some researchers have also advanced the objection that the risk of disease progression is as high as 5% to 6% over the course of conservative treatment.3,10 Furthermore, some studies reported that one third of patients who underwent conservative treatment ultimately had disease recurrence, which is a significantly higher proportion than that in patients who underwent radical surgery.15,17,24,45–49 Consequently, we recommend that all patients who receive conservative treatment be followed closely and undergo radical surgery immediately after giving birth.

CONCLUSION

Because of the advantages of performing uterine biopsy under dynamic and direct vision, we believe that hysteroscopy is one of the most accurate and reliable methods to diagnose intrauterine lesions, especially for early EC. Combined hysteroscopic resection and progestin therapy is an innovative and feasible treatment for young women with stage Ia EC who wish to preserve their fertility, with regard to improving the pregnancy rate under close follow-up. Overall, hysteroscopy is a safe, reliable, and effective procedure for patients with early EC, but its efficacy requires further confirmation by multicenter studies.

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