Original Article
Fertility-conservation combined therapy with hysteroscopic resection and oral progesterone for local early stage endometrial carcinoma in young women

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Abstract: Objects: This paper explored the suitable population for the combined therapy of hysteroscopic resection and oral megestrol acetate (MA) to treat local stage I endometrial cancer. Therapeutic effectiveness, safety, as well as pregnancy rate and relapse rate after treatment were also examined. The aim was to provide guidance for the treating similar cases in the future. Methods: This perspective study analyzed the clinical data of early stage endometrial cancer patients who have received combined therapy of hysteroscopic resection of local endometrial lesion and oral administration of MA at the Obstetrics and Gynecology Hospital of Fudan University, Shanghai. Results: A total of six patients met the entry criteria and were enrolled into the trial. All of them achieved a pathologic complete response to hysteroscopic resection of local lesion combined with oral administration of MA for 3 months to 6 months. Among the patients, three became pregnant after natural conception and had healthy infants delivered vaginally at full term without assistance. No relapse occurred in the follow-up study over 48.5 months on average. Conclusions: In early-stage endometrial cancer, young patients who had already given birth demand may receive hysteroscopic resection combined with oral administration of MA as conservative treatment. The patients can consider natural conception after complete remission, but a close follow-up was crucial to ensuring that the patients were free from other factors affecting childbearing ability.

Keywords: Endometrial cancer, fertility-conservation therapy, hysteroscopic resection, oral progesterone

Introduction

Endometrial cancer is one of the common malignant tumors in women worldwide, with increasing morbidity and mortality in recent years. In China, more and more young women suffer from the disease [1-3]. Nearly 14% of endometrial cancer patients are reportedly premenopausal women, and 3% to 5% of them are younger than 40. Among endometrial cancer patients younger than 40, about 80% have stage I disease and 50%-60% have grade I disease [2, 4].

The standard treatment of stage I endometrial cancer is total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy, sometimes combined with adjuvant chemotherapy or radiotherapy if necessary. However, this regimen results in the loss of childbearing ability. Given that young women with endometrial cancer usually have a history of sterility and infertility, half of them less than 45 years old are nullipara [3]. For patients who are unmarried or have birth demand, receiving such a radical hysterectomy is unacceptable. Thus, keeping the childbearing ability and improving life quality is important for young patients with stage I endometrial cancer.

Progestin has been used to treat recurrent endometrial cancer for more than 50 years and is also used in endometrial cancer patients with medical contraindication to surgery or anesthesia. An increasing cases of young patients with endometrial cancer successfully conservatively treated by progestin have been reported, with various therapeutic regimens including oral medroxyprogesterone acetate (MPA) [5], megestrol acetate (MA) [6], the levonorgestrel intrauterine system [7], and hysteroscopy resection combined with progestin therapy [8]. Fertility-sparing treatment for early-stage endometrial cancer has achieved a pooled regression rate...
of 76.2%, a relapse rate of 40.6%, and a live birth rate of 28% [9]. Nevertheless, considering the absence of a randomized controlled trial, no evidence-based practice guidelines for the optimum drug, dose, interval, or course of treatment exist. More studies on pregnancy and recurrence rate using different treatment are needed [10].

The present study was based on the outcome of a prospective analysis of the clinical data of six patients with local stage I endometrial cancer who had received hysteroscopy resection combined with MA therapy at the Obstetrics and Gynecology Hospital of Fudan University. The suitable target population, curative effect, safety, pregnancy rate, and recurrence rate for endometrial cancer patients with such combined fertility-sparing therapy was examined to provide some disposal instruction for the treatment of similar cases in the future.

Subjects and methods

Patient selection and general information

A prospective study was performed to analyze the clinicopathological data, treatment effects, pregnancy, and relapse of the young patients with well-differentiated endometrial cancer who had been conservatively treated at the Obstetrics and Gynecology Hospital of Fudan University from January 1, 2006 to February 31, 2012. Follow-up is at least 2 years and up to 9 years. To be eligible for study enrollment, the patient must 1) be <40 years old, 2) have the intent to preserve fertility and plan to conceive a baby as soon as possible after remission, 3) suffer from well-differentiated local endometrial adenocarcinoma, 4) be positive for progesterone receptor, 5) not have myometrial invasion or extrauterine foci, 6) have a normal level of serum CA125 (<35 KU/L), 7) have normal hepatic and renal functions, 8) not have thromboembolism or mastocarcinoma, 9) be closely followed up with good compliance, and 10) must sign the informed consent form.

Methods

Appraisal before treatment: The appraisal included the following: 1) inquiring about the patient’s general conditions, such as age and menstrual history; 2) assessing the patient’s fertility and wishes; 3) testing hepatic and renal functions and coagulation; 4) conducting diagnostic curettage or both biopsy under hysteroscopy and diagnostic curettage, clarifying the diagnosis, and ruling out medium- and poor-differentiation endometrial cancer; 5) determining the estrogen and progesterone receptor to forecast the effects of progestogen conservative therapy; 6) conducting imageological diagnosis that mainly includes transvaginal ultrasound (TVU) and magnetic resonance imaging (MRI) to rule out myometrial invasion or lymph node metastasis; 7) determining carcinoma antigen (CA) 125 to rule out complicated ovarian cancer; and 8) conducting diagnostic laparoscopy for patients who are suspected to suffer from adnexal lesions.

Regimen of fertility-sparing combined therapy with hysteroscopic resection and oral progesterone: Hysteroscopic resection of local lesion: the foci of patients who have local foci including the shallow muscular layer and its surrounding tissues (at least 5 mm outside) should be resected by loop electrode. The patient should then undergo pathological examination separately with endometrial tissues and shallow muscular layer tissues of the other parts acquired from the diagnostic curettage. All histopathological reports can represent the correlation between the foci and its surrounding endometrial tissues and shallow muscular layer.

Progestogen therapy: the patients received 160 mg of MA per day for 20 days each month or received continued treatment for 3 months. The patients received hysteroscopy and diagnostic curettage every 3 months. The treatment effects were then evaluated according to the histopathological examination result. Patients who achieved complete response (CR) after 3 months were advised to continue taking the medicine for 3-6 months and conceive a baby as soon as possible. For those who had not planned well to conceive a baby, follow-up was conducted at 3 month intervals. If partial response (PR) was achieved, the medicine was continually taken for 3 months, and the dose was increased to 320 mg per day. Hysterectomy was adopted if toxic or side effects appeared if the patients required surgery, or if the treatment effects were not good (i.e., patients showed no response (NR) after receiving the treatment for 3 months or only PR after 6 months).
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Evaluation standards for the effects: The evaluation standards were acquired by reference to literature [11]. CR was considered when pathologies had completely disappeared and no carcinoma tissues or atypical hyperplasia tissues existed. PR was considered when pathologies had been relieved to atypical hyperplasia. NR was considered when pathologies persisted. Recurrence was considered when carcinoma tissues reappeared after CR.

Follow-up: Patients were subjected to hysteroscopy, diagnostic curettage, B ultrasonic, and MRI examination every 3 months to evaluate therapeutic effects and recurrence. Indicators of toxic and side effects were recorded, including weight, hepatic and renal functions, coagulation, thromboembolism, blood pressure, and blood sugar.

The simplified scheme of the treatment and follow-up is shown in Figure 1.

Statistical analysis

Statistical analysis was conducted with SPSS 16.0 software. The significance level was $\alpha = 0.05$.

Results

Enrollment and follow-up

A total of six patients aged 25 years to 34 years (average = 29.5 years) were included through appraisal before treatment. Their ages at menarche were between 11 years and 14 years. Five of the six patients had a history of menorrhagia or menostaxis, and only one patient had normal menstruation. Four of the six had received biopsy by hysteroscopy and diagnostic curettage before the conservative treatment, one had received hysteroscopy combined with laparoscopy and diagnostic curettage, and one had received only diagnostic curettage. All six patients’ pathological diagnoses revealed that they suffered localized stage I endometrial adenocarcinoma with tumor-free resection margins and had positive progesterone receptors.

Therapeutic effects and recurrence rate

All six patients achieved CR after local resection of foci by hysteroscopy and progestogen therapy for 3 months. During follow-up, the patients received reexamination by hysteroscopy, TVU, and MRI. The average time of follow-up was 48.5 months. No relapse occurred up to January 25, 2015.

Toxic and side effects

Four patients gained weight to different degrees after taking progestogen. In one patient, hepatic dysfunction occurred with slightly increased ALT & LDH levels, but she quickly recovered after 2 months of drug withdrawal. No serious toxic and side effects such as thromboembolism, hypertension, and hyperglycemia occurred.

Pregnancy rate and pregnancy outcome

So far, three of the six patients became pregnant after natural conception and vaginally delivered healthy infants at full term without assistance. Within the other three unpregnant patients, one had received IVF but failed, one kept unmarried, and one became unmarried one year later and did not plan to conceive.
Table 1 Patients’ general conditions, clinical characteristics, therapeutic response, and follow-up results.

Discussion

This paper reports the clinical trial results of fertility-sparing therapy of six young patients who suffered early-stage endometrial cancer. All six patients who received hysteroscopic resection of local lesion combined with oral administration of MA achieved CR. Three of them successfully conceived and delivered a healthy baby. Our preliminary study demonstrated that satisfactory effects were achieved if the patients received combined therapy based on strictly defined indicators.

This scheme was more suitable for treating local lesions of endometrial cancer. On one hand, hysteroscopic resection can be used to judge the pathological grade from the aspect of histology and whether the foci has invaded the myometrium scale, as well as other important information that helps determine the therapeutic schedule. On the other hand, even if the resection of foci by hysterectomy cannot completely remove the potential foci, it can maximally reduce the foci and dislodge most carcinoma tissues, thereby improving the effects of progestogen therapy. In fact, surgical resection combined with drug therapy is now preferred for treating various tumors. Previous studies have revealed that some patients suffering from endometrial cancer successfully conceived babies after receiving resection of foci by hysterectomy and progestogen therapy. Mazzon et al. [8] conducted surgical treatment by hysterectomy. They resected the foci and its surrounding endometria, as well as partial myometrium, in six endometrial cancer patients. After the surgery, the patients took progestin orally for 6 months and then tried to conceive babies. So far, four of these patients successfully delivered babies. Laurelli et al. [7] resected the foci and shallow muscular layer of 14 patients with early-stage endometrial cancer. After the surgery, four patients took MA 160 mg/day orally for 6 months. Then, a levonorgestrel-medicated intrauterine device was placed in eight patients and taken out 12 months later. During follow-up (23 months to 89 months; median time = 50 months), three patients who desired fertility successfully delivered a baby. Yasuda et al. [12] reported that one patient with stage IA endometrial cancer had foci confined to the left cornu of the uterus after administering MPA for 6 weeks. Considering that she strongly asked to preserve fertility, she received wedge resection of the left cornu of uterus, ovary, and partial uterus walls. She finally achieved full-term delivery after local surgical resection. Noticeably, this kind of surgery was only suitable for patients whose foci were confined to one side of the uterine cavity or near the cornu of uterus, and the resection margins must be free of tumors. If numerous uterus tissues were resected and the uterine cavity had been significantly changed, pregnancy after the surgery would be influenced.

A standard period of progestogen therapy, as well as the time of withdrawal after achieving CR, has not yet been established. Niwa et al. [13] believed that progestogen therapy should continue for at least 6 months or until 2 months after lesions disappear. However, some scholars pointed out that therapy should last for more than one year to achieve high efficiency [14]. In the present research, patients who continued to use medicine for 3 months after CR have never relapsed since drug withdrawal. Therefore, for women who achieved CR after conservative treatment and decided not to conceive a baby immediately, withdrawal after continuing consolidation therapy for 3 months to 6 months was feasible. However, more samples and a longer follow-up are required to verify this presumption.

Regarding the conception method after achieving CR by conservative treatment, the majority of scholars recommend assisted reproductive technology, which can hasten the time of conception, increase the success rate of pregnancy, and prevent increased reoccurrence rate after CR. The reason is some complications such as polycystic ovary syndrome and obesity (which are common in young patients with endometrial cancer) affect natural conception [13]. However, such complication factors did not exist in the six patients in this study whose menstrual cycle and ovulatory function remained normal, though one of them received IVF later and failed for unknown reason. Three of four married patients chose to conceive naturally after the conservative therapy, and all succeeded in getting pregnant, though one of them received IVF later and failed for unknown reason. Therefore, if the patients had no complica-
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Table 1. Clinical characteristics and follow-up of the six patients

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
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<tbody>
<tr>
<td>Age at Diagnosis (y)</td>
<td>31</td>
<td>28</td>
<td>34</td>
<td>27</td>
<td>25</td>
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<tr>
<td>Marital status at Diagnosis</td>
<td>married</td>
<td>unmarried</td>
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<td>unmarried</td>
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<tr>
<td>Height (cm)</td>
<td>160</td>
<td>164</td>
<td>173</td>
<td>157</td>
<td>162</td>
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<tr>
<td>BMI before treatment (kg/m²)</td>
<td>18.75</td>
<td>22.90</td>
<td>21.70</td>
<td>17.85</td>
<td>19.80</td>
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<tr>
<td>BMI after treatment (kg/m²)</td>
<td>20.71</td>
<td>23.05</td>
<td>21.94</td>
<td>23.93</td>
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<td>GOPO</td>
<td>G1PO</td>
<td>GOPO</td>
<td>GOPO</td>
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<tr>
<td>Age of menarche (y)</td>
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<td>13</td>
<td>14</td>
<td>12</td>
<td>14</td>
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<tr>
<td>Symptomatology</td>
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<td>AUB</td>
<td>AUB</td>
<td>AUB</td>
</tr>
<tr>
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<td>HYS + D&amp;C</td>
<td>HYS + D&amp;C</td>
<td>HYS + D&amp;C</td>
<td>HYS + D&amp;C</td>
<td>D&amp;C</td>
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<td>E-G1</td>
<td>E-G1</td>
<td>E-G1</td>
<td>E-G1</td>
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<tr>
<td>Stage of disease</td>
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<td>IA</td>
<td>IA</td>
<td>IA</td>
<td>IA</td>
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<tr>
<td>Therapeutic Regimen</td>
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<td>HR; PT for 5 months</td>
<td>HR; PT for 4 months</td>
<td>HR; PT for 6 months</td>
</tr>
<tr>
<td>Therapy effect after 3 months of MA therapy</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
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<td>Follow-up time (months)</td>
<td>91</td>
<td>44</td>
<td>49</td>
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<td>Follow-up interval (months)</td>
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<td>Follow-up result</td>
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<td>NED</td>
<td>NED</td>
<td>NED</td>
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<td>Side effect</td>
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<td>NO</td>
<td>weight gain, raised serum ALT &amp; LDH level</td>
<td>weight gain</td>
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<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
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<td>NFTD</td>
<td>NO</td>
<td>NFTD</td>
</tr>
<tr>
<td>Interval between drug withdrawal and pregnancy (months)</td>
<td>10</td>
<td>NO</td>
<td>20</td>
<td>NO</td>
<td>6</td>
</tr>
</tbody>
</table>

Note: MA, megestrol acetate; CR, complete response; AUB, abnormal uterine bleeding; HYS, hysteroscopy; LAP, laparoscopy; E-G1, well-differentiated endometrial cancer (G1); HR, hysteroscopic resection; PT, progesterone therapy (oral administration of MA 160 mg qd); NED, no evidence of disease; NFTD, normal full term delivery.
tions affecting childbearing ability and did not accept assisted reproductive technology, they can be allowed to conceive naturally considering cost and emotional factors.

Myometrial invasion is one the key factors influencing the prognosis of endometrial cancer. According to literature [15], pelvic lymph node metastasis occurs in only 1% of endometrial cancer without myometrial invasion but occurs in 25% of endometrial cancer with deep myometrial invasion. Therefore, assessment of the depth of the myometrial invasion (DMI) is very important. TVU and MRI are the main methods of measuring DMI [16, 17]. However, imaging diagnosis has limitations and poses risks of missed diagnosis and misdiagnosis [17, 18]. In the current research, TVU and MRI were used for the preliminary appraisal of myometrial invasion. On this basis, the method of hysteroscopic resection of foci was further used to make a definite diagnosis of myometrial invasion under the foci. To rule out concurrent ovarian cancer, lymph node metastasis, and metastasis of other parts of the pelvic cavity, combined hysteroscopy and laparoscopy in one patient was also conducted. The overall appraisal of the patients before treatment ensured the indication of the conservative treatment and avoided the omission of the potential high risks, thereby reducing the risks of conservative treatment.

Pregnancy exerts no contributive or relievable influence on endometrial cancer. No final conclusion has been made as to whether the uterus should be excised after delivery. Some studies have pointed out that 24% of patients of endometrial cancer on whom hormonotherapy is effective have a relapse in the average follow-up of 19 months (6 months to 44 months) [14]. This finding suggested that progestogen therapy of endometrial cancer poses some risks such that even if CR is achieved, long-term and close follow-up should be conducted. Most scholars currently recommend hysterectomy after delivery. However, some scholars prefer close observation and argue that those who have normal childbirth could receive diagnostic curettage 6 weeks after delivery. Examinations must be conducted during surgery, specifically for those who delivered by caesarean section, including examination of the ovarium, abdominal rinse cells, pelvic cavity, samples of para-aortic lymph nodes, and biopsy of any suspected foci. Those who preserve the uterus should be closely observed for at least 2 years. On the first year, they should receive diagnostic curettage by hysteroscopy for every 3 months, which should be reduced to every 6 months on the second year [8]. Three patients in the present study had not receive hysterectomy after delivery but only regular and close follow-up, which negated any evidence of relapse. In fact, reports that patients who have relapse after conservative treatment can reportedly conceive babies successfully after the second conservative treatment [19]. For patients who have delivered after conservative treatment and again desire pregnancy, an alternative is to suspend hysterectomy with a close follow-up, e.g., hysteroscopy every 3 months, assessment for the indicators of CA125 and MRI examination, and so on.

Most importantly, conservative treatment is not the standard method of treating endometrial cancer even for young patients. Conservative treatment is not advisable to all patients with early endometrial cancer. Ramirez et al. [14] reviewed 21 published studies involving the clinical data of progestogen therapy of 81 patients suffering early well-differentiated endometrial cancer. They found that the effective rate of conservative treatment is 76%. However, some patients did not response to progestin. Hence, treatment failed [20] and other patients relapsed after treatment [21], or even worsen [22]. In the current research, the CR rate reached 100% by resection of foci with hysteroscopy and progestogen therapy. However, this research was based on strictly defined indicators, which may not be suitable for patients with diffused endometrial cancer. Given the small number of the samples, the clinical value of the combined therapy of early-stage endometrial cancer may not be conclusive and should be verified by further studies using larger sample sizes.

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Disclosure of conflict of interest

None.

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