

Safe fertility-preserving management in a young woman with endometrial cancer

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Summary

Endometrial cancer (EC) is a malignant cancer originating from the uterine endometrium. Although the incidence of endometrial cancer in reproductive age is relatively low, its impact on pregnancy outcome is critical. To date, it is difficult to find a standard method which can be referred to these patients who have a strong desire to preserve fertility. Presented is a report of a 35-year-old women with early-stage Endometrial cancer treated with progestin and levonorgestrel-releasing intrauterine system (LNG-IUS) with a good prognosis.

Key words: Endometrial cancer; Fertility-preserving; Progestin; Levonorgestrel-releasing intrauterine system.

Introduction

The incidence of endometrial cancer (EC) in premenopausal women who still want to become pregnant has increased significantly in recently [1]. As more women choose to defer childbearing until later in their life, the feasibility and safety of fertility-sparing EC management has been increasingly researched [2].

To detect a more conservative and safe management plan that preserves fertility for those who have not completed their child-bearing, the authors report a 35-year-old woman that achieved a positive effect to treat her early-stage EC using the progestin and levonorgestrel-releasing intrauterine system (LNG-IUS).

Case Report

A 35-year-old nulligravid woman presented at the gynecological clinic with her primary complaints being prolonged bleeding in the most recent seven months and irregular bleeding for the previous eight days. Her body mass index was 24.3 kg/m², with her body weight: 62 kg and height: 160 cm. A pelvic examination showed no abnormality except a mildly enlarged uterus (the size of uterus was appropriately 8 × 6 × 6 cm). Transvaginal ultrasonography showed the mid-high echogenic dumping in the intrauterine cavity and the endometrial thickness at 21 mm (Figure 1A). The blood test of reproductive hormones showed FSH 5.79 mIU/ml, LH 3.2 mIU/ml, E2 19.6 pg/ml, P 0.30 ng/ml, PRL 3.1 ng/ml, and TTE 0.15 ng/ml. The routine blood test showed hemoglobin at 114 g/L. A hysteroscopic examination in the next day and revealed apparent and disorderly endometrial thickening, polypoid proliferation, with an abundant blood supply (See Figure 1B). A resection of endometrial polyps and curettage was then performed with

the final pathology results confirming grade 1 endometrial adenocarcinoma (Figure 1C). The patient had a strong desire to one day become pregnant and rejected a hysterectomy. A conservative treatment approach was proposed and accepted by the patient. A pelvic-enhanced MRI was arranged and the patient was instructed to take megestrol acetate (MA) at 160 mg daily. MRI (Figure 1D) showed a hyperechoic cavity and no muscle layer of the uterus had been invaded, the cervix and the appendages (tubo-ovary) were normal, with no enlarged pelvic lymph nodes. The second hysteroscopy had been performed after one month of taking MA. The screening showed that the uterine lesion had shrunk compared to the initial imaging, but a cauliflower-like neoplasm was observed. The authors resected the endometrial tumor and placed the LNG-IUS in the uterine cavity. The pathology results reconfirmed endometrial adenocarcinoma. The patient continued taking MA 160 mg daily and after six months a third hysteroscopy was performed, with complete remission being achieved (Figure 1E). During the ten-month follow-up period, there was no recurrence of disease.

Discussion

Approximately 2–14% of EC cases are diagnosed in reproductive-aged women [3]. Given that more women are choosing to defer their childbearing until later in life, the safety and feasibility of conservative fertility-sparing EC management has been increasingly studied [4]. However, candidates for the conservative management are generally young women with limited endometrium, well-differentiated and endometrioid EC [5]. The current standard initial treatment for early-staged EC is total hysterectomy and bilateral salpingo-oophorectomy and/or pelvic and para-aortic lymph node dissection [6]. However, this

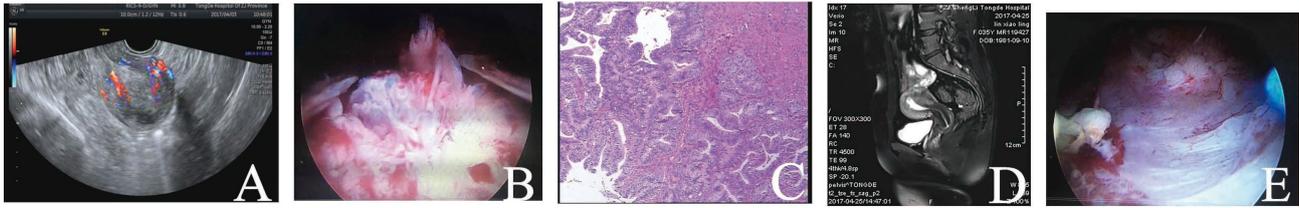


Figure 1. — A) Ultrasonic image shows the highly thickened endometrial wall. B) Hysterosalpingographic image shows highly thickened and diffuse irregularity of the endometrial wall. C) Histopathologic findings of hysteroscopic endometrial biopsy. Slides demonstrate well-differentiated grade I endometrioid adenocarcinoma (H&E stain, $\times 200$). D) Images obtained using pelvic MRI. Sagittal image reveals no myometrial invasion and a mass-like lesion in the uterine cavity, but with no significant lymph node enlargement. E) Complete remission was achieved in endometrial thickness of uterus after six months of treatments.

definitive approach may not be acceptable in selected patients with early stage, well-differentiated, and endometrioid type who have a strong desire to preserve their fertility in spite of oncologic risk [7]

Recent research show hormonal therapy is an attractive and effective alternative and is commonly used in the treatment of advanced EC with low-grade endometrial carcinoma [8]. Progestins are often the first medical treatment option for EC. Study shows progestins can affect differentiations of endometrial glands, inhibit estrogen receptor function, and promote apoptosis, Some progestins have also an anti-angiogenic effect [9]. However, there is no medical consensus about the optimal progestin, drug dosing, or duration of treatments, surveillance modalities, and frequency after treatment are also not standardized [10]. The most common regimens are medroxyprogesterone acetate (MPA) at 500–600 mg daily and megestrol acetate (MA) at 160 mg daily for a minimum of 6–9 months. Similarly, in a series of grade 1 EC cases previously published, a wide range of MA and MPA doses have been reported, ranging from 2.5 mg to 800 mg daily for MPA and 10 mg to 400 mg daily for MA [11]. Ushijima et al. [12] observed a better response with MPA at 600 mg compared with 200 mg or 400 mg daily, and other investigative groups have adopted this high-dose MPA regimen with similar outcomes [13]. The choice of progestin, dosing, and duration of administration should be individualized to minimize risks such as thrombophlebitis, sleep disorders, headaches, leg cramps, and weight gain [14, 15]. The two most commonly adopted regimens with initial response rates between 60% and 80% and recurrence rates between 25% and 40% [16].

Compared with oral progestin, LNG-IUS has been found to have less systemic side effects and higher efficacy as a treatment for well-differentiated early stage EC [17]. LNG-IUS is a T-shaped device that releases 20 $\mu\text{g}/\text{day}$ of LNG into the uterine cavity over a five-year period [18]. LNG-IUS provides, contrasted with the relatively low serum levels, locally high concentrations and steady-release of LNG in the endometrium. This leads to decidualization of the stroma, mucosal thinning, and eventually, by suppression of endometrial growth, an inactive endometrium [19]. The LNG-IUS has not been as well studied as oral progestins,

but complete response rates from 40% to 100% have been reported in premenopausal women with well-differentiated, early stage EC [20].

The objective of this manuscript is to analyze the contemporary oncologic and reproductive outcomes in conservatively treated women with early-stage endometrial carcinoma and to determine if there are differences in hormonal response and fertility rates between current cohorts [21]. Here the authors report a 35-year-old Stage IA, grade 1 endometrioid cancer patient with LNG-IUS and supplemental oral progestin, after six months, a hysteroscopy was performed to evaluate the result of treatment, and showed the endometrium had become almost normal (See Figure 1E). As a follow-up, the patient became pregnant within three months of the treatment. The authors highlight the efficacy and safety of continuous progestin therapy with LNG-IUS in the treatment of low grade endometrioid carcinoma, but this study was limited by a relatively short follow-up period.

Hysteroscopic resection is essential for a good prognosis for early stage EC. Many clinicians [22, 23] have studied this strategy, in young women with intramucous G1 EC, resulted in a complete regression rate of 96.3% (26/27), with a recurrence rate of 7.7% (2/26). In the presented case, during the second hysteroscopy, the authors performed an endometrial tumor resection, which may have played a key role in her positive prognosis.

LNG-IUS and supplemental oral progestin appear to be a safe and effective management for early-stage endometrial cancer patients who desire to retain their reproductive potential. Close surveillance to evaluate treatment response is of paramount importance and a three-month interval appears to be the most frequent approach [24]. Various intervals of follow-up have been reported, ranging from endometrial sampling every month to every 6–7 months [25]; however, a three-month interval appears to be the most frequent approach [26]. Given that the relapse rate is higher than 40% post-childbirth, women should also consider hysterectomy, which remains the standard treatment. Hysteroscopy, being the undisputed gold standard for the examination of the uterine cavity, is a routine procedure in these women [27].

Conservative treatment with progestins and LNG-

IUS is generally considered safe and feasible fertility-sparing approach only for young women with well-differentiated, early-stage EC with no myometrial invasion. Various methods to evaluate myometrial invasion have been studied, including transvaginal ultrasonography and CT, and contrast-enhanced MRI. With MRI being the most commonly used method to estimate the depth of myometrial involvement [28, 29]. Prior to commencement of progestin therapy, it is crucial to rule out myometrial invasion and adnexal involvement.

In conclusion, with intensive surveillance to detect disease persistence or recurrence, LNG-IUS and supplemental oral progestin appear to be a safe and moderately effective treatment in women diagnosed with well-differentiated and early-stage EC who desire to retain their reproductive potential. A careful stage and follow-up of the patients is essential to achieve success with this protocol. Further close surveillance to evaluate treatment with hormonal therapy is necessary according to risk of treatment failure. As the original predisposing factors for endometrial malignancy often persist, long term follow-up is essential.

Authors' contributions

S. liu and W. Lv: study design and manuscript writing. F. Ruan, M. Shi, Y. Liu, W. Li: performed research. B. Bi, H. Dan: literature review and data analysis.

Ethics approval and consent to participate

Written consent were obtained with the informed consent of all participants. The institutional review board of the Tongde Hospital of Zhejiang Province approved the study, code [2019]009.

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Conflict of interest

There are no conflicts of interest to declare for any of the authors.

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