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Original Article

Clinicopathological analysis of fertility-sparing treatment and pregnancy outcomes in young women with early-stage endometrial carcinoma

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Abstract: Background: Although the peak incidence of endometrial carcinoma is in postmenopausal women, it affects young women who wish to preserve fertility. The aim of this study was to assess oncologic and reproductive outcomes of fertility-sparing treatment using hysteroscopic resection followed by progesterone for early-stage endometrial carcinoma in young women in the western region of China. Methods: Retrospective analysis is used for analyzing the clinicopathological data, recent curative effect, and pregnancy outcomes of eight patients with early-stage endometrial carcinoma, who were managed conservatively for fertility-sparing purposes in West China Second University Hospital, Sichuan University from June 16, 2008, to December 31, 2010. Results: We evaluated eight patients whose median age was 31 years (range 23-37 years). The median follow-up time was 79.5 months (range 63-93 months) and none had recurrence yet. Of the eight patients, six had endometrial carcinoma (stage IA, G1-2) and two had malignant endometrial polyps. Five cases were treated by hysteroscopic resection followed by administration of high-dose progesterone, and the other three cases, after being pathologically tested with hysteroscopy, were changed to radical treatment or radiotherapy. In five cases who were received hormone therapy, four had successful pregnancies (three conceived naturally, and one used artificial reproductive technology) a median 7.5 months from the end of therapy (range 1-12 months), resulting in three live births. While three patients delivered at term via a cesarean section, one patient had an induced abortion on account of family considerations. The remaining patient failed to become pregnant due to the complications of polycystic ovary syndrome (PCOS). Conclusions: Combination of hysteroscopic resection and progesterone therapy represent a safe and feasible conservative management of early-stage endometrial carcinoma in selected patients wishing to preserve fertility. Key factors to success with this approach include choosing suitable cases under accurate clinicopathological diagnosis, thorough patient counseling, and close postsurgical follow-up.

Keywords: Endometrial carcinoma, fertility preservation, hysteroscopy, hormone therapy, long-term follow-up

Introduction

Endometrial carcinoma generally occurs in menopausal women. Approximately 10% of women will be diagnosed before menopause, and those who are under 40 years old account for 5% to 29%, and young patients are tending to increase [1, 2]. Surgery is the preferred treatment for women with endometrial carcinoma, which includes hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy, while surgical staging offers the most accurate prognostic information. The patients who have been treated in the early stage have better prognosis. However, young patients with early-stage endometrial carcinoma often have a history of infertility, with low-risk pathologic types and well-differentiated histologic grade, as well as without extrauterine metastasis. Therefore, they generally have a strong desire

to preserve fertility. As for these patients, in 1960s and 1970s, hormone therapy (generally progesterone) had been attempted as a conservative treatment overseas [3]. Growing evidence demonstrates that fertility-preserving treatment is feasible for young women with early-stage, low-grade endometrial carcinoma. However, there is still a lack of published data on long-term outcomes and prognostic factors.

Therefore, to accumulate data, we performed a retrospective review of our institutional experience on the clinical data of eight cases who received conservative treatment measures for well-differentiated endometrial carcinoma at presumed stage IA for long-term outcomes and prognostic factors.

Methods

Patients selection

From June 16, 2008, to December 31, 2010, there were altogether eight patients with a strong desire to preserve their fertility potential who were enrolled for conservative therapy at the Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, China.

Inclusion criteria were: (1) age younger than 40 years; (2) the following histological diagnosis: endometrial adenocarcinoma or adenoacanthoma, endometrial polyp canceration; (3) grade 1 or grade 2 differentiation; (4) absence of myometrial invasion, cervical invasion, and extrauterine spread according to the results of transvaginal ultrasound or magnetic resonance imaging; (5) normal hepatic and renal function during therapy; (6) without contraindications for hormone treatment; (7) convenient for close follow-up; and (8) a strong desire to preserve fertility. Exclusion criteria included: (1) unusual histologic subtypes, such as serous carcinoma, clear cell carcinoma, mucinous carcinoma, and so on; (2) poorly differentiated; (3) serious cardiac insufficiency; (4) history of thrombosis; (5) contraindications for progesterone treatment; and (6) depression.

Fertility-sparing treatment

Eligible patients were managed conservatively by a combination of hysteroscopic resection of the tumor and hormone therapy for fertility-sparing purposes. First of all, they were counseled comprehensively for the option of fertility-sparing treatment and the risks of recurrence or progression of disease, and signed informed consent. Next, under general anesthesia, an operative hysteroscopy was performed to remove lesions. The cervix was fully dilated to 10 mm with Hegar's dilator, and the uterine cavity was distended by a medium of 5% glucose injection or 0.9% physiological saline, so as to maintain intrauterine pressure ≤130 mm Hg. A 5-mm cutting loop electrode and recommended pure cutting output power (monopolar 60 W, bipolar 40 W) were used to resect the tumor lesion. The original histologic slides and the immunohistochemistry results always were reviewed by two gynecologic cytopathologists independently. Those who were proved to be well, with medium-differentiated endometrial adenocarcinoma or endometrial polyp canceration without invasion of myometrium and of resection margins by postoperative pathologic examination, were treated with high-dose progesterone. Medication regimen of megestrol acetate (MA) 160 mg or medroxyprogesterone acetate (MPA) 250 mg was taken orally every day in combination with liver-protecting treatment by administration of bifendate, creatinine, and vitamin C, which continued for 6 months at least. Patients were advised to prepare for pregnancy immediately after completing their hormone therapy. If necessary, assisted reproductive technology could be carried out. When childbearing completed, they were encouraged to undergo surgical treatment. If postoperative pathologic examination indicated invasion of myometrium or of resection margins, then traditional surgery would be conducted. Although four of eight patients were treated before 2009, the FIGO stages were reassigned according to the 2009 FIGO surgical staging classification.

Evaluation of therapeutic effects and follow-up

In the period of medication, liver function was regularly examined. Evaluation of therapeutic effects was performed by hysteroscopic resection or dilatation and curettage every 3 months for the first year. The following criteria were adopted: complete response (CR) was defined as total absence of tumor cells during the follow-up pathologic examination of biopsy specimens after hormone therapy. Time to CR was calculated from the start of treatment to first negative biopsy. No response (NR) was indicated if negative biopsy lasted less than 6 months with subsequent progression. Recurrence was

Table 1. General characteristics of the study participants with and without CR

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age (y)	23	25	35	32	26	37	30	33
BMI (Kg/m^2)	21.78	21.08	20.19	25.71	25.63	22.66	26.18	29.69
Gravidity	0	0	2	0	0	0	0	0
Parity	0	0	1	0	0	0	0	0
Infertility (y)	5	-	-	3	6	8	-	3
Menarche (y)	12	12	13	14	16	13	14	13
PCOS (y)	-	-	-	-	3	-	-	-
Symptomatology	Menstrual irregularities	Menorrhagia	Menorrhagia	Menorrhagia	Menstrual irregularities	Menometrorrhagia	Menorrhagia	Menstrual irregularities
TVS	Increased endometrial thickness	Nothing abnormal detected	Intrauterine strong echo	Intrauterine strong echo	Increased endometrial thickness	Intrauterine heterogeneous echo	Nothing abnormal detected	Increased endometrial thickness
Histology	EA, G2	Focal cancer of adenomyomatous endometrial polyp	EA, G1	Suspected gland malignant transformation in polyps	EA, G1, ER (+++), PR (+++), P53 (+), Ki 67 positive rate 50%	EA, G1-G2, With invasion to superficial layer of myometrium	EA, G2, With invasion to superficial layer of myometrium	EA, G2, ER (+++), PR (+++), P53 (-), Ki 67 positive rate 70%
FIGO Stage	IA	IA	IA	IA	IA	IA	IA	IA

EA, endometrial adenocarcinoma; G1, well differentiated; G2, moderate differentiated; PR, progesterone receptor; ER, estrogen receptor; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; TVS, transvaginal ultrasonography.

Table 2. Results and follow-up

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Surgical treatment	HYS+biopsy	HYS+biopsy	HYS+biopsy	HYS+biopsy	HYS+biopsy	HYS+biopsy	HYS+biopsy	HYS+biopsy
Drug treatment	MA 160 mg, qd	MA 160 mg, qd	MA 160 mg, qd	MA 160 mg, qd	MPA 250 mg, qd	-	-	-
Treatment time (m)	4	6	6	6	6	-	-	-
Curative effect	Not assessed	Not assessed	A few glandular atypical hyperplasia	Focal complex hyperplasia	Decidual changes	None	None	None
Remission time (m)	-	-	8	6	4	-	-	-
Pregnancy time	One month after drug withdrawal	11 months after drug withdrawal	4 months after drug withdrawal	12 months after drug withdrawal	-	-	-	-
Delivery mode	Cesarean section	Cesarean section	Abortion	Cesarean section	-	-	-	-
Gestational week (w)	39^{+3}	38^{+4}		39^{+4}	-	-	-	-
Recurrence	None	None	None	None	None	None	None	None
Follow-up (m)	89	88	71	79	89	63	93	64

HYS, hysteroscopy; MA, megestrol acetate; MPA, Medroxyprogesterone Acetate.

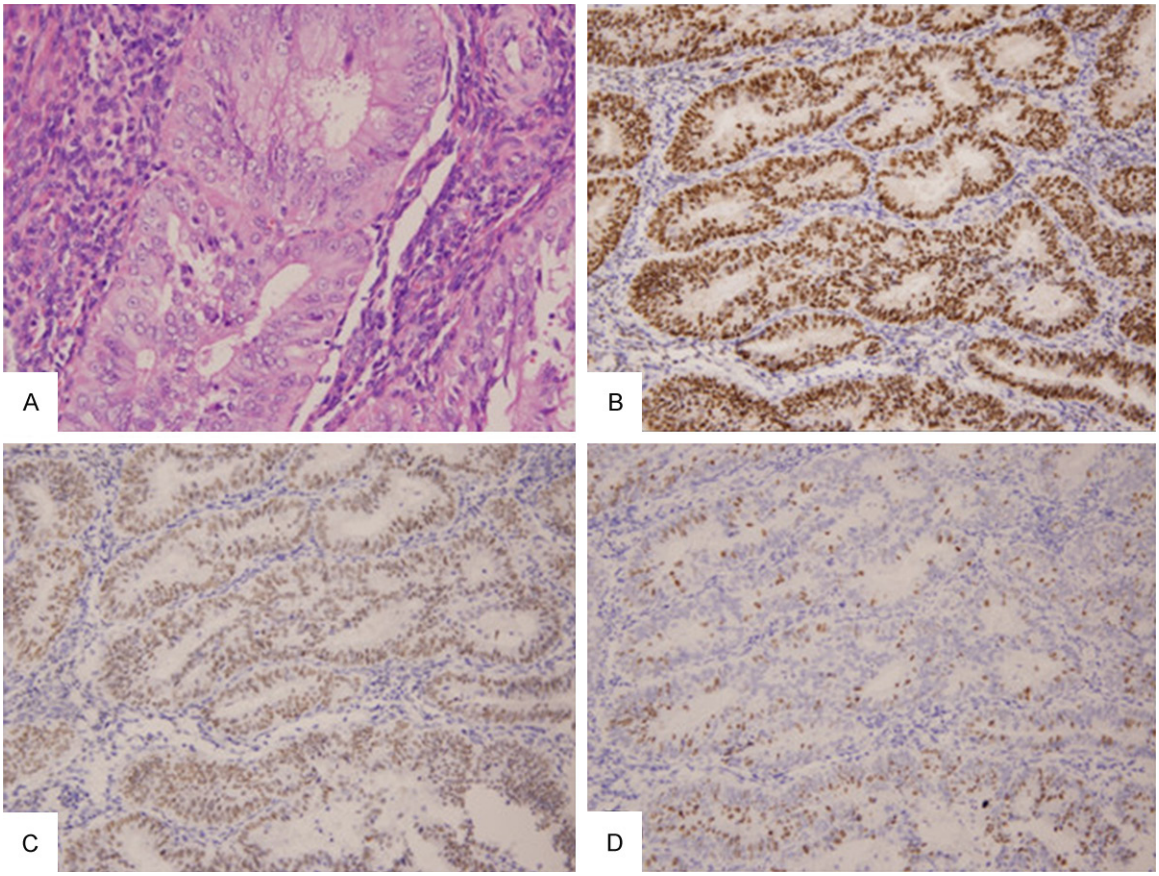

Figure 1. Photomicrographs of Endometrioid adenocarcinoma. A. High power view of well-differentiated endometrioid adenocarcinoma (IHC×400). B. Strong immunoreactivity for progesterone receptor (PR) in the endometrioid adenocarcinoma (IHC×200). C. Strong immunoreactivity for estrogen receptor (ER) (IHC×200). D. The positive rate of Ki67 is 50% (IHC×200).

defined by reappearance of cancerous lesion after achieving CR lasting for at least 6 months [4, 5]. If the patient showed NR on the first evaluation, the plan was to switch to traditional surgery. After complete remission, close follow-up in the outpatient clinic is still necessary.

Results

Patient characteristics

Median patient age was 31 years (range 23-37 years). The body mass index (BMI) ranged from 20.19 to 29.69 kg/m^2 (median, 24.15 kg/m^2), and four patients' BMIs were > 25 (50%). Five out of eight suffered primary infertility, in which one case suffered from polycystic ovarian syndrome (PCOS). One case was complicated by rheumatic heart disease and atrial fibrillation after cardiac valve replacement. Clinical characteristics of the patients are detailed in **Table 1**. Most of the eight patients took menstrual disorder and menorrhagia as clinical manifestations. Preoperative transvaginal ultrasonography indicated that there was no evidence of myometrial invasion or cervical invasion, nor extrauterine spread. Three patients were biopsied with diagnostic hysteroscopy——in two women the diagnoses were made during infertility workup. In addition, workup for irregular bleeding led to the diagnosis of the other five patients by dilatation and curettage.

All eight patients were treated with hysteroscopic resection of tumor lesion and the endometrium near the lesion. In three patients, postoperative pathologic examination suggested myometrial invasion, while one of them was complicated by rheumatic heart disease and atrial fibrillation. By considering higher risks of surgery, whole pelvic radiation and an intracavitary implant radiation treatment were chosen

by this patient. Two cases were changed to subradical hysterectomy with salpingo-oophorectomy, with pelvic and periaortic lymph node resection. Among the five cases complying with standards in postoperative pathologic examination, one patient completed 6 months of therapy with MPA 250 mg daily and four patients were treated with MA 160 mg daily for 4-6 months (**Table 2**). Three patients were in complete remission after 4 to 8 months' progesterone treatment; two patients with poor compliance were not assessed by endometrial biopsy, but examined by transvaginal ultrasonography, and then they became normally pregnant. During drug therapy, one patient complained of weight gain with edema, which spontaneously resolved after hormone treatment.

Pregnancy outcomes

Median follow-up time was 79.5 months (range 63-93 months), and none had recurrence during this period. Five patients treated with endoscopic surgery and hormone therapy showed CR lasting at least 63 months. At present, four out of five had successful pregnancies, in which three had achieved spontaneous pregnancies, and one conceived with the help of assisted reproductive technology (ART) a median 7.5 months from the end of therapy (range 1-12 months). Whereas three patients delivered at term via a cesarean section, one patient had an induced abortion because of family considerations (**Table 2**). The average weight of the newborns was 3,550 g (3,500-4,050 g), and the average length was 51 cm (50-52 cm). Two out of three were female. The remaining one patient failed to become pregnant due to the complications of PCOS and is actively attempting to conceive.

Discussion

Etiology and high risk factors

Endometrial carcinoma in young women under 40 years of age is generally estrogen-dependent. The American Cancer Society (ACS) indicates that women are at an increased risk of endometrial cancer due to a history of unopposed estrogen therapy, tamoxifen therapy, late menopause, nulliparity, infertility, failure to ovulate, and/or obesity [6]. The mechanism may be because of prolonged periods of estrogenic stimulation of the endometrium without the counteracting effect of progesterone. Therefore, endometrium undergoes hyperplasia and even malignant transformation. Fugiwara had reported that the incidence of endometrial carcinoma (EC) and atypical hyperplasia (AH) detected from routine infertility investigations at Tochigi Central Clinic was 0.03% (6/19,826) and that of endometrial carcinoma was 0.02% (4/19,826) [2], but the overall endometrial carcinoma incidence among 30-34 years old in Japan was 0.0027% and 0.0053% in 35-39 years old [7]. Hence, the disease incidence of infertile patients was 3-7 times higher than the overall incidence. Our study showed that five cases were complicated with primary infertility. As for these patients, it is possible that owing to anovulation or ovulatory disorder, the endometrium was continuously stimulated by estrogens without the counteracting effect of progesterone and then underwent pathological changes. Besides, during pregnancy, endometrium correspondently changes with the effects of estrogens and progestogens generated by the placenta; in lactation, due to the influence of hypothalamus and hypophysis, ovarian function is temporarily inhibited and endometrium is free from the stimulation of estrogens. Therefore, the endometrium of the infertile patients cannot be specially protected in the extraordinary period. As for PCOS patients, ovarian follicles are unable to mature and to ovulate, while endometrium is continuously stimulated by estrogen. The lack of the adjustment of progesterone and regular shedding of endometrium leads to the proliferative changes of endometrium [8]. The risk of developing endometrial cancer for PCOS patients is four times higher than that of the general population of the same age. Among the patients of endometrial cancer under 40 years old, about 19% to 25% of patients have PCOS, whereas in this research it was 12.5%.

Strict indications

Currently, as to the young patients with endometrial cancer who received fertility-sparing treatment, literature reports that most can achieve complete remission, and possibly give birth, but still few patients relapse [9, 10]. So indications for fertility-sparing treatment of early-stage endometrial cancer should be stringently controlled. It is generally considered that

the following requirements need to be meet: under 40 years old; a strong desire to preserve fertility; histological type is endometrial adenocarcinoma or adenoacanthoma, well differentiated; progesterone receptor is positive; absence of myometrial invasion, cervical invasion, and extrauterine spread according to the results of transvaginal ultrasound or MRI; normal hepatic and renal function; no contraindications for drug treatment; convenient for close follow-up; normal liver and renal function; and without drug treatment contraindications. Some scholars also put forward that laparoscopic evaluation including adnexal exploration, peritoneal cytology, and possibly pelvic lymphadenectomy should be performed to confirm the absence of extrauterine disease [11]. Imai et al. reported that patients with grade 2 endometrial carcinoma responded initially to medroxyprogesterone acetate [10]. In our research, one case with grade 2 carcinoma who initially responded to conservative treatment has successfully conceived and given birth to one healthy infant. Regarding moderately differentiated (grade 2) adenocarcinoma, conservative treatment could be an alternative to hysterectomy with close follow-up during therapy period and after giving birth. The curative effect and any signs of recurrence should be assessed as soon as possible. Complete response (CR) is reported to be significantly related to positive expression of progesterone receptor (PR) [12]. As a result, positive expression of PR is the precondition of the use of progestogen for fertility-preserving treatment (**Figure 1**). In this research, the detection rate of PR before treatment is just 25% (2/8), which needs to be paid great attention.

In addition, assessing whether pathological changes are entirely localized to the endometrium in the preoperative staging is very important for predicting curative effect and prognosis. At present, transvaginal sonography (TVS) and magnetic resonance imaging (MRI) are widely adopted to estimate the depth of myometrial invasion and cervical infiltration. MRI can also evaluate metastasis of pelvic lymph nodes or other organs. Savelli has reported that contrast-enhanced MRI and TVS perform equally well in the assessment of myometrial invasion, meanwhile TVS shows a trend toward better performance in the detection of cervical lesions [13]. TVS is used the most widely. However, in most literature, MRI is more accurate than TVS for diagnosing early endometrial cancer and staging, but is more expensive and time consuming. Therefore, according to the situation, TVS could potentially be proposed as the first-line imaging test in patients with endometrial carcinoma. If TVS gives images of poor quality or precise preoperative staging is crucial, MRI could be conducted as a second-line imaging examination [13]. But, for women desiring future fertility, it is reasonable that a combination of both transvaginal sonography and MRI could be more accurate in detecting myometrial and cervical invasion [5]. This research employs conservative surgery and high-dose progestogen in treatment. After hysteroscopic resection, pathological examination can precisely confirm whether there is invasion of myometrium or resection margins. We believe hysteroscopic resection is the best procedure to evaluate tumor differentiation degree and the myometrial involvement, thus determining the treatment options. Compared with the administration of progestogen only, the combination treatment can reduce tumor loading, improve therapeutic effect of hormone treatment, and shorten treatment time [14-16].

Treatment plan and therapeutic effect evaluation

There are mainly two protocols presently are used for fertility-sparing management on young patients with early-stage endometrial cancer: hysteroscopic resection followed by oral progesterone therapy and single use of high-dose progestogen treatment.

However, there is no unified dosage and administration of progesterone treatment. Generally, treatment could include oral megestrol acetate (MA) 160-320 mg/d or medroxyprogesterone acetate (MPA) 200-500 mg/d, intramuscular injection of hydroxyprogesterone caproate 1-3 g/week, and so forth. After documentation of complete remission, the patients then were closely followed up in the outpatient clinic. During progesterone treatment, vaginal ultrasonography, diagnostic dilatation and curettage, or hysteroscopy with biopsy are performed every 3 months for the first year and every 6 months for the next 2 years. It is reported that the anticancer effects of progesterone

on endometrial cancer cells show on the 10th week of treatment [17]. Ramirez et al. summarized that in 62 cases of grade 1 endometrial adenocarcinoma who were treated with hormonal therapy, the median time to response was 12 weeks (range, 4-60 weeks) [18]. Consequently, the first assessment of progesterone's curative effect should not come before the 12th week since the beginning of treatment. According to the literature, most cases reached complete remission after 6 months of progesterone treatment. In the first assessment, those patients who were not in complete remission would be additionally treated with course under close monitoring as long as there was no evidence of tumor progression. Those patients without significant improvement after continuous treatment should be treated in standard therapeutic schedule, to avoid being affected adversely. As for the patients who were not effectively treated by progestogen, there are still some reports on the successful treatment by using tamoxifen and gonadotropin-releasing hormone analogue (GnRHa), or levonorgestrel-release intrauterine device (LNG-IUD) plus GnRHa [14, 19, 20]. The duration of the treatment is inconclusive. Niwa et al. [21] considered that progesterone treatment should be applied for 6 months or 2 months after complete pathological remission. Some scholars also proposed that, in order to obtain a higher effective rate, the treatment time should not be less than 1 year [18]. In this research, the average complete remission time of endometrial cancer was 6 months. With review of the literature, it is considered that the duration of hormonal therapy required to maximize therapeutic response is at least 6 months. That is, even patients who were assessed to have had pathologic lesions disappear in the third month ought to take consolidation therapy, until the pathologic results of endometrial biopsies are negative two consecutive times. Currently, it is suggested to assess therapeutic effects by hysteroscopic biopsy instead of diagnostic curettage in blind sight.

Selection of ART

In our study, three cases achieved spontaneous pregnancies, and one conceived with the help of ART. Current studies indicate that conservative treatment of well-differentiated early-stage endometrial carcinoma in young patients, combined with ART, if needed, does not seem to worsen the prognosis [22, 23]. Consequently, after the remission of progesterone treatment, patients can be naturally pregnant or with help of ART. However, further evaluations are still required.

Given the risks of disease progression or relapse, close monitoring is still required after delivery. Whether hysterectomy and bilateral salpingo-oophorectomy is conducted after delivery depends on patient's age, risk of recurrence, and tolerance of drug therapy. If surgery is not performed, close observation with endometrial sampling every 6 months is advisable [24]. Those who want to avoid pregnancy are encouraged to use oral contraception or a progestin intrauterine device, or intramuscular injection of 150 mg MPA every 12 weeks to maintain the treatment effect. Besides, early detection of recurrence with the use of regular transvaginal ultrasound, monitoring of serum CA125, as well as at least one hysteroscopy every half a year is important.

Conclusions

In conclusion, data reported here show that the majority of patients with grade 1-2, stage IA (without myometrial invasion) endometrial carcinoma, who underwent a combination of hysteroscopic resection and progesterone therapy, achieved childbearing naturally or with ART. Furthermore, none of the five patients have had recurrence up to date with a long-term follow-up. Hence, this conservative treatment, under strict indication and close follow-up, might provide the opportunity for young women with stage IA endometrial carcinoma to preserve fertility. Further optimization and standardization of this therapeutic regimen may increase treatment efficacy, which needs larger prospective multicenter randomized controlled clinical trials to confirm.

Disclosure of conflict of interest

None.

Authors' contribution

QZ and GS designed and conducted the study; QZ and JYR collected the patients' clinical information and follow-up data. QZ and TH analyzed and interpreted the data. QZ drafted the manu-

script; GS and HQL edited and revised the manuscript. All authors read and approved the final version of the manuscript.

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