

Fertility-preserving treatment in women with early endometrial cancer: the Chinese experience

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Abstract: Endometrial cancer (EC) is the most common malignant tumor of the female reproductive tract in developed countries and the second most common gynecologic malignancy in China. Although EC is most often diagnosed in postmenopausal women, the increase in obesity rates and other lifestyle changes has been accompanied by an increase in the prevalence of EC among younger women. Approximately 4% of patients are diagnosed before the age of 40 years and before having given birth. Such patients may have a strong desire to preserve their fertility despite oncologic risks and thus may be reluctant to undergo standard treatment for EC, which includes hysterectomy, bilateral salpingo-oophorectomy, and surgical staging. Therefore, more conservative treatment approaches may need to be discussed, along with their associated oncologic and reproductive outcomes. In fact, various studies have confirmed the effectiveness and safety of conservative treatment in EC. This review aimed to provide a concise yet informative overview of the current status of fertility-preserving treatment for EC in China, as well as to summarize the latest and ongoing research efforts in this area.

Keywords: endometrial cancer, conservative treatment, Chinese, fertility

Introduction

Endometrial cancer (EC) is the leading gynecologic malignancy in developed countries. In recent years, with the increase in global obesity rates, the incidence rate of EC in China has also risen, with ~63,400 newly diagnosed cases in 2015.¹ While EC is more prevalent in postmenopausal women, 7.1% of patients are diagnosed between the ages of 20 and 44 years.² As a substantial number of reproductive-age women are delaying childbearing, the rate of EC diagnosis in nulliparous women has been increasing as well. In fact, it is estimated that 70%–88% of women with EC in this population have not completed childbearing at the time of diagnosis.³ In addition, since the adoption of the two-child per family policy in China, an increasing number of EC patients have a strong desire to preserve their fertility. However, the standard management for EC involves hysterectomy and bilateral salpingo-oophorectomy with or without pelvic lymphadenectomy, which deprives patients of the chance of future pregnancy. Conservative treatment has emerged as an important alternative for younger EC patients who desire to retain their fertility despite oncologic risks. Therefore, the effectiveness of conservative treatment for EC represents an important topic of discussion.

In younger women with EC, conservative treatment is feasible because many ECs diagnosed in this population are early-stage, well-differentiated endometrioid endometrial carcinomas with favorable prognosis.² Indeed, several studies have confirmed

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the effectiveness of conservative treatment for EC,^{4,5} reporting that younger patients with low-grade EC had excellent survival regardless of the primary therapy chosen (hormone therapy vs primary surgery).⁶

In China, the conservative treatment of gynecological malignancies is based on the “Standardization study on the preservation of reproductive function in gynecological malignant tumors”, a key project of the “Eleventh Five-Year Plan” (2006–2010), supported by the National Science and Technology Foundation. Since then, major clinical centers in China have begun providing fertility-preserving treatments to women with early-stage cervical, endometrial, or ovarian cancers. However, the effectiveness of such treatments varies substantially in clinical practice, and clinicians often find it challenging to address certain issues. In 2014, the Gynecologic Oncology Branch of the Chinese Medical Association established the clinical diagnostic and therapeutic guidelines for fertility-preserving treatment of gynecological malignancies, in order to provide patients and medical practitioners with up-to-date scientific evidence and recommendations for effective therapeutic strategies.⁷ Since then, the conservative treatment of gynecological malignancies has received increasing attention, and many related studies are currently underway. The present review summarizes the current state of fertility-preserving treatment for EC in China and provides a literature overview reflecting the latest research trends in this direction.

Candidates for conservative treatment

The guidelines developed by the Gynecologic Oncology Branch of the Chinese Medical Association establish the eligibility of early-stage EC patients for fertility-preserving treatment based on the following:⁷ 1) age <40 years; 2) strong desire to preserve fertility; 3) diagnosis of well-differentiated endometrioid adenocarcinoma; 4) lesions confined to the endometrium, without myometrial infiltration or extrauterine metastasis; 5) positive progesterone receptor (PR) status for patients who are candidates for progestin therapy; 6) no contraindications to progestin for patients who are candidates for progestin therapy; 7) good compliance and full understanding of the advantages and risks associated with conservative treatment.

Currently, domestic and international guidelines agree that only patients with highly differentiated endometrioid adenocarcinoma, strong fertility desire, and no myometrial invasion may be considered for conservative therapy,^{7–10} because such patients have a low risk of cancer progression

during conservative treatment. In fact, even if disease progression occurs, such patients have a 5-year survival rate comparable to that of women who received definitive surgery at diagnosis.¹⁰ New research indicates that well-differentiated G1 endometrioid adenocarcinoma with minimal myometrial invasion can be treated with conservative hysteroscopic surgery.¹¹ However, due to the limited number of cases studied to date, the safety and efficacy of conservative treatment in this particular population remain to be confirmed. In addition, only the Chinese guideline maintains the age requirement (aged ≤40 years) for EC patients to be considered candidates for conservative treatment. With the adoption of China’s second-child policy and the development of assisted reproductive technology (ART), it remains to be determined whether the age requirement for fertility-preserving treatment for EC may be relaxed.

Pretreatment assessment

Preretreatment assessment is particularly important and takes into consideration disease history, previous treatment methods and associated response, comorbidities, checkup findings, physical status, pathological findings, and lesion severity based on imaging examination or laparoscopy.⁷ While the optimal imaging modality for pretreatment assessment of myometrial invasion has not been established, transvaginal ultrasound and magnetic resonance imaging are frequently used.¹⁰ Imaging is not only helpful to detect myometrial invasion but also to exclude synchronous ovarian tumors or suspicious lymphadenopathy. Although laparoscopic evaluation of metastatic status is not currently recommended, laparoscopy and biopsy are necessary under certain special circumstances such as in patients with imaging-suspected concurrent ovarian cancer or lymph node involvement.

Conservative treatment options

Hormonal therapy

Progestin treatment is the most frequently reported approach for conservative management of early-stage EC. In 1997, Kim et al first reported that EC patients conceived successfully after progestin treatment.¹² Since then, a number of retrospective studies have demonstrated the role of progestin therapy in the conservative management of EC.¹³ A total of 15 studies covering 405 patients with stage IA EC treated with progestin were published between 2006 and 2017 in China (Table 1).^{4,14–27} In China, the therapeutic effect of progestin agents was first described in 2006 by Yu et al,²⁷ who described 25 patients (8 with EC and 17 with severe atypical hyperplasia) treated with medroxyprogesterone acetate

Table 1 Studies on conservative treatment of EC in China

Study	Year	Age (years)	No	Pathological diagnosis	Therapy	Duration (months)	CR rate	Recurrence	Pregnancy	Delivery	Follow-up (months)
Treatment of progestin											
Yu et al ²⁷	2006	29 (20–35)	25	AH(17) + EC(8)	MPA 250–500 mg/d or MA or hydroxyprogesterone caproate	EC: 6.4 (3–10) AH: 7.3 (3–11) 5.3±2.8	EC: 71.4% (5/7) AH: 82.4% (14/17) 90.8% (40/44)	EC: 20% (1/5) AH: 23.1% (3/13) 20.6% (7/34)	28.6% (4/14)	21.4% (3/14)	5–14
Yu et al ¹⁴	2012	27 (22–37)	48	EC	MPA 250–500 mg/d or MA 160–320 mg/d	6 (3–12)	71.4% (15/21)	20% (3/15)	40% (4/10)	30% (3/10)	31.7 (4–91)
Wang et al ¹⁵	2011	31 (21–39)	24	EC	MPA 250–500 mg/d or MA 160–320 mg/d	7.5 (3–9)	66.7% (4/6)	NA	75% (3/4)	75% (3/4)	23.5 (4–92)
Mao et al ¹⁶	2010	28 (26–31)	6	EC	MPA 250–500 mg/d or MA 160 mg/d	6 (1–18)	85% (17/20)	23.5% (4/17)	11.8% (2/17)	5.9% (2/17)	26 (9–60)
Shan et al ¹⁷	2012	30 (20–36)	20	AH (6) + EC (14)	MA 160 mg/d	6.2±2.8	89% (34/38)	NA	40% (10/25)	28% (7/25)	NA
Cao et al ¹⁸	2013	29 (23–40)	38	EC	MPA 500 mg/d, or MA 320 mg–480 mg/d	NA	80.8%	28.6%	25% (2/8)	12.5% (1/8)	32 (15–66)
Shan et al ¹⁹	2013	30 (18–38)	26	AH(12) + EC(14)	MA 160 mg/d	6.2	EC: 64.3% (9/14) 84.4% (27/32)	EC: 33.3% (3/9) 33.3% (9/27)	NA	NA	32.5 (10–92)
Zhou et al ²⁰	2015	30 (20–40)	32	AH(13) + EC(19)	MPA 250 mg/d, or MA 160 mg/d	NA	EC: 78.9% (15/19) 58.5% (24/41)	20.8% (5/24) 20% (1/5)	NA	NA	NA
Li et al ²¹	2017	27 (23–31)	41	EC	MA 160 mg/d	6.4	62.5% (5/8)	NA	0/5	0/5	34.6 (7–114)
Yu et al ²²	2009	28	8	EC	MPA 250–500 mg/d	6 (3–12)	72.7% (32/44)	12.5% (4/32)	38.9% (7/18)	NA	22.4
Qian and Chen ²³	2015	33 (26–39)	44	EC	MPA 250–500 mg/d or MA 160–320 mg/d	4 (2–11)	81.1% (30/37)	50% (15/30)	36.4% (4/11)	27.3% (3/11)	78.6 (19.1–252.8)
Wang et al ²⁴	2014	32 (18–30)	37	EC	MA 160 mg/d± anastrozole	6 (3–24)	73.0% (27/37)	29.6% (8/27)	29.6% (8/27)	18.5% (5/27)	54 (4–148)
Chen et al ⁴	2016	32 (21–41)	37	EC	MPA 250–500 mg/d, or MA 160–480 mg/d, or progestin + GnRH _a , or progestin + LNG-IUS	9.14±1.31	82.3% (14/17)	14.3% (2/14)	18.2% (2/11)	9.1% (1/11)	26.2
Zhang ²⁵	2017	31	17	EC	MA 160 mg/d± tamoxifen ± metformin	6 (3–13)	84.3% (43/51)	41% (16/39)	NA	NA	61 (15–95)
Yang et al ²⁶	2015	33 (24–39)	51	EC	MA 20–200 mg/d, or MPA 100–400 mg/d, or norethisterone 20 mg/d, or progestin + LNG-IUS	NA	NA	NA	NA	NA	NA
Treatment of hysteroscopic resection combined with progestin											
Li et al ²¹	2017	27 (23–31)	40	EC	Hysteroscopic resection + dydrogesterone 30 mg/d	NA	80% (32/40)	3.10% (1/32)	NA	NA	NA
Li et al ²⁵	2013	NA	8	EC	Hysteroscopic resection + LNG-IUS	3–9	87.5% (7/8)	14.3% (1/7)	57.1% (4/7)	42.9% (3/7)	39 (11–77)
Wang et al ²⁶	2015	30 (25–34)	6	EC	Hysteroscopic resection + MA 160 mg/d	NA	100% (6/6)	0	50% (3/6)	50% (3/6)	26–91

(Continued)

Table 1 (Continued)

Study	Year	Age (years)	No	Pathological diagnosis	Therapy	Duration (months)	CR rate	Recurrence	Pregnancy	Delivery	Follow-up (months)
Wang et al ³⁷	2017	27 (25–39)	11	EC	Hysteroscopic resection + MPA 250–500 mg/d Or MA 160–320 mg/d	6 (3–12)	81.8% (9/11)	0	63.6% (7/11)	54.5% (6/11)	82.3 (15–132)
Yu et al ⁴⁶	2016	27 (22–35)	5	EC	Hysteroscopic resection + progestins	NA	100% (5/5)	0	80% (4/5)	80% (4/5)	24
Deng et al ⁴⁷	2017	29 (23–35)	16	EC	Hysteroscopic resection + MA 160 mg/d or MPA 250 mg/d	NA	75% (12/16)	25% (3/12)	66.7% (8/12)	50% (6/12)	54 (17–90)
Hu et al ⁴⁸	2016	33 (25–39)	22	EC	Hysteroscopic resection + MA/ LNG-IUS/MA + LNG-IUS	10	90.9% (20/22)	0	54.5% (12/22)	40.9% (9/22)	NA
Chen ⁹	2015	32 (25–40)	13	EC	Hysteroscopic resection + MA 160–320 mg/d	NA	100% (13/13)	7.7% (1/13)	53.8% (7/13)	46.2% (6/13)	NA
Treatment of GnRH-a combined with LNG-IUS or letrozole											
Zhou et al ³¹	2017	31 (21–42)	29	AH(12) + EC(17)	GnRH-a + letrozole or GnRH-a + IUD	5.0±2.9	93.1% (27/29) EC: 88.2% (15/17)	6.90% (2/29) EC: 6.7% (1/15)	15.4% (2/13)	0/13	18.7 (5.6–54.9)

Notes: Data are presented as mean ±SD, median (range), or unless otherwise specified.

Abbreviations: AH, atypical hyperplasia; EC, endometrial cancer; GnRH-a, gonadotropin-releasing hormone agonist; NA, not available; MA, megestrol acetate; MPA, medroxyprogesterone acetate; LNG-IUS, levonorgestrel-releasing intrauterine system.

(MPA). The average age of the patients was 28.6 years (range, 20–35 years). Of the eight patients with EC, six responded to treatment (average response time, 2.5 months; range, 1–3 months) and five achieved complete response (CR; average time to CR, 6.4 months; range, 3–10 months). Of those who achieved CR, one (20%) relapsed at 30 months after remission. Subsequently, Yu et al¹⁴ reported the result of a multicenter study examining the role of hormonal therapy in the conservative management of EC. The study period spanned from 1998 to 2011, totaling 48 patients treated with progestins. The median age was 27 years (range, 22–37 years) and 90.8% (40/48) of patients achieved CR. The average time to CR was 5.3±2.8 months. Recurrence was noted in 20.6% of the 34 patients who had responded to treatment initially and been followed up. The average time to recurrence was 23.7 months (range, 8–45 months). Later studies reported a CR rate of 58.5%–89%, with a recurrence rate of 14.3%–50%.

Most patients described in the literature received treatment with either MPA or megestrol acetate (MA), but there are controversies about the efficacy of these progestogens. Whereas MA treatment was previously reported to be associated with higher remission rate and lower recurrence rate,²⁸ the latest large-scale clinical study reported comparable efficacy of these two oral progestins, with a lower recurrence rate for MPA.²⁹ Therefore, it is worthwhile to continue exploring which medication can yield superior clinical effectiveness. High-dose progesterone therapy is beneficial for reversing EC but causes various adverse side effects. No definitive consensus has been reached on the optimal dose and duration of progestin treatment, which vary across studies. Currently, the most commonly reported regimens include MPA at 250–600 mg/day or MA at 160–480 mg/day.^{8,30} In China, MPA is commonly administered at 250–600 mg/day and MA at 160–320 mg/day.^{4,14–25} Only Yang et al²⁶ reported the usage of oral progestogens at lower doses, with MPA at 100–400 mg/day and MA at 20–200 mg/day without interruption.

Hysteroscopic resection and progesterone therapy

Long-term oral administration of large doses of progesterone has adverse side effects, which restricts its use in certain populations and limits compliance among young women. Therefore, research efforts have focused on developing a more effective and convenient treatment to help improve compliance and alleviate the side effects associated with oral progesterone. Other strategies including levonorgestrel-releasing intrauterine system (LNG-IUS) and gonadotropin-releasing

hormone agonist (GnRH-a) therapy, used alone or in combination, have been explored as alternative options for conservative therapy in women with EC because the effectiveness of such strategies is comparable to that of high-dose oral progesterone.^{7,31,32}

Hysteroscopic resection combined with progesterone therapy is a new type of conservative treatment. Hysteroscopic resection involves resection of the tumor, of a small layer of the myometrium underlying the lesion (two-step technique), and of the endometrium adjacent to the tumor (three-step technique).³³ More than a decade of research has not only confirmed that hysteroscopic resection is effective for treating early-stage, highly differentiated endometrioid adenocarcinoma in patients with a strong desire to retain fertility, but that hysteroscopic resection is superior to traditional conservative treatment.³³ The findings of the two largest studies on the effect of fertility-sparing, combined therapy involving hysteroscopic resection and medical treatment strongly suggest that this combined approach is comparable to progestin therapies in terms of treatment response rates and pregnancy rates.^{33,34} In 2013, Li et al³⁵ described the first Chinese case series involving patients who received combined hysteroscopic resection and progestin therapy. This case series included eight patients who underwent hysteroscopic resection of the endometrial lesions and shallow muscular layer within 2–3 mm below the lesion, followed by insertion of an LNG-IUS (Mirena; Bayer HealthCare Pharmaceutical Inc, Whippany, NJ, USA). Seven of eight patients achieved CR, whereas one patient had tumor relapse and underwent hysterectomy and bilateral salpingo-oophorectomy at 5 months after hysteroscopic resection. Four patients became pregnant within 3–6 months after treatment completion, and three patients delivered successfully. Later, Wang et al³⁶ reported a series of six patients who underwent hysteroscopic resection of the local lesion, of the shallow muscular layer, and of the surrounding tissues within at least 5 mm (three-step technique). In all patients, EC was confirmed as stage IA, and MA treatment was indicated at 160 mg/day for 20 days each month or continuously for 3 months. All six patients achieved CR at 3 months and no recurrence occurred during an average follow-up of 48.5 months. Three patients conceived naturally and delivered healthy infants at full term. A similar study conducted by Wang et al³⁷ described 11 young women with stage IA EC, who received hysteroscopic resection (two-step technique) combined with progestin therapy (MPA at 250–500 mg/day or MA at 160–320 mg/day). All patients achieved at least partial remission within 3 months, and nine achieved CR within 3–12 months. During an average follow-

up of 82.3 months, two patients underwent definitive surgery after completion of fertility and all patients were disease-free. Such findings were consistent between studies conducted in China and those conducted in other countries, suggesting that combined treatment involving hysteroscopic endometrial focal resection followed by LNG-IUS insertion can be an effective and safe approach for the management of EC in young women who desire to preserve fertility. Nevertheless, any recommendations based on these conclusions should be drafted with utmost care because the supporting studies had retrospective design and covered a limited number of patients.

GnRH-a therapy combined with LNG-IUS insertion or oral letrozole

Previous studies have confirmed the effectiveness of GnRH-a in patients with EC.^{38,39} In recent years, LNG-IUS insertion has been proposed as an alternative option for treating endometrial intraepithelial neoplasia and EC.⁴⁰ Unlike oral progestin, LNG-IUS provides very high doses of progestin to the local endometrium without serious systemic adverse effects. Letrozole, which is a third-generation aromatase inhibitor, was reported to have synergistic effect with the above mentioned therapies for reversing EC.^{41,42} In China, only one study covered cases of EC and complex atypical hyperplasia (n=29) managed conservatively with combined GnRH-a and LNG-IUS/letrozole therapy.³¹ During a median follow-up of 18.7 months, 88.2% (15/17) of patients with EC achieved CR, one of whom had recurrence.

Management after completion of conservative treatment

Women with a desire to conceive

Patients who have achieved CR and wish to conceive are advised to attempt to do so as soon as possible, especially if they have risk factors such as thin endometrium, older age, and history of recurrence.⁴³ Pregnancy can reduce the rate of recurrence,⁴⁴ and it is generally believed that it is safe for patients to become pregnant starting at 3 months after achieving CR.⁴⁵ However, regular oncologic follow-up should be continued during pregnancy, maintaining a follow-up interval of 6 months.¹⁰

The published literature confirms that patients with early-stage EC managed conservatively have promising fertility outcomes. The pregnancy data from studies conducted in China are summarized in Table 1. The only multicenter study, which was conducted by Yu et al,¹⁴ reported that 33.3% (9/27) of the treated women became pregnant and 18.5%

(5/27) delivered successfully after completing therapy. The average time from treatment completion to pregnancy was 12.2 months (range, 4–25 months). Subsequent studies that included patients aged >15 years reported pregnancy rates ranging from 12.5% to 50% and delivery rates ranging from 9.1% to 30% after progestin therapy.^{14,15,18,20,21,23,24,26} As for the pregnancy outcome of patients managed by the hysteroscopic approach, seven studies provided pregnancy data, reporting pregnancy rates ranging from 50% to 80% and live-birth rates ranging from 40.9% to 80%.^{35–37,46–49} However, it should be noted that the highest documented pregnancy and birth rates were based on a series of only five patients.⁴⁶ Although conventional wisdom suggests that hysteroscopic resection may lead to complications such as intrauterine adhesions and intimal fibrosis, which may affect pregnancy, no intrauterine adhesions were noted in previous studies on hysteroscopic resection, which reported very high pregnancy and live-birth rates. These findings suggest that hysteroscopic resection may have no significant adverse effects on pregnancy outcomes, though further verification is warranted. The only study of patients receiving GnRH-a combined with letrozole/LNG-IUS therapy, two of 13 women who attempted to conceive achieved pregnancy spontaneously, with no successful delivery. Twelve women who attempted to conceive underwent ART but there was no delivery until the last follow-up.³¹

Regarding the optimal choice of reproductive strategy following conservative treatment, EC patients with no history of infertility may consider natural conception, but the pregnancy rate is expected to be low due to thin endometrium. Therefore, ARTs are recommended in women with a strong desire to conceive following EC treatment. Indeed, several studies have shown that pregnancy rate is higher in patients who used ART than in those who attempted natural conception^{20,20,50,51} and that ART does not affect the prognosis of EC.^{6,52} However, an increased incidence of perinatal complications including preterm birth, preeclampsia, prolificacy, and need for cesarean section was reported by Chao et al⁵³ in EC patients who became pregnant using ART. Therefore, women attempting to conceive using ART should undergo close antenatal follow-up.

Women without pregnancy intention

For patients who have achieved CR but do not intend to become pregnant, the clinical practice guidelines issued by the European Society for Medical Oncology recommend oral administration of low-dose progesterone but do not establish a specific regimen (dosage, continuous or periodic administration).^{10,54} The Chinese guideline suggests that both

periodic treatment with oral short-acting contraceptives and LNG-IUS insertion represent suitable options.

Women who have completed childbearing

Because recurrence rates after CR remain high, almost all clinical practice guidelines recommend that patients who have completed fertility should undergo hysterectomy.^{10,54} The Chinese guideline also recommends that patients who have completed fertility can be inserted with an LNG-IUS to prevent tumor recurrence.⁷ As an increasing number of patients plan to conceive more than one child, further study should clarify whether patients who have completed fertility can receive maintenance therapy only, allowing the possibility of future pregnancy.

Women with cancer recurrence

EC recurrence is defined as the presence of an endometrial lesion after CR to conservative treatment. EC recurrence rates following CR remain high (24%–40%).^{28,30,55} To develop strategies for decreasing the risk of EC recurrence, it is necessary to identify the influencing factors. Koskas et al²⁸ conducted a systematic review of prognostic factors of oncologic and reproductive outcomes in fertility-sparing management of EC. This study included 370 patients from 24 studies and reported that none of the factors evaluated (age, gravidity status, obesity, previous infertility, hormonal therapy) was associated with an increased risk of recurrence. However, in China, a retrospective study conducted by Chen et al⁴ reported that older age (≥ 35 years), obesity (body mass index ≥ 30 kg/m²), longer time to CR, and consistent infertility after conservative treatment were associated with an increased risk of recurrence. Whether factors mentioned above are the influencing factors of recurrence deserves future investigation.

There is no consensus regarding the optimal management strategy for patients with early-stage EC who experience recurrence after fertility-preserving treatment. Only the guidelines issued in 2015 by the European Society for Gynecological Oncology indicate that high-dose progestogen therapy can be given again to patients who relapse after CR, but this recommendation is restricted to nulliparous women.¹⁰ Some researchers suggest that standard surgery including hysterectomy should be performed immediately in patients with recurrence, while others propose that repeated conservative treatment is safe and effective in patients with recurrence who still meet the criteria for initial conservative treatment.¹⁰ A limited number of studies reported that

patients who relapsed after fertility-preserving therapy achieved CR again with prolonged progesterone therapy (Table 2).^{56–62} In China, the largest cohort study focused on repeated conservative treatment in patients with recurrent EC was conducted by Yu et al⁶³ in Peking Union Medical College Hospital. Of the 36 patients with recurrence after primary fertility-sparing treatment, 76.2% achieved CR again after a second round of conservative treatment. Two of 16 patients who achieved CR and attempted to conceive became pregnant and delivered successfully. These results suggest promising outcomes of repeated conservative treatment in patients with recurrent EC after CR to primary fertility-preserving treatment. Future clinical studies should clarify the optimal regimen (dose, timing) and follow-up protocol (timing, investigations) for repeated conservative treatment after relapse.

Other factors affecting the indication for conservative treatment

The risk of hereditary nonpolyposis colorectal cancer (Lynch/HNPCC) syndrome in EC patients younger than 50 years is 5%–10%.⁶⁴ Therefore, patients with early-stage EC and a family history of colorectal cancer should undergo immunohistochemistry evaluation to determine the expression of Lynch syndrome-related genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) before deciding the indication for conservative treatment. Patients with loss of expression of these genes should undergo a gene test; if genetic defects are found, conservative treatment should not be indicated or should be stopped. At present, there is no effective treatment for EC in patients with Lynch syndrome. Future advances in conservative treatment strategies may allow patients with Lynch syndrome to become suitable candidates for conservative treatment, but only under close follow-up.

Progress in basic research

Progesterin resistance is the main obstacle to successful conservative therapy in young women with EC, as up to 30% of patients fail to respond to progesterin due to primary or acquired progesterin resistance.^{65,66} Several studies have investigated the mechanisms contributing to progesterin resistance. Survivin, which is a key regulator of antiapoptotic networks, is overexpressed in both endometrial hyperplasia and EC.^{67,68} Chen et al⁶⁹ found that the expression of survivin can be downregulated by progesterin. Dysregulation of survivin expression may contribute to progesterin resistance in the hyperplastic endometrium. Progesterone inhibits the proliferation of EC cells and reverses their malignant biological behavior through binding to the nuclear PR. Thus, progesterin cannot inhibit EC cells that do not express PR and may even promote cell proliferation.⁷⁰ Gu et al⁷⁰ showed that, in the absence of PR mediation, progesterin-induced activation of the PI3K/Akt pathway plays an important role in progesterin resistance of EC cells, suggesting that inhibition of the PI3K/Akt pathway might restore PR expression and reverse progesterin resistance in EC. Other pathways involved in progesterin resistance include upregulation of EGFR expression, overexpression of glyoxalase I, and insulin resistance.^{71–73} Ai et al⁷³ indicated that overexpression of EGFR reduced the sensitivity of EC cells to progesterin and inhibited cell apoptosis. Thus, EGFR tyrosine kinase inhibitors can suppress the proliferation of EC cells and may be effective in the treatment of EC. Furthermore, Zhang et al⁷² demonstrated that metformin can reverse progesterin resistance by downregulation of glyoxalase I expression, suggesting that combined therapy with metformin and progesterin may be effective in treating EC.

Ongoing clinical trials

Nowadays, several prospective clinical trials aiming to evaluate different strategies for conservative management of

Table 2 Studies on repeated treatment of recurrent stage I EC

Study	Year	No. of cases	Primary CR	Recurrence	No. of repeated treatment	Second CR	Follow-up time (months)
Gotlieb et al ⁵⁶	2003	13 EC	100%	46.2% (6/13)	4	100% (4/4)	6–358
Ramirez et al ⁵⁷	2004	81 EC	76% (62/81)	24% (15/62)	7	72% (5/7)	36–90
Ushijima et al ⁵⁸	2007	28 EC + 17 AH	EC: 55% (12/22) AH: 82% (14/17)	EC: 57.1% (8/14) AH: 38% (6/16)	8	75% (6/8)	25–73
Perri et al ⁵⁹	2011	27 EC	89% (24/27)	62% (15/24)	11	100% (11/11)	7.8–412
Park et al ⁶⁰	2013	NA	NA	31.9% (45/141)	33	84.8% (28/33)	24–160
Yamagami et al ⁶¹	2018	97 EC	90.7% (88/97)	63.2% (55/87)	53	98.1% (53/54)	4.5–208.7
Tamauchi et al ⁶²	2018	9 EC	88.9% (8/9)	87.5% (7/8)	6	100% (6/6)	NA
Yu et al ⁶³	2018	156 EC	93.6% (146/156)	34.6% (36/104)	25	76.2% (16/21)	9–77

Abbreviations: CR, complete response; AH, atypical hyperplasia; EC, endometrial cancer; NA, not available.

Table 3 List of ongoing clinical trials in China

NCT number	Status	Study title	Conditions	Interventions	Locations
NCT03538704	Recruiting	Effect of fertility-sparing therapy of early endometrial cancer	Endometrial cancer	Drug: metformin	Peking University People's Hospital, Beijing, China
NCT03463252	Recruiting	Value of LNG-IUS as fertility-preserving treatment of EAH and EC	Endometrial cancer; endometrial atypical hyperplasia	Drug: progesterone Device: mirena	West China Second University Hospital, Chengdu, Sichuan, China
NCT03241914	Recruiting	Megestrol acetate plus LNG-IUS in young women with early endometrial cancer	Endometrial neoplasm malignant stage I	Drug: megestrol acetate Device: LNG-IUS	Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China
NCT01968317	Completed	Megestrol acetate plus metformin to megestrol acetate in patients with endometrial atypical hyperplasia or early stage endometrial adenocarcinoma	Endometrial atypical hyperplasia Endometrial adenocarcinoma	Drug: megestrol acetate and metformin Drug: megestrol acetate	Obstetrics and Gynecology Hospital, Fudan University Fudan University Shanghai Cancer Center Shanghai Changning Maternity and Infant Health Hospital, Shanghai, China

Abbreviations: EC, endometrial cancer; LNG-IUS, levonorgestrel-releasing intrauterine system; EAH, endometrial atypical hyperplasia.

EC are taking place across China (Table 3). Recruitment is currently ongoing for a clinical trial at West China Second University Hospital, aiming to analyze the effectiveness of LNG-IUS insertion for fertility-sparing treatment of endometrial atypical hyperplasia and early endometrial carcinoma (clinicaltrials.gov NCT03463252). Patients who are enrolled are randomly allocated to one of three treatment groups (MPA only, MPA + LNG-IUS, LNG-IUS only), and the primary outcomes include pathological response, pregnancy rate, and live-birth rate. The study aims to enroll 224 participants. Recruitment is also ongoing in a prospective, multicenter, open-label, randomized, controlled clinical trial sponsored by Peking Union People's Hospital. The study aims to enroll 80 patients with early-stage EC and body mass index ≥ 25 kg/m² to evaluate the effect of fertility-sparing therapy with or without metformin (NCT03538704).

Recruitment was recently completed in a multicenter clinical trial sponsored by Xiaojun Chen aiming to explore whether combined therapy with MA and metformin would be more effective than therapy with MA alone in terms of restoring the endometrial tissue to a normal state in patients with endometrial atypical hyperplasia or early-stage EC (NCT01968317). One hundred and fifty patients have been recruited. Fudan University is currently conducting a non-inferiority study comparing the effectiveness of combined therapy with MA + LNG-IUS and therapy with MA alone in terms of restoring the endometrial tissue to a normal state in

patients with early-stage EC (NCT03241914). The primary outcomes include pathological response rates and response time in each treatment arm, while secondary outcomes include treatment-related adverse events, rate of relapse, rate of pregnancy, and patients' compliance. This study also evaluates whether the use of combined therapy can shorten the treatment duration, which would represent an advantage in terms of cost and comfort to the patients.

Conclusion

In younger women with stage IA EC, fertility-preserving treatment is feasible and effective. Apart from oral progestin therapy, LNG-IUS insertion, hysteroscopic resection, and GnRH-a therapy, alone or in combination, have also shown therapeutic promise, but further research is warranted to confirm their effectiveness and safety. After treatment completion, women who wish to conceive are encouraged to attempt to do so as soon as possible. ART is recommended especially in women having a history of infertility. For patients with recurrence after fertility-preserving treatment, repeated fertility-preserving treatment can still achieve a promising response, allowing the possibility of future pregnancy. Further studies are needed to clarify the mechanisms underlying resistance and to develop sensitization strategies in patients with progestin resistance. The outcomes of ongoing and future prospective clinical trials are expected to help clarify the optimal treatment strategy for EC in different patient populations.

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Disclosure

The authors report no conflicts of interest in this work.

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