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Original Article

Fertility-preserving treatment of stage IA, well-differentiated endometrial carcinoma in young women with hysteroscopic resection and high-dose progesterone therapy

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ABSTRACT

Objective: The standard treatment for endometrial cancer is surgery with hysterectomy. However, this procedure will cause infertility in young women who desire to preserve pregnant ability. Conservative management with hormone therapy has been shown to be satisfactory in both tumor control and fertility preservation. Recently, hysteroscopic tumor resection followed by progestin therapy has been reported to be an alternative strategy. In this study we present our experience with this approach.
Materials and methods: Six young patients (30–36 years old) diagnosed with grade 1 stage IA endometrial cancer who wished to preserve fertility were enrolled for this treatment procedure. The patients underwent hysteroscopic tumor resection followed by oral progestin therapy with either megestrol acetate or medroxyprogesterone acetate for at least 6 months. Interval hysteroscopy with biopsy was performed during the treatment course to evaluate disease response.
Results: All of the six patients had complete tumor remission after hysteroscopic resection and progestin therapy (five in 6 months, one in 9 months). In a median follow-up of 32 months (range 4–49months), one patient became pregnant spontaneously and delivered a full-term healthy baby via cesarean section. She received a definite surgery 3 months later, and the pathology confirmed no tumor existence. The other five patients were also free of disease at the last follow-up.
Conclusion: Hysteroscopic tumor resection followed by progestin therapy for early-stage and well-differentiated endometrial cancer is a safe conservative treatment strategy. It could be an option for young patients who wish to preserve fertility.

Introduction

Endometrial cancer is the most common gynecological cancer in developed countries. It mainly affects women of postmenopausal age, however, approximately 4–5% of patients are younger than 40 years and most of them have stage I, grade 1 disease. In addition, these patients usually have a better overall 5-year disease-free survival than older women [1].

Although most stage I, grade 1 endometrial cancers are curable with surgical resection and a favorable outcome can be expected, sacrificing the uterus is often unacceptable for young patients who wish to preserve fertility. A conservative and feasible approach to treat this specific group of patients is therefore an important issue.

Because endometrial cancer is well-known as an estrogen-related neoplasm, treatment of this disease with progestins was described as early as decades ago [2–4]. Currently, high-dose progestin therapy has been proved effective in treating early-stage and well-differentiated endometrial cancer [5–9]. This approach meets the requirement of successful disease control while preserving fertility, and it has widely been accepted for the management of young patients whose disease status is suitable for such therapy.

Hysteroscopic tumor resection is another treatment strategy for early-stage endometrial cancer. It was first reported in single case trials [10,11]. This procedure may provide a direct and targeted approach for endometrial lesions. Several subsequent series reported that hysteroscopic tumor resection followed by progestin

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therapy revealed satisfactory oncologic outcomes. A previous literature review included four studies with a total of 36 patients who were treated with hysteroscopic surgery followed by progestin therapy. The complete response rate was 88.9% with tumor recurrence in four patients. Nine patients had a successful pregnancy after achieving complete remission with a pregnancy rate of 25% [12]. Other later studies also reported similar oncologic outcomes and even better fertility rates [13,14].

In this report, we present six young patients with stage I, grade 1 and solitary endometrial carcinoma who were treated with hysteroscopic tumor resection followed by progestin therapy.

Materials and methods

From 2013 to 2017, six nulliparous women under 40 years of age were diagnosed with stage IA, grade 1 endometrioid endometrial carcinoma. The tumors were positive for estrogen and or progesterone receptors by immnohistochemical studies, and all of the patients wished to preserve fertility. These patients were recruited for the conservative treatment strategy after being counseled about the procedures and the possible risk of tumor recurrence, and all provided informed consent.

The histological type and tumor grading were confirmed by two pathologists from hysteroscopic biopsies. Magnetic resonance imaging (MRI) examination was performed after the pathological diagnosis had been made to evaluate if there is myometrial invasion. The patients then received hysteroscopic tumor resection under general anesthesia with the uterine cavity distended with normal saline under gravity inflow of 70 mm Hg pressure. The outflow fluid was collected and the amount was monitored. A 5-mm cutting loop electrode with 100 W of power was used to resect the tumor lesion and the nearby endometrium until the myometrium underlying the lesion was visualized.

When the tumor histology and grading were further confirmed as endometrioid carcinoma with grade 1 differentiation and there was no lymphovascular space invasion noted in the final pathologic examination, the patients received postoperative progestin therapy of either megestrol acetate (MA) 160 mg daily or medroxyprogesterone acetate (MPA) 500 mg daily for at least 6 months. To monitor disease status, the patients underwent a hysteroscopic biopsy or uterine curettage during follow-up with an interval of 3–4 months depending on the previous pathological findings. A complete response was defined as the absence of any degree of endometrial hyperplasia. The patients were then encouraged to prepare for pregnancy. If the patient did not plan to become pregnant at that time, levonorgestrel IUD was used as maintenance therapy, and the patients were followed up at outpatient department every 3 months. A diagnostic hysteroscopic or uterine curettage biopsy was performed if abnormal uterine bleeding or an endometrial lesion was suspected in an ultrasound examination. The patient was shifted to a complete staging operation if persistent disease was noted after hormone therapy for 6 months or tumor recurrence was confirmed by pathology at follow-up.

Results

The clinical characteristics of the six patients are summarized in Table 1. The age of the patients ranged from 30 to 36 years, and their body mass index ranged from 28.2 to 36.9. Three patients received MPA and three patients received MA as hormone therapy after hysteroscopic tumor resection. Three patients received two hysteroscopic biopsies, one patient received three hysteroscoic biopsies, and one patient received four hysteroscopic biopsies during follow-up. The other patient (case 6) received uterine curettage alone twice to monitor the tumor response.

Table 1
Clinical characteristics of patients (n = 6).

Patient	1	2	3	4	5	6
Age (yr)	34	36	30	31	36	35
BMI	28.2	29.9	35.9	23.6	24.6	36.9
EM thickness (cm)[a]	2.2	1.8	2.3	1.2	2.2	2.6
MRI staging	IA	IA	IA	IA	IA	IA
ER/PR	+/+	+/+	+/+	+/+	+/−	+/+
Hormone therapy	MPA	MA	MA	MPA	MPA	MA
Disease monitoring	hys	hys	hys	hys	hys	D&C
Biopsy number[b]	4	3	2	2	2	2
Time to CR (mo)	9	6	6	6	6	6
Follow-up (mo)	39	49	44	25	21	4
Fertility desire	yes	yes	no	yes	yes	yes
Child bearing	0	1	0	0	0	0

BMI = body mass index; EM = endometrium; MRI = magnetic resonance imaging; ER/PR = estrogen receptor/progesterone receptor; hys = hysteroscopy; CR = complete response.
[a] Measured by ultrasound examination.
[b] Number of biopsy during follow-up.

The median follow-up time from the date of complete remission was 32 months (range 4–49 months). The tumors regressed to atypical endometrial hyperplasia in five patients, and complex atypical endometrial hyperplasia in one patient (case 1) after hormone therapy for 3 months. A complete response was confirmed in five patients after 6 months of hormone therapy, while case 1 needed 9 months to reach a complete response.

No intrauterine adhesion was noted among the five patients who received hysteroscopic examinations during follow-up. However, severe endometrial atrophy with cystic change was noted in one patient (case 1). No other side effect associated with the hormone therapy was noted.

One patient (case 2) became pregnant spontaneously, and she received a cesarean section and delivered a healthy baby at 38 weeks of gestation. A complete staging operation was performed 3 months later, and no evidence of disease was confirmed. Four women are still trying to get pregnant but only two are receiving artificial reproductive technology. The remaining patient has no plan to conceive at present, she is using levonorgestrel IUD as maintenance therapy. All of the six patients were free of disease at the last follow-up.

Discussion

Conservative treatment for early-stage endometrial cancer in young women has widely been accepted as an alternative to definitive surgical management, as it can both treat the disease and preserve fertility. Currently, the most commonly used strategy is selecting suitable candidates who are diagnosed as stage IA grade 1 endometrioid carcinoma with tumor confined at the endometrium by either MRI or transvaginal ultrasound [15]. High-dose progestin with either MPA at a dose of 400–600 mg/d or MA at a dose of 160–320 mg/d for at least 6 months is recommended [16]. Tumor response rate to conservative therapy has been reported from 50% to 75% [5–9]. A previous systematic review and meta-analysis reported that the pooled live birth rate was 28% in 325 women treated with progestins [5]. However, the reported tumor recurrence rate after conservative management ranges from 30% to 40% [5–9]. Moreover, a Taiwanese series reported that the 5-, 10-, and 15-year cumulative recurrence-free survival rates were 51%, 51%, and 34%, respectively [17]. The high recurrence rate and relatively low long-term survival rate should not be underestimated. Therefore, patients should be encouraged to get pregnant as early as

possible when complete remission of disease is confirmed by pathology examination. A definite surgery is strongly indicated after childbearing to avoid tumor recurrence. In patients with no immediate desire to conceive, maintenance therapy with the insertion of levonorgestrel IUD is recommended [16,18].

Direct tumor resection via hysteroscopy can remove the tumor quickly and effectively. It is reasonable to assume that the tumor control rate with hormone therapy after hysteroscopic resection of the main tumor will be higher because of a reduction in tumor volume. It would also be interesting to investigate whether the duration of postoperative progestin therapy can be shortened after hysteroscopic resection.

Intraperitoneal spread of tumor cells through the fallopian tubes during hysteroscopy has been challenged when making a hysteroscopic diagnosis of endometrial cancer. The increase in intrauterine pressure during perfusion of distention media may increase the risk of dissemination of malignant cells into the peritoneal cavity. Two previous meta-analyses reported that patients who underwent hysteroscopy had a higher rate of malignant peritoneal cytology compared to those who did not undergo hysteroscopy [19,20]. However, another controlled randomized study reported that diagnostic hysteroscopy did not cause an increase in pelvic recurrence rate compared to the non-hysteroscopy group after more than 5 years of follow-up. In addition, no differences in overall survival and disease-free survival were noted between the two groups of patients [21]. At present, hysteroscopy is still regarded to be a safe diagnostic procedure for endometrial cancer [20,21], however, whether the therapeutic use of hysteroscopy would affect the patients' prognosis deserves to observe.

In a review study by Alonso et al., four of 36 cases receiving hysteroscopic resection of endometrial cancer had tumor recurrence, but all the recurrences were either hyperplasia or atypical hyperplasia [12]. A long-term follow-up study included 28 patients with stage IA, grade 1–2 disease who received hysteroscopic resection and postoperative oral megestrol acetate or levonorgestrel IUD insertion. In that study, two patients (7.1%) had persistent disease, one patient (3.6%) had progressive disease and underwent definitive surgery. Another two patients had recurrent disease after a median follow-up of 92 months (range, 6–172 months) [22]. Both of the two patients with recurrence had synchronous ovarian endometrioid carcinoma after staging surgery (stage IIB grade 1 and stage IA, grade 1). Whether the ovarian cancers were related to the previous hysteroscopy could not be clearly confirmed.

A recent meta-analysis compared the effects of three fertility-preserving treatment modalities (oral progestin only, hysteroscopic resection followed by progestin therapy, and levonorgestrel IUD combined with gonadotropin-releasing hormone therapy) on complete remission rate, recurrence rate, and pregnancy rate [23]. The results showed that the hysteroscopy group had the highest complete remission rate (95.3%), and that the oral progestin group had the highest recurrence rate (30.7%). The pregnancy rate was similar among the three groups (52.1%, 47.8%, and 56.0%, respectively). Therefore, hysteroscopic tumor resection followed by progestin therapy seems to be a promising option in treating young patients with early-stage grade 1 endometrial cancer who desire to preserve fertility.

Despite the positive effects of therapeutic hysteroscopic tumor resection, some problems still need to be elucidated. For example, the possibility of the spread of cancer cells into peritoneal cavity still should to be concerned. In addition, whether the injury to the basal layer of endometrium or underlying myometrium by thermal effect or mechanical destruction would bring negative impact on the pregnancy outcome also awaits answer [24]. At present, hysteroscopic tumor resection plus progestin therapy remains a topic of debate, and further data are needed to confirm its safety and feasibility [25].

In conclusion, hysteroscopic tumor resection plus progestational therapy could be considered as a safe treatment strategy with regard to oncological concern. Its pregnancy rate seems not inferior to the hormone therapy. However, careful selection of the candidates and a thorough counseling about tumor treatment and fertility plan are absolutely necessary before starting the treatment.

Conflict of interest

The authors declare no conflict of interest.

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