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ORIGINAL ARTICLE

Prolonged conservative treatment in patients with recurrent endometrial cancer after primary fertility-sparing therapy: 15-year experience

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Abstract

Objective To evaluate the efficacy and prognosis of repeated treatment on patients with recurrent endometrial cancer (EC) after complete remission for primary fertility-preserving therapy.

Materials and methods We performed a retrospective study of patients with presumed stage IA endometrial cancer who had recurrence after achieving complete remission by fertility-preserving management at the Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, from January 2003 to April 2018. For each patient, medical records and pathology reports were reviewed. The demographic features, treatment efficacy, tumor prognosis, and reproductive outcome were analyzed.

Results Of the 41 recurrent patients with a median disease-free interval period of 16 months (range, 5–55 months), 23 were diagnosed at recurrence as EC, and 18 were diagnosed as atypical hyperplasia (AH) or endometrial intraepithelial neoplasia (EIN). 26 patients received repeated fertility-preserving treatment, and 23 patients were evaluable for efficacy. The complete response (CR) rate of repeated treatment (19/23, 82.6%) was lower than that of primary fertility-preserving treatment (161/170, 94.7%) with borderline significance ($P=0.053$). The CR rate of AH/EIN patients was higher than that of EC patients with no statistical difference (92.9% vs 66.7%, $P=0.260$). Among 19 patients achieved CR, 3 got pregnant and delivered successfully, while 3 had a second relapse. Four cases failed to response to the repeated treatment and underwent definitive surgery. 15 patients referred to definitive surgery directly after recurrence and one of them had a pelvic recurrence after 120 months. All patients are alive without evidence of disease at last follow-up.

Conclusions For patients with recurrent EC after primary fertility-preserving treatment, repeated fertility-preserving treatment can still achieve a promising response and patients have possibilities of completing childbirth.

Keywords Endometrial cancer · Recurrence · Fertility-preserving therapy · Oncofertility

Introduction

Endometrial cancer (EC) is one of the most common gynecological malignancies. The incidence has gradually increased in decades [1, 2]. About 25% of the patients are diagnosed in premenopausal women and 5–7% patients are younger than 40 [3, 4]. A significant number of reproductive-age women are delaying childbearing, which has led to an increase in the number of nulliparous women at the time of their diagnosis [4]. A higher proportion of EC diagnosed in younger age group is characterized by well-differentiated endometrioid endometrial carcinoma (EEC) and early stage. It has been shown that they may have a more favorable prognosis than older patients [4]. Therefore, conservative management to

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preserve fertility in young patients with EC has gradually arose great attention in recent years.

In 1997, Kim et al. [5] reported EC patients conceived successfully after progestin treatment for the first time. As the improvement of selection of cases, therapeutic dose, endometrial evaluation, and follow-up system, the use of progestin in fertility preservation is gradually standardized and its effectiveness has also been confirmed [6–8]. Other therapies which include gonadotrophin-releasing hormone agonist(GnRH-a), intrauterine devices containing progestin, or a combination of these therapies have also been reported in a limited number of cases [9, 10]. It has been reported that the remission rate of patients with endometrial cancer is 50–80%, and the pregnancy rate is 25–30%. However, the recurrence rate is as high as 24–40% [6–11]. Moreover, some patients still wish to retain fertility at the time of relapse, but little is known about the outcome of repeated conservative treatment. For now, few reports on the efficacy of repeated conservative treatment against recurrent EC have been published [12, 13].

The aim of the current study is to analyze the efficacy and prognosis of repeated conservative treatment in cases with recurrence after fertility-preserving treatment against early EC.

Materials and methods

Study design and patients

We reviewed the medical records of patients with EEC who suffered from recurrence after achieving complete response by fertility-preserving treatment and had an evaluable therapeutic effect in Peking Union Medical College Hospital from January 2003 to April 2018. This retrospective study was approved by the Ethics Committee of Peking Union Medical College Hospital. Recurrent disease was defined as the presence of atypical hyperplasia/endometrial intraepithelial neoplasia (AH/EIN) or EC after a complete response to conservative treatment. All the pathology slides were reviewed by 2 experienced gynecologic pathologists. According to the degree of the lesion, AH can be divided into mild, moderate, and severe AH. Mild atypical hyperplasia (AH1): the outline of the gland is slightly irregular, and the glandular epithelial cells are mildly shaped. Severe atypical hyperplasia (AH3): the outline of the gland is obviously irregularly branched, with budding and papillary structures in the glandular cavity, and glandular epithelial cells are abnormally shaped. Moderate atypical hyperplasia (AH2): the lesion lies somewhere in between.

Patients were included for repeated fertility-preserving treatment if they fulfilled the following conditions: (1) aged younger than 45 years, having a strong desire to preserve fertility; (2) diagnosed as AH/EIN or well-differentiated endometrioid endometrial carcinoma (EEC) which was confirmed by two gynecologic pathologists; (3) lesions confined to endometrium by imaging (ultrasound or MRI); (4) had good compliance for treatment; (5) without contraindications for medications; and (6) signed informed consent form and approved by the ethics committee. Patients with myometrial invasion, cervical stromal invasion, or extrauterine lesions were treated with a standard treatment including hysterectomy. Furthermore, patients who did not wish to preserve their fertility were also excluded.

For each patient, the clinical data of recurrence including recurrence pathology, drug dose, therapeutic time and efficacy, prognosis, and pregnancy outcome were collected.

Repeated fertility-preserving treatment

Type and dose of drugs The medication for repeated treatment was in accordance with the initial regimen (MPA 500 mg/day or MA 160 mg bid; injection of gonadotropin-releasing hormone agonist (GnRH-a) every 4 weeks combined with letrozole 2.5 mg/day or levonorgestrel-releasing intrauterine system(LNG-IUS) inserted [10, 14]. For patients with abnormal liver function, obesity, or family history of deep venous thrombosis (DVT), the initial progestin therapy was changed to GnRH-a combined with letrozole or ING-IUS. After achievement of complete response, patients with recurrent pathology of EEC or AH3 would be administered for another 1–3 months for consolidation therapy.

Evaluation The patients underwent follow-up with ultrasound examination for clinical observation every month and endometrial sampling via hysteroscopy and curettage to assess the endometrial response every 3 months. Complete response (CR) was defined as the absence of evidence of hyperplasia or carcinoma. Partial response (PR) was defined as histologic regression or endometrial decidual change. Stable Disease (SD) was defined as the persistence of EC or AH/EIN. Progressive Disease (PD) was defined as progression to a lesion of higher grade or clinically progressive disease including myometrial invasion, extrauterine disease, or lymph node metastasis. The recurrence-free interval (RFI) was defined as the period from the end of initial treatment to the time at which recurrence was pathologically confirmed. The follow-up duration was defined as the period from the end of initial treatment to the time of last contact.

Maintenance and follow-up after CR Patients who wished to have child rapidly referred to the Department of Reproductive Endocrinology to receive assisted reproductive technology (ART). Those who had no birth plan temporary continued with LNG-IUS or oral low-dose cyclic progestin (dydrogesterone 10 mg bid or MPA 10 mg/

day from 15th to 24th days of the menstrual cycle) and received evaluation of CA125 and pelvic ultrasound every 3 months. Endometrial biopsy by hysteroscopy or D&C was performed every 6 months for endometrial evaluation.

Statistical analysis

Statistical analyses were performed using SPSS Statistics ver. 24 (IBM Corp., Armonk, NY, USA). The mean and median values were compared using Student *t* test or Mann–Whitney *U* test after the Kolmogorov–Smirnov test for evaluating the normality of distribution of variables. Frequency distribution was compared using Chi-squared test; however, if the expected frequency was less than 5, the Fisher's exact test was used. All *P* values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Characteristics of patients with recurrence

There was a total of 170 EEC patients who had undergone fertility-preserving treatment with evaluable therapeutic effect in Peking Union Medical College Hospital. 161 (161/170, 94.7%) patients achieved CR after initial treatment, and 113 cases of which were followed up for more than 6 months after CR. 41 (41/113, 36.3%) cases suffered relapse disease after achieving CR and were included in this analysis (Fig. 1).

Clinical characteristics of patients with recurrence are shown in Table 1. Of all 41 patients with recurrence, 41 patients received ultrasound examination, and 21 (51.2%) patients were also examined with MRI. Of patients received MRI, 14.3% (3/21) were suspected with myometrial infiltration (2 for superficial myometrial infiltration and 1 for deep

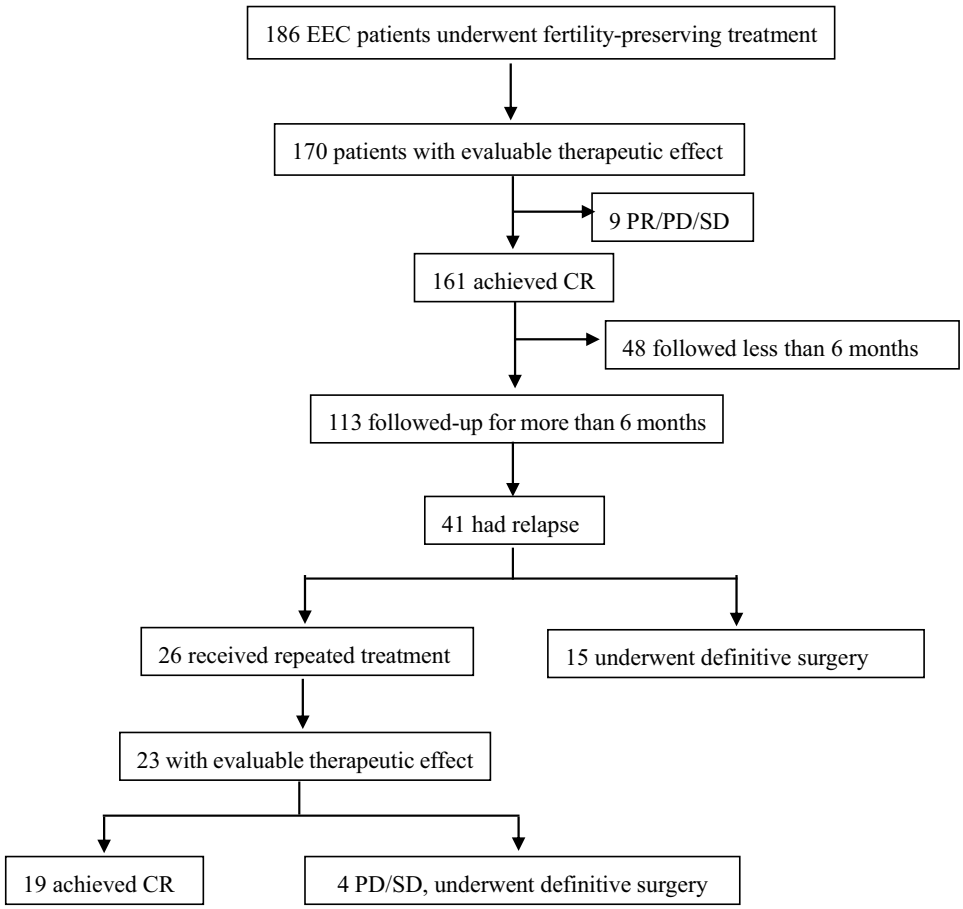

Fig. 1 Study profile. *EEC* endometrioid endometrial cancer, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CR* complete response

Note: EEC, endometrioid endometrial cancer; PR, partial response; SD, stable disease; PD; progressive disease; CR, complete response.

Table 1 Clinical characteristics of patients with recurrence

Characteristics	
Age	29 (22–40)
Body mass index	25.4 (19.0–35.0)
History of infertility(%)	34 (81.0%)
Polycystic ovarian syndrome (%)	17 (40.5%)
Median initial CR time (month)	6 (2–12)
Median initial therapic time (month)	9 (2–15)
Pathology of recurrence	
AH/EIN	18 (43.9%)
EC	23 (56.1%)
Imaging examination	
MRI and ultrasound	21(51.2%)
Ultrasound	41(100%)
Recurrence-free interval (month)	16 (5–55)
Median follow-up period (month)	33 (5-160)

CR complete response, *AH* atypical hyperplasia, *EIN* endometrial intraepithelial neoplasia, *MRI* magnetic resonance imaging, MRI

myometrial infiltration) and all of them referred to definitive surgery directly after recurrence, which has also been proven by final pathology. However, of the remaining 18 patients without imaging evidence of myometrial infiltration, 6 patients eventually received definitive surgery and 3 were confirmed with superficial muscular infiltration. The period from the termination of the initial treatment to recurrence was 5–55 months. The median recurrence-free interval was 16 months. At the time of relapse, 18 and 23 patients were pathologically diagnosed with AH/EIN and EEC, respectively. The median follow-up duration was 33 (5–160) months.

Treatment and outcome of patients after recurrence

Drug and dose selection of repeated fertility-preserving treatment

26 of the 41 relapsed patients received repeated treatment for fertility preservation. 19 (73.1%) patients were treated according to the initial treatment regimen and 7 patients' regimen was changed. The details of treatment regimen and prognosis are shown in Supplementary Table 1. Two cases changed from MPA to GnRH-a combined with letrozole/LNG-IUS due to abnormal liver function. One patient with obesity and family history of DVT changed from MA to GnRH-a combined with LNG-IUS. Two cases originally chose primary regimen MPA/MA and subsequently change regimen to GnRH-a combined with letrozole due to poor response. One case of AH1-2 and one case of EIN received natural progesterone cycle withdrawal therapy and achieved CR after 5–6 months of treatment.

Outcome of patients receiving repeated fertility-preserving treatment

Of 26 patients who received repeated conservative treatment after relapse, 23 patients' therapeutic effect can be evaluated and the remaining 3 patients were still under treatment (Table 2). In the second-round preserving treatment, 19 patients (19/23, 82.6%) achieved CR which tended to be lower than the CR rate of initial treatment ($P = 0.053$) (Table 3). There is no significant difference in the duration to achieve CR between the initial and repeated treatment groups (6.0 vs 5.8 months, respectively) (Table 3). In patients who have had complete response to repeated conservative treatment, 3 patients had a second recurrence and 1 patient had a third recurrence. Two patients received a third-round treatment at second recurrence and achieved CR, and one referred to definitive surgery directly after the second recurrence.

Four patients underwent definitive surgery after failure (2 SD, 2 PD) of conservative treatment (Table 4). One of them underwent complete staging surgery and all of them retained one or both of the ovaries. On the basis of pathological findings, 2 cases were diagnosed as stage IA EC and 2 cases were diagnosed as double cancer (FIGO stage IA EC and FIGO stage IA OC) according to the criteria described by Scully and Young [15]. Notably,

Table 2 Outcome of initial and repeated treatment

Characteristics	Initial treatment	Repeated treatment	*P* value
CR rate	94.7% (161/170)	82.6% (19/23)	0.053
Therapeutic time to achieve CR (month)	6.0 (2–25)	5.8 (3–18)	0.574

Table 3 Treatment after relapse fertility-sparing therapy

Pathology of relapse	Repeated fertility preservation treatment group				Surgery group
	CR	No response	Unable to evaluate	Remission rate (%)*	
EC (23)	6	3	1	66.7	13
AH/EIN (18)	13	1	2	92.9	2
Total (41)	19	4	3	82.6	15

CR complete response, *EC* endometrial cancer, *AH* atypical hyperplasia, *EIN* endometrial intraepithelial neoplasia

*$P = 0.260$

Table 4 Clinicopathological characteristics of patients undergoing surgery after ineffective conservative treatment

Case	Pathology of relapse	Surgery	Final Pathology	Stage	Adjuvant therapy	Follow-up time (month)	Prognosis
1	G1 EEC	LH + RSO + LS	G1 EEC, superficial myometrial infiltration, and lower segment of uterus involvement, LVSI(-)	EC: IA	VBT + CT	66	NED
			Right ovarian G1 EA	OC: IA			
2	G1 EEC	TAH + LSO + RS + PLN	G1-2 EEC, superficial myometrial infiltration, with lower segment of uterus involvement, LVSI(-)	EC: IA	NA	32	NA
			Left ovarian G1 EA	OC: IA			
3	G1 EEC	LH + BS + PLN + PALN	G2 EEC, superficial myometrial infiltration, with lower segment of uterus involvement, LVSI(-), LN(-)	IA	VBT	55	NED
4	AH2-3	LH + BS	G1 EEC, superficial myometrial infiltration, LVSI(-)	IA	No	82	NED

EEC endometrioid endometrial carcinoma, *EA* endometrioid adenocarcinoma, *OC* ovarian cancer, *LH* laparoscopic hysterectomy, *PLN* pelvic lymphadenectomy, *PLN* para-aortic lymphadenectomy, *TAH* transabdominal hysterectomy, *LSO* left salpingo- oophorectomy, *RSO* right salpingo- oophorectomy, *BS* bilateral salpingectomy, *LS* left salpingectomy, *LVSI* lymphovascular space invasion, *VBT* vaginal brachytherapy, CT chemotherapy (paclitaxel and carboplatin), *NED* no evidence of disease, *NA* not available

the pathology of 2 patients contained G2 endometrioid carcinoma, and all patients had pathologically confirmed superficial muscular infiltration which were not detected by pretreatment ultrasound. Moreover, preoperative image in Case 1 did not find any signs of coexisting intraparenchymal ovarian cancers. Case 1 received 6 cycles of paclitaxel and carboplatin combined with vaginal brachytherapy. Case 2 refused to receive adjuvant therapy postoperatively. Over the mean follow-up period of 59 months (range, 32–82 months), all patients were alive and free of disease except one patient lost to follow-up.

27 of 41 patients attempted to become pregnant after achieving CR in primary fertility-preserving treatment, and 3 achieved pregnancy before recurrence. Of 19 patients who achieved CR in second-round treatment, 13 patients expected to become pregnant immediately. Eight patients referred to assisted reproduction and 5 patients tried to conceive spontaneously. A total of 3 women achieved 4 times of clinical pregnancies. The mean period of time from CR to pregnancy was 25.6 months (range 7–48). Three patients (3/13, 23.1%) delivered at full term. Patients with complete remission were followed up for 17–110 months and 3 patients had a second relapse (3/19, 15.8%). Two patients still chose to preserve fertility and both of them achieved CR. The other patient underwent laparoscopic hysterectomy, bilateral salpingectomy, pelvic lymphadenectomy, and bilateral ovary biopsy. The postoperative pathology reported grade 2 endometrioid carcinoma with superficial myometrial invasion. The FIGO stage was IA. Currently, she was followed up for 9 months without evidence of tumor recurrence.

Patients referring to definitive surgery after recurrence

15 patients (AH/EIN 2 cases, EC 13 cases) underwent definitive surgery directly after recurrence and one of them returned to local hospital and lost to follow-up. The clinicopathological characteristics and prognosis of patients referring to definitive surgery at our hospital after recurrence are shown in Table 5.

Of the 14 patients undergoing surgery in our hospital, 7 received laparoscopic staging surgery, 6 received hysterectomy and bilateral salpingectomy, and 1 patient received hysterectomy and right salpingo-oophorectomy because of concurrent ovarian cyst. The postoperative pathology suggested 10 cases of stage IA EC, 1 case of stage IIIA EC, 2 cases of AH/EIN, and 1 case of double cancer (FIGO stage IA EC and FIGO stage IA OC). Adjuvant therapy was given to 2 cases (case 9 and case 12) in the form of chemotherapy with or without radiotherapy. One patient received secondary surgery and chemotherapy due to pelvic recurrence (left ureteral metastasis) at the 120th month after initial surgery and was free of disease at last follow-up. The other 13 patients were all alive without recurrence at the time of last contact, which was at a mean of 39 months (rang, 18–103 months).

Comparison between EC and AH/EIN in repeated fertility-preserving treatment

Treatment of patients after recurrence is shown in Table 2. Of the 23 patients with EC, 10 received repeated

Table 5 Clinicopathological characteristics and prognosis of patients referring to surgery after recurrence

Case	Pathology of relapse	Surgery	Final pathology	Stage	Adjuvant therapy	Follow-up time (month)	Prognosis
1	G1 EEC	LH + BS + PLN + ovary biopsy	G1EEC, superficial myometrial infiltration, LVSI(-), LN(-)	IA	No	52	NED
2	G1-2 EEC	LH + BS	G1-2 EEC,superficial myometrial infiltration, LVSI(-)	IA	No	18	NED
3	G1 EEC	LH + BS + PLN	G1EEC, superficial myometrial infiltration, LVSI(-), LN(-)	IA	No	34	NED
4	G1 EEC	TAH + RSO	G1EEC, superficial myometrial infiltration, LVSI(-)	IA	No	160	Recurrence at 120 month (Surgery + CT) NED
5	EIN	LH + BS + Ovary biopsy	G1EEC, superficial myometrial infiltration, LVSI(-)	IA	No	19	NED
6	G2 EEC	LH + BS + PLN	G2 EEC, intramucosa, LVSI(-), LN(-)	IA	No	28	NED
7	G1 EEC	LH + BS	G1 EEC, intramucosa, LVSI(-)	IA	No	52	NED
8	AH3	LH + BS	AH1-2	–	No	24	NED
9	G2 EEC	TRH + BSO + omenectomy + PLN + PALN + appenectomy	G2 EEC, deep myometrial infiltration, with lower segment of uterus, cervix and ovaries involvement, LVSI(+), LN(-)	IIIA	EBRT+ VBT + CT	103	NED
10	G1 EEC	LH + BS	G1 EEC, intramucosa, LVSI(-)	IA	No	31	NED
11	G1 EEC	LH + BS + PLN + Ovary biopsy	G1EC, superficial myometrial infiltration,, LVSI(-), LN(-)	IA	No	30	NED
12	G1-2 EEC	TAH + BSO + Omenectomy + appendectomy + multiple punch biopsy + PLN + PALN	G1-2 EEC, intramucosa, LVSI(-), LN(-)	EC: IA	CT	61	NED
			G1 EA right ovary	OC: IA			
13	G1 EEC	LH + BS	G1 EEC, intramucosa,, LVSI(-)	IA	No	19	NED
14	G1 EEC	LH + BS + PLN	AH2-3, LN(-)	–	No	39	NED

EEC endometrioid endometrial carcinoma, *EA* endometrioid adenocarcinoma, *OC* ovarian cancer, *LH* laparoscopic hysterectomy, *BSO* bilateral salpingo- oophorectomy, *PLN* pelvic lymphadenectomy, *PLN* para-aortic lymphadenectomy, *TAH* transabdominal hysterectomy, *RSO* right salpingo-oophorectomy, *BS* bilateral salpingectomy, *TRH* transabdominal radical hysterectomy, *EBRT* external beam radiotherapy, *VBT* vaginal brachytherapy, *CT* chemotherapy (paclitaxel and carboplatin), *NED* no evidence of disease

fertility-preserving treatment and 9 patients' therapeutic efficacy could be evaluated. Six patients achieved CR (6/9, 66.6%) and 3 patients' treatment was ineffective (1 SD, 2 PD). The other 13 cases referred to surgery at the time of recurrence, with 1 suspected lymph node metastasis, 5 suspected myometrial infiltration, 2 having completed childbirth, 1 case of ovarian involvement, and 1 case of suspected carcinosarcoma component, and 3 cases refused to retain reproductive function again.

Of the 18 patients with AH/EIN, 16 received repeated fertility-preserving treatment. 13 patients (13/14, 92.9%) achieved CR and 2 patients were still under treatment. The remaining 2 patients underwent surgery after relapse, of which one had completed childbirth and the other one refused to retain the reproductive function again. The CR rate of EC patients (66.7%) was lower than that of AH/EIN patients (92.9%), while no significant difference was observed ($P=0.260$).

Discussion

Fertility-preserving treatment in young patients with early endometrial cancer is an accepted concept today, while limited data are available on prolonged conservative treatment [12, 13, 16]. The present study investigated the efficacy and safety of repeated fertility-preserving therapy for patients with recurrent EC who wish to preserve their fertility. In our series, 26 cases received repeated treatment, and our study represents one of the largest studies on this issue to date. The results of this retrospective study suggest that repeated conservative treatment is feasible and can allow young patients with EEC to conceive, even when treatment periods are prolonged.

Fertility-sparing management is well known and is increasingly adopted for young women with presumed FIGO stage IA, grade 1, endometrioid carcinoma of the uterus who wish to preserve their fertility. However, the CR rate of conservative treatment varies in different studies. Progestin treatment is the most frequently reported approach for conservative management of early stage EC. Qin et al. [17] performed a systematic review and meta-analysis to evaluate the efficacy and safety of oral progestin treatment for early stage endometrial cancer. The authors identified 25 studies with 445 patients. Overall, 82.4% patients showed a response to hormonal therapy. Another meta-analysis reported 74% of patients with complex atypical hyperplasia and 72% of patients with grade 1 Stage I EC achieved a pathological complete response to oral progestin [18]. Due to the bothersome side effects of long-term oral administration of large doses of progesterone, other therapies including levonorgestrel-releasing intrauterine system (LNG-IUS), gonadotrophin-releasing hormone agonist (GnRH-a), or a combination of both therapies, have been explored as alternative options for EC conservation therapy, which are proved to be comparable to oral high-dose progesterone [10, 19]. Zhou et al. [10] reported that a CR rate of 88.2% in EC patients after GnRH-a combination treatment. Kim et al. [19] demonstrated a CR rate of 80% (4/5) in EC patients treated with MPA and LNG-IUS. In our single-center study, the CR rate in initial fertility-sparing management was slightly higher (94.7%) compared to the previous reports. It might be related to the strict screening criteria and a large number of cases in our institution. In addition, it is noteworthy that conservative treatment in our center is not confined to one regimen, and whether this contributes to the higher CR rate still needs further research to confirm.

Although majority of patients showed complete response to conservative treatment, the recurrence rate of conservative treatment is relatively high, up to 16.7–62% and it probability increases continually with time [11, 14, 16, 20, 21]. In the present study, 36.3% patients had recurrence after initial therapy which agreed with the previous studies and 15.8% patients even had a second recurrence. Therefore, long-term monitoring and regular evaluation is of great importance. No consensus has been reached on the treatment of recurrence after fertility preservation. Treatment at recurrence when a patient is still interested in childbearing remains a challenge. In the present study, 63.4% patients received a second round of fertility-sparing management and the remaining underwent definitive surgical management including hysterectomy. The indications and protocol of repeated conservative treatment are rarely mentioned in the previous literature [12, 13]. In our institution, patients who still want to preserve their fertility at recurrence should meet the criteria for initial conservative treatment. The type and dosage of drugs in the repeated treatment should be in accordance with the regimen in initial treatment. Only patients with mild-to-moderate atypical hyperplasia can adjust regimen to low-dose cyclic progestin [22].

The outcomes of repeated conservative treatment are rarely reported in the previous literature [12, 13]. In 2013, a Korean study [12] reported 33 cases tried progestin re-treatment at recurrence and 85% achieved complete response. During follow-up, five patients (17.9%) had second recurrence. However, the Korean study did not compare the CR rates of patients with different recurrent pathologies. Recently, Yamagami et al. [13] reported that CR rates in repeated treatment groups were 96.4% and 98.1%, respectively, among patients with atypical endometrial hyperplasia and G1 EEC. However, the patients included in this cohort were not restricted to those with an initial pathology of endometrial cancer. In the present study, the CR rate after re-treatment (82.6%) tended to be lower than that of the initial treatment (94.7%). We speculate that the reasons of lower response rate in re-treatment group may be related to

the pathological progression after recurrence and the insensitivity of imaging assessment of the superficial muscular involvement. In addition, a lower CR rate was noticed in EC group compared to that of AH/EIN group (66.7% vs 92.9%), while there was no significant group difference. Considering the limited number of patients and some patients are still under treatment, whose therapeutic efficacy is unable to assess, we hypothesize that a future study with larger samples may attain statistical significance.

Regarding the surgical procedure for patients after recurrence, the main controversy concentrates on whether or not the ovaries can be preserved. There is still no real consensus on this issue. Yet, some reports have emphasized the risk of advanced disease at the time of recurrence and the incidence of synchronous ovarian cancer in young EC patients [23, 24]. Signorelli et al. [23] described 2 patients with negative imaging findings pretreatment had coexisting intraparenchymal ovarian cancers (sized 15 and 12 mm, respectively). Yamazawa et al. [24] also reported 2 cases who were found to have synchronous endometrial and ovarian cancers at recurrence. Both of them received adjuvant chemotherapy (3 courses of paclitaxel and carboplatin) postoperatively and were free of disease after a mean follow-up of 39 months. However, it is not uncommon for young EC patients to have synchronous ovarian cancer, and a retrospective study demonstrated the incidence of double cancer in patients younger than 45 was 14% compared with 2% in the older group [25]. In the present study, 1 patient were found to have ovarian metastasis and 3 patients had synchronous ovarian cancer (G1 EA), while the pretreatment or preoperative imaging assessment of 1 patient (Case 1 in Table 4) did not find any obvious abnormality of ovary. In view of the above, some scholars have suggested that EC patients who wanted to preserve fertility should be routinely performed laparoscopy to exclude the possibility of synchronous ovarian tumors. Laparoscopic examination also provides a feasible assessment for the exclusion of ovarian involvement in patients who wants to receive repeated conservative treatment after relapse. Nevertheless, patients should be informed that minimal myometrial invasion or small, intraparenchymal ovarian cancer may not be detected before the conservative treatment is initiated. Encouragingly, the previous studies have suggested that conservative treatment does not change the course of disease in cases with synchronous endometrial and ovarian carcinoma [23, 24, 26]. In addition, research findings have confirmed that the preservation of ovaries for patients with G2 or G3 endometrial carcinoma, which are limited to the endometrium, did not affect survival and prognosis [27]. Of the 18 relapsed patients who finally underwent surgical treatment in our hospital, 16 preserved at least one ovary. After a mean follow-up of 50 months, only one patient developed pelvic recurrence and underwent reoperation. The patient has been followed up for 160 months with no evidence of disease. The other patients were all alive and disease-free. Our results also suggested that conservative treatment does not change the course of disease and delaying definitive surgical treatment did not worse the prognosis. However, it should be noted that about 9–12% of young women with endometrial cancer are associated with Lynch syndrome, and the incidence of synchronous or long-term ovarian cancer is significantly increased in this population [28, 29]. Therefore, patients with a family history of cancer or having high risk of ovarian cancer (such as BRCA mutation carrier, Lynch syndrome patients) are not recommended to preserve ovaries.

Pregnancy is one of the ultimate goals of fertility-sparing treatment in young patients with endometrial cancer. According to reports in the literature, the pregnancy rate after complete remission is about 30% [11, 17]. Yamagami et al. [13] reported a pregnancy rate of 11.1% in patients with AH and 20.8% in patients with EC after repeated progestin treatment. After a second-round fertility-sparing management, 3 patients who expected to become pregnant immediately in our study conceived and delivered successfully. The above result indicates that patients can achieve pregnancy after being re-treated for recurrent disease.

The present study has a few limitations that should be discussed. First, this was a single-center retrospective study and multiple conservative treatment regimens were used. Second, some cases were lost follow-up and it was not possible to collect those patients' clinical data. Third, a number of patients were still under treatment until last follow-up which may influence the results of the research. However, it is one of the largest studies which is focused on repeated fertility-sparing management in patients with recurrent endometrial cancer.

In conclusion, repeated treatment is still effective in patients with EC recurrence after conservative therapy and there is still the possibility of completing their family planning. However, it should be noted that the efficacy of the re-treatment seems to be lower than that of the initial treatment. In addition, the therapeutic effect of patients with recurrent pathology of endometrial cancer tends to be less effective than patients with recurrent pathology of AH/EIN. There is an urgent need for more effective methods of screening myometrial invasion and ovarian involvement before starting conservative treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

References

1. Jemal A, Bray F, Center MM et al (2011) Global cancer statistics. CA Cancer J Clin 61(2):69–90
2. Chen W, Zheng R, Baade PD et al (2016) Cancer statistics in China, 2015. CA Cancer J Clin 66(2):115–132
3. Rackow BW, Arici A (2006) Endometrial cancer and fertility. Curr Opin Obstet Gynecol 18(3):245–252
4. Corzo C, Santillan NB, Westin SN et al (2018) Updates on conservative management of endometrial cancer. J Minim Invasive Gynecol 25(2):308–313
5. Kim YB, Holschneider CH, Ghosh K et al (1997) Progestin alone as primary treatment of endometrial carcinoma in premenopausal women. Report of seven cases and review of the literature. Cancer 79(2):320–327
6. Ramirez PT, Frumovitz M, Bodurka DC et al (2004) Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol 95(1):133–138
7. Gallos ID, Yap J, Rajkhowa M et al (2012) Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 207(4):266 e261–e212
8. Baek JS, Lee WH, Kang WD et al (2016) Fertility-preserving treatment in complex atypical hyperplasia and early endometrial cancer in young women with oral progestin: is it effective? Obstet Gynecol Sci 59(1):24–31
9. Pronin SM, Novikova OV, Andreeva JY et al (2015) Fertility-sparing treatment of early endometrial cancer and complex atypical hyperplasia in young women of childbearing potential. Int J Gynecol Cancer 25(6):1010–1014
10. Zhou H, Cao D, Yang J et al (2017) Gonadotropin-releasing hormone agonist combined with a levonorgestrel-releasing intrauterine system or letrozole for fertility-preserving treatment of endometrial carcinoma and complex atypical hyperplasia in young women. Int J Gynecol Cancer 27(6):1178–1182
11. Koskas M, Uzan J, Luton D et al (2014) Prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of endometrial atypical hyperplasia and adenocarcinoma: systematic review and meta-analysis. Fertil Steril 101(3):785–794
12. Park JY, Lee SH, Seong SJ et al (2013) Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin. Gynecol Oncol 129(1):7–11
13. Yamagami W, Susumu N, Makabe T et al (2018) Is repeated high-dose medroxyprogesterone acetate (MPA) therapy permissible for patients with early stage endometrial cancer or atypical endometrial hyperplasia who desire preserving fertility? J Gynecol Oncol 29(2):e21
14. Yu M, Yang JX, Wu M et al (2009) Fertility-preserving treatment in young women with well-differentiated endometrial carcinoma and severe atypical hyperplasia of endometrium. Fertil Steril 92(6):2122–2124
15. Scully RE, Young RH, Clement PB (1998) Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament, Atlas of Tumor Pathology. Armed Forces Institute of Pathology, Bethesda
16. Perri T, Korach J, Gotlieb WH et al (2011) Prolonged conservative treatment of endometrial cancer patients: more than 1 pregnancy can be achieved. Int J Gynecol Cancer 21(1):72–78
17. Qin Y, Yu Z, Yang J et al (2016) Oral progestin treatment for early-stage endometrial cancer: a systematic review and meta-analysis. Int J Gynecol Cancer 26(6):1081–1091
18. Baker J, Obermair A, Gebski V et al (2012) Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. Gynecol Oncol 125(1):263–270
19. Kim MK, Yoon BS, Park H et al (2011) Conservative treatment with medroxyprogesterone acetate plus levonorgestrel intrauterine system for early-stage endometrial cancer in young women: pilot study. Int J Gynecol Cancer 21(4):673–677
20. Ushijima K, Yahata H, Yoshikawa H et al (2007) Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol 25(19):2798–2803
21. Eftekhar Z, Izadi-Mood N, Yarandi F et al (2009) Efficacy of megestrol acetate (megace) in the treatment of patients with early endometrial adenocarcinoma: our experiences with 21 patients. Int J Gynecol Cancer 19(2):249–252
22. Parkash V, Fadare O, Tornos C et al (2015) Committee opinion no. 631: endometrial intraepithelial neoplasia. Obstet Gynecol 126(4):897
23. Signorelli M, Caspani G, Bonazzi C et al (2009) Fertility-sparing treatment in young women with endometrial cancer or atypical complex hyperplasia: a prospective single-institution experience of 21 cases. BJOG 116(1):114–118
24. Yamazawa K, Hirai M, Fujito A et al (2007) Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. Hum Reprod 22(7):1953–1958
25. Navarria I, Usel M, Rapiti E et al (2009) Young patients with endometrial cancer: how many could be eligible for fertility-sparing treatment? Gynecol Oncol 114(3):448–451
26. Hurst SA, Hartzfeld KM, Del Priore G (2008) Occult myometrial recurrence after progesterone therapy to preserve fertility in a young patient with endometrial cancer. Fertil Steril 89(3):724. e721–724.e723
27. Gonthier C, Trefoux-Bourdet A, Koskas M (2017) Impact of conservative managements in young women with grade 2 or 3 endometrial adenocarcinoma confined to the endometrium. Int J Gynecol Cancer 27(3):493–499
28. Lu KH, Schorge JO, Rodabaugh KJ et al (2007) Prospective determination of prevalence of lynch syndrome in young women with endometrial cancer. J Clin Oncol 25(33):5158–5164
29. Kohlmann W, Gruber SB (2012) Lynch syndrome. In: Pagon RA, Adam MP, Ardinger HH et al (eds) GeneReviews. University of Washington, Seattle