



Treatment efficiency of comprehensive hysteroscopic evaluation and lesion resection combined with progestin therapy in young women with endometrial atypical hyperplasia and endometrial cancer

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HIGHLIGHTS

- Mean treatment duration to achieve CR was 6.7 ± 0.3 months, using progestin therapy combined with hysteroscopic evaluation.
- Endometrial lesion size ≤ 2 cm correlated with a shorter treatment period to achieve CR.
- Comprehensive hysteroscopic evaluation seems to be effective for EAH and EEC patients who wish to preserve fertility.

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ABSTRACT

Objective. This study aimed to evaluate the efficacy of comprehensive hysteroscopic evaluation and lesion resection combined with progestin therapy in young patients with endometrial atypical hyperplasia (EAH) and early stage endometrial cancer (EEC) who wished to preserve their fertility.

Methods. Patients with EAH ($n = 120$) or well-differentiated EEC ($n = 40$, FIGO stage IA, without myometrial invasion) were retrospectively included. All patients received constant oral progestin combined with hysteroscopic evaluation every 3 months until achieving complete response (CR). The location, number and size of each suspected lesion or cluster were detailedly recorded during the hysteroscopy.

Results. The median age was 32.0 year-old (range, 22–47 year-old). Totally 148 patients (97.4%) achieved CR while 3 EAH and 1 EEC patients presented with disease progression, and 8 patients were still in treatment. The mean treatment duration for achieving CR was 6.7 ± 0.3 months (range, 1–18 months). After adjusting for patient age, body mass index (BMI), history of pregnancy and type of conservative therapies, lesion size ≤ 2 cm (OR, 0.701; 95% CI, 0.496–0.991; $P = 0.045$) was significantly correlated with shorter treatment time to achieve CR. Among 60 patients attempted to conceive after achieving CR, 45.0% (15/60) had been pregnant, 25.0% (15/60) delivered live birth, 13.3% (8/60) are still in pregnancy, while 6.7% experienced spontaneous abortion.

Conclusion. Comprehensive hysteroscopic evaluation and lesion resection plus progestin therapy seem to be an effective and safe fertility sparing therapy for patients with EAH or EEC. Endometrial lesion size ≤ 2 cm correlated with a shorter treatment period to achieve CR.

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1. Introduction

Twenty-five percent of endometrial cancer (EC) cases are diagnosed in premenopausal women, up to 5% of those are younger than 40-year-old [1]. Given that young women with EC usually have suffered from infertility, half of them are nullipara [2]. Thus, conservative treatment for these patients is strongly demanded, also for women with endometrial atypical hyperplasia (EAH)-a

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precancerous stage of endometrioid endometrial cancer [3]. Conservative treatment modalities for EAH or early-stage endometrioid endometrial cancer (EEC) patients are mainly progestin therapies, including medroxyprogesterone acetate (MPA), megestrol acetate (MA), and levonorgestrel intrauterine system (LNG-IUS) [4–6]. Reports showed 75–85% of EAH and 50–75% of EEC patients could achieve complete response (CR) [7,8]. Dilatation and curettage (D&C) is a traditional diagnostic method in this fertility-sparing setting [9]. Most institutions perform D&C for diagnosing the disease and monitoring the therapeutic effects of progestin. However, there are concerns regarding using D&C for the diagnosis and follow-up. Firstly, blind D&C might miss endometrial lesion, which could be more serious lesion than those found by D&C. Secondly, the lesions missed by D&C might demise the progestin therapeutic effects. Blind D&C might also harm normal endometrium which is precious for these women desiring for fertility. In this circumstance, hysteroscopic resection combined with progestin treatment has been reported as an effective fertility conservative treatment for EEC and EAH, resulting in a relatively universal CR rate as 90–100% [10–12]. However, the case number of these reports is relatively small. Also, whether the status of endometrial lesion (location or size) evaluated by hysteroscopy may impact on the treatment outcome has not been investigated.

In this study, we aimed to assess the efficiency of comprehensive hysteroscopic evaluation and resection combined with progestin therapy for EEC and EAH patients who demand fertility preservation. The impact of the status of endometrial lesion (such as location or size of the lesion) evaluated by hysteroscopy on the treatment efficacy were also evaluated.

2. Materials and methods

2.1. Study population

Patients receiving conservative treatment in Obstetrics and Gynecology Hospital of Fudan University from January 2013 to July 2017 were retrospectively investigated. This study was approved by the Ethics Committees of Obstetrics and Gynecology Hospital of Fudan University. All patients were given full information regarding risks of both surgical and conservative treatments. All patients had signed consents regarding the conservative therapy and using their clinical data for research purpose.

All patients were pathologically diagnosed by endometrial biopsy through dilation and curettage (D&C) with or without hysteroscopy. Pathologic diagnosis was confirmed by two experienced gynecological pathologists according to the World Health Organization (WHO) pathological classification (2014). If their opinions differed, a seminar was held in the pathological department for the final diagnosis. The inclusion criteria for conservative treatment follows NCCN guideline 2018 [13], which include: (1) histologically proven EAH, or well-differentiated EEC G1 without myometrial invasion; (2) no signs of suspicious extrauterine involvement on enhanced magnetic resonance imaging (MRI) or enhanced computed tomography (CT) or ultrasound; (3) younger than 45 years old; (4) had strong willingness to preserve fertility; (5) had no contraindication for progestin treatment or pregnancy; (6) not pregnant; (7) had good compliance for treatment. For patients with suspected myometrial invasion on imaging study, hysteroscopic resection of endometrium and myometrium underneath at the suspected lesion would be conducted. Cases with myometrium invasion confirmed by pathological diagnosis were recommended for hysterectomy and excluded from this study. Because the goal of this study was to evaluate the role of hysteroscopy as the first-line treatment on fertility preserving treatment in EEC and EAH patients, patients who received progestin treatment for at least one month before first hysteroscopic evaluation was excluded from the present study.

2.2. Patient evaluation

Demographic, clinical, and pathological data as well as follow-up information were retrospectively collected. Blood samples were tested for fasting blood glucose (FBG), fasting insulin (FINS) and lipid panel. All patients were evaluated by pelvic examination and ultrasound scan, while enhanced abdominal and pelvic MRI (preferred) or CT were required for EEC patients.

Body mass index (BMI) and the homeostasis model assessment-insulin resistance (HOMA-IR) index were calculated, and metabolic syndrome (MS) criteria were evaluated for every patient recruited [14]. HOMA-IR index [FBG (mmol/L) × FINS (μU/mL) / 22.5] was used to evaluate IR status. Patients with HOMA-IR ≥ 2.95 were considered to be insulin-resistant. Overweight was defined as BMI ≥ 25 kg/m².

2.3. Comprehensive hysteroscopic evaluation and lesion resection

Comprehensive hysteroscopic evaluation was carried out before initiation of progestin treatment and was repeated every three months during the whole course of treatment. If the patient was initially diagnosed with EAH or EEC by endometrial biopsy through D&C or Pipelle without hysteroscopy, hysteroscopic evaluation would be arranged within one month after endometrial biopsy to standardize the endometrial evaluation before conservative treatment.

For comprehensive hysteroscopic evaluation, the location, number and size of each suspected lesion or cluster were recorded in detail. The size and shape of uterine cavity, thickness and character of the endometrium, condition of both fallopian tube orifices, and existence of any scar or adhesion were also recorded. Area around the orifices of fallopian tubes, and the lower segment near internal orifice of cervix should be carefully evaluated. We defined lesions as “close to the orifice of fallopian tube” if the lesion was <5 mm from the orifice of fallopian tube. Size of punctiform or polypoidal lesions was evaluated by basal diameter but not the diameter of lesions. The size of cluster or sheet-like lesion was evaluated with the maximum diameter. We recorded one punctiform or polypoidal lesion as a single lesion. Cluster, sheet-like, or multiple lesions were recorded as non-single lesion.

Hysteroscopic comprehensive lesion resection was carried out after general evaluation. All suspected lesions were removed completely, and the basal layer of endometrium should be protected as much as possible. Punctiform or polypoidal lesions were removed by miniature scissors, while clusters were removed by curettage. For the sake of endometrial basal layer, electronic resection was used only if myometrial invasion was suspected according to enhanced MR/CT images. With image guidance, electronic resection was performed using a 5 mm cutting-loop-electrode to remove the suspected lesion and the myometrium beneath in block, which can provide the pathologists with a better sample for evaluation of myometrium invasion. A random endometrial biopsy would also be done in the area where no obvious endometrial lesion was found. In particular, the operator avoided endometrium injury to the extent he could.

All specimens were recorded and sent separately for pathological diagnosis.

2.4. Conservative treatment and evaluation of therapeutic effects

Progestin treatment started once hysteroscopic evaluation was done. Complete hysteroscopic evaluation and resection of lesions was carried out every 3 months during the medical treatment to evaluate therapeutic effects (Fig. 1).

The response to conservative treatment was assessed histologically using specimens obtained during each hysteroscopic evaluation. CR was defined as the absence of hyperplasia or carcinoma. Partial response (PR) was defined as pathological improvement. No response (NR) was defined as persistence of lesion as originally diagnosed. Progression was defined as evidence of endometrial cancer for EAH

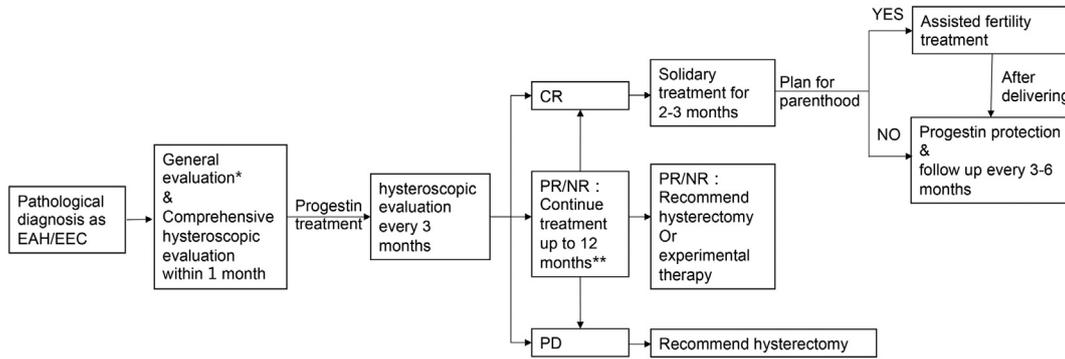


Fig. 1. Flowchart for management of EAH and EEC patients receiving conservative treatment. *: Including general information collection, liver/renal function, expert pathology review, and imaging evaluation such as ultrasound and/or enhanced MR/CT. **: For patients remained NR after 6 months of treatment but refused hysterectomy, a multiple disciplinary discussion would be held for individual case, and alternative treatment would be given.

patients or evidence with higher pathological progression, or myometrial invasion, or extra-uterine metastasis for EEC patients. Definitive hysterectomy would be suggested if the patient remained NR for 6 months or there were evidences of progression. For patients remained NR after 6 months of treatment but refused hysterectomy, a multiple disciplinary discussion would be held for individual case, and alternative treatment would be given. These alternative treatments included 160 mg MA per day combined with 1500 mg metformin per day (for those who used MA alone), ethinylestradiol cyproterone one pill per day for 21 days out of 28 day-cycle combined with metformin 1500 mg/day, levonorgestrel intrauterine system (LNG-IUS) insertion or GnRH-a intramuscular injection.

Once the patient achieved CR, the same regimen would be administered for another 2–3 months for treatment consolidation. CR patients were followed up every 3 to 6 months. Ultrasound and endometrial biopsy by Pipelle were used to evaluate the endometrium. Enhanced pelvic MR, serum CA-125 and HE-4 were used for follow-up of EEC patients annually.

For CR patients without recent pregnancy plan, low-dose cyclic progestin, oral contraceptive pills, or a LNG-IUS was administered to prevent recurrence. CR patients who desired pregnancy were encouraged to conceive with or without active assisted reproduction technology (ART) under close surveillance of our multiple disciplinary team. In cases of successful conception, pregnant patients were followed up according to a routine obstetrical schedule, plus a follow-up visit six months after delivery. Patients who successfully completed childbearing were encouraged to undergo definitive surgery although most of them refused operation and continued preventive regimen as LNG-IUS.

Adverse effects were recorded during the entire treatment and follow-up afterwards, including weight gain, thrombosis, lactic acidosis, impaired liver and renal function, and other complaints.

All patients were followed till March 2018.

2.5. Statistical analysis

Duration to achieve CR was measured from the time point of initiating progestin treatment to the CR diagnosed pathologically.

All data were presented as medians, means or proportions. The intra-group differences for continuous values were compared by Student’s *t*-test or the Mann-Whitney *U* test where appropriate. Frequency distributions were compared using the Chi-squared test or Fisher’s exact test. Therapeutic duration was estimated by the Kaplan–Meier method and compared between groups using log-rank test. A cox regression model was used for univariate analysis and multivariate analysis of the relationship between covariates and CR in response to treatment. P value < 0.05 in two-sided tests was regarded as significant. All statistical analyses were performed using SPSS for Mac (version 20.0; IBM).

3. Results

3.1. Patient characteristics

A total of 120 EAH and 40 EEC patients who met inclusion criteria were evaluated (Fig. 2). The characteristics of patients are shown in Table 1. The median age at diagnosis was 32 year-old (range 22–47 year-old). One 47 year-old EAH patient insisted on uterus preservation was also included. Median BMI was 24.30 kg/m² (range 16.37–44.06 kg/m²) and median HOMA-IR was 2.49 (range 0.44–16.17).

Totally 154 of 160 patients (96.25%) received oral megestrol acetate (MA) at the dose of 160 mg/day. Among them 69 patients also received metformin 1500 mg/day. For the rest 6 of 160 patients, four women were given LNG-IUS whereas the other two took Diane-35 1 pill/day combined with metformin 1500 mg/day.

The median follow-up time from the date of initiating treatment in our center to the last follow up was 20 months (range, 6–64 months). The median follow-up time from the date of achieving CR to the last follow up was 13 months (range, 1–53 months).

3.2. Outcome of conservative treatment

Out of the 160 patients, 8 patients were still in treatment (5 were in treatment of 6 months and 3 were in treatment in 8 months). The cumulative CR rate was 97.4% (148/160) at the 18th month of the follow-up, including 112 EAH patients (97.4%) and 36 EEC patients (97.3%). At the 12th month of the follow-up, 136 out of 152 patients (89.5%) achieved CR, including 104 EAH patients (88.9%) and 32 EEC patients (91.4%). The mean treatment duration for achieving CR was 6.7 ± 0.3 months (range, 1–18 months), 6.8 ± 0.4 months (1–18 months) for

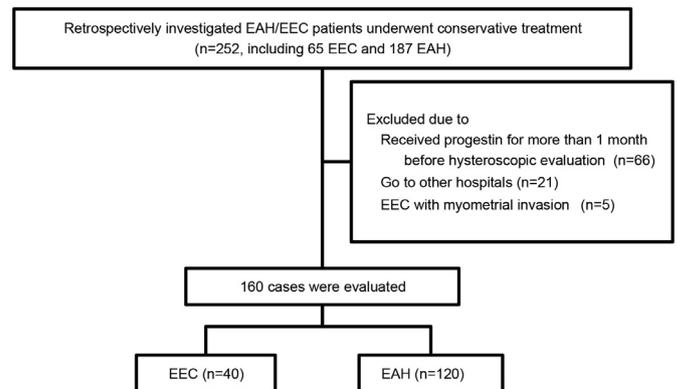


Fig. 2. Flowchart of the screening of study population.

Table 1
General characteristics of the study population.

Variable	Included			Excluded		
	Total	EAH	EEC	Total	EAH	EEC
Patient number (n)	160	120	40	66	51	15
Age at diagnosis (years)	32.0 (22–47)	33.0 (22–47)	31.0 (23–42)	32.5 (20–44)	33.0 (20–44)	31.0 (25–41)
Median (range)						
BMI (kg/m ²)	24.30	23.89	24.37	24.13	24.23	23.92
Median (range)	(16.37–44.06)	(16.37–44.06)	(18.29–36.45)	(15.63–35.94)	(15.94–35.94)	(15.63–32.46)
HOMA-IR	2.49	2.30	3.84	2.71	2.85	2.61
Median (range)	(0.44–16.17)	(0.44–15.80)	(0.55–16.17)	(0.44–16.50)	(0.87–16.5)	(0.44–10.67)
Hypertension, n (%)	9 (5.6)	7 (5.8)	2 (5.0)	2 (3.0)	1 (2.0)	1 (6.7)
Diabetes mellitus, n (%)	6 (3.8)	5 (4.2)	1 (2.5)	2 (3.0)	1 (2.0)	1 (6.7)
Nulliparous, n (%)	27 (16.9)	24 (20.0)	3 (7.5)	15 (22.7)	12 (23.5)	3 (20.0)
Progestin therapy, n (%)						
MA	85 (53.1)	64 (53.3)	21 (52.5)	29 (43.9)	25 (49.0)	4 (26.7)
MA + metformin	69 (43.1)	49 (40.8)	20 (50.0)	23 (34.8)	14 (27.5)	9 (60.0)
LNG-IUD	4 (2.5)	3 (2.5)	1 (2.5)	5 (7.6)	4 (7.8)	1 (6.7)
Diane-35	2 (1.3)	2 (1.7)	0 (0.0)	5 (7.6)	5 (9.8)	0 (0.0)
MA + LNG-IUD	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.1)	3 (5.8)	1 (6.7)
CR ^a , n (%)	148 (97.4)	112 (97.4)	36 (97.3)	62 (93.9)	48 (94.1)	14 (93.3)
Mean treatment duration to CR in our center ^b (range) (months)	6.7 ± 0.3 (1–18)	6.8 ± 0.4 (1–18)	6.4 ± 0.6 (1–18)	5.8 ± 0.7 (0–26)	5.6 ± 0.8 (0–26)	6.1 ± 0.9 (0–12)
Median treatment duration before transferring to our center (range) (months)	–	–	–	6 (1–21)	4 (1–21)	7 (1–14)
Total treatment duration to CR ^c (months)	6.7 ± 0.3 (1–18)	6.8 ± 0.4 (1–18)	6.4 ± 0.6 (1–18)	12.2 ± 1.0 (1–38)	11.9 ± 1.2 (1–38)	13.1 ± 1.5 (4–24)
Median follow-up duration (range) (months)	13 (1–53)	13.5 (1–36)	9 (3–53)	12.5 (1–24)	12.5 (1–51)	12.5 (1–51)
Relapse rate, % (n)	5.4 (8/148)	3.6 (4/112)	11.1 (4/36)	14.5 (9/62)	6.3 (3/48)	42.9 (6/14)
Median duration to relapse (range) (months)	7 (3–28)	8 (3–26)	7 (4–28)	7 (3–26)	7 (7–7)	6.5 (3–26)
Pregnant rate ^d , % (n)	45.0 (27/60)	47.7 (21/44)	37.5 (6/16)	35.3 (12/34)	36.4 (8/22)	33.3 (4/12)

EEC, early-stage endometrioid endometrial cancer; EAH, endometrial atypical hyperplasia; BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance; MA, megestrol acetate; LNG-IUD, levonorgestrel intrauterine device; CR, complete response.

^a Cumulative response rate till the last follow up.

^b For excluded group, the treatment duration in other hospitals before transferring to our center was not calculated.

^c The treatment duration from initiation of conservative treatment to CR.

^d Pregnant rate among patients who plan for parenthood.

EAH, and 6.4 ± 0.6 months (1–18 months) for EEC respectively (Fig. 3A).

Four patients did not achieve CR in our study. One EEC patient presented with disease progression after 10 months of progestin treatment, she received hysterectomy and the final pathologic result showed endometrioid cancer G1 with superficial myometrium invasion. One EAH patient remained NR after 23 months of progestin treatment, and continued conservative treatment till the last follow up. Two EAH patients presented with progressive disease. One of them underwent definitive surgery after 3 months of progestin therapy and the final pathological report showed endometrioid cancer G1 stage IA. Another EAH patient was diagnosed as endometrioid cancer G1 by hysteroscopic evaluation and endometrial biopsy after 7 months of progestin treatment. This patient insisted on conservative treatment despite information of her high risk of disease progression and recurrence. A multiple disciplinary discussion was held for her case, and because there was no evidence of myometrium and extra-uterine involvement, GnRH-a combined with oral letrozole was given as an experimental treatment for her [15]. Her recent pathologic evaluation showed as EAH.

No severe adverse event related to medication and hysteroscopy was observed, such as thromboembolism, severe renal or liver dysfunction, severe infection or uterus perforation, etc.

Among the 148 patients who achieved CR, sixty patients planned for the parenthood. Twenty-seven of them (27/60, 45.0%) achieved at least one pregnancy (median follow-up duration = 7 months, range of 1–25 months). Spontaneous abortion rate was 6.7% (4 out of 60 cases) and live birth rate was 25.0% (15 out of 60 cases), respectively. Eight patients are still in pregnancy, among whom 5 are in late pregnancy. The relapse rate was 5.4% (8/148) and the median time interval to recurrence was 7 months (range, 3–28 months).

A total of 51 EAH and 15 EEC patients were excluded for progestin-used history. Their prior therapeutic methods included low-dose cyclic

progestin (8 cases), high-dose cyclic progestin (1 cases), high-dose continued progestin (50 cases), oral contraceptive pills (3 cases), or LNG-IUS (4 cases). Before seeking for treatment in our hospital, these patients had accepted treatment for 1 to 45 months. The CR rate was 93.9% (62/66) and treatment duration to CR was 12.2 ± 1.0 months (Table 1). We did not analyze the 66 excluded patients, because their previous treatment before transferring to our center might affect the treatment efficiency, particularly some patients had poorer therapeutic outcome in initial hospitals.

3.3. Endometrial lesion size significantly affected conservative treatment effects

Finally, we evaluated possible factors affecting CR rate and therapeutic duration to achieve CR (Table 2). No difference was found in cumulative CR rate between EAH and EEC group (Fig. 3A). Univariate Cox regression analysis showed that BMI <25 kg/m² (odds ratio [OR], 0.687; 95% confidence interval [CI], 0.496–0.954; P = 0.025) and lesion size ≤2 cm (OR, 0.701; 95% CI, 0.496–0.989; P = 0.024) were significantly associated with shorter treatment duration to achieve CR. The mean treatment duration for patients with BMI <25.0 kg/m² or BMI ≥25.0 kg/m² were 6.0 ± 0.4 months and 7.6 ± 0.5 months respectively, P = 0.012 (Fig. 3B and Table 2). Patients with lesion size ≤2 cm or lesion size > 2 cm achieved CR in 5.9 ± 0.4 months and 7.4 ± 0.5 months respectively, P = 0.024 (Fig. 3C and Table 2). After adjusting for age, BMI and therapeutic regimen, lesion size ≤2 cm remained the significant correlation with better therapeutic effects (OR, 0.701; 95% CI, 0.496–0.991; P = 0.045) (Table 2).

Lesions located in the area close to the orifice of fallopian tube or at lower segment of uterine cavity were not found to affect therapeutic effects in our study (Table 2).

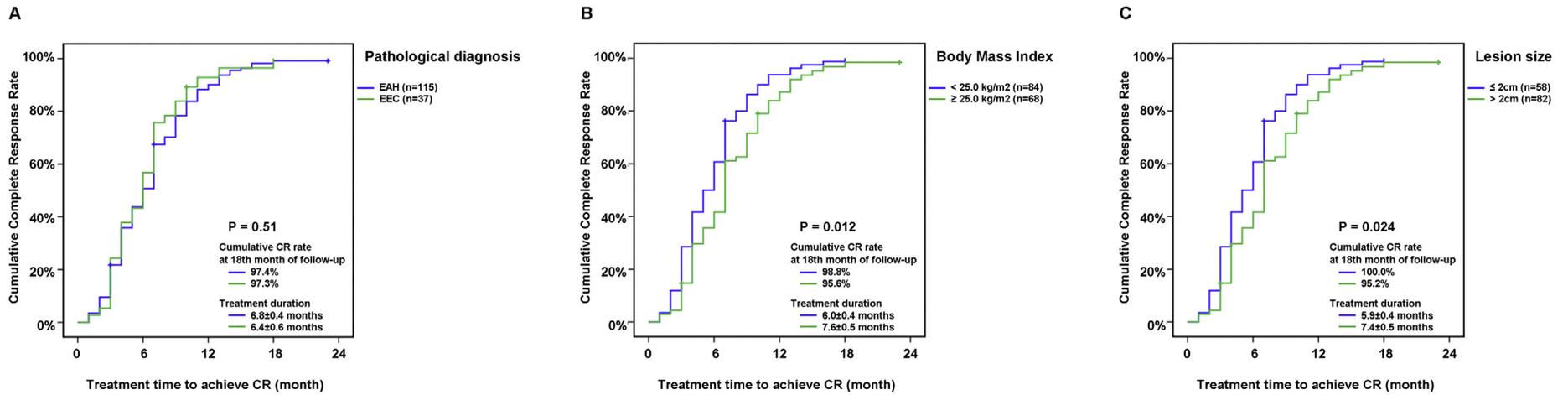


Fig. 3. Cumulative CR rate in EAH and EEC patients. A. The cumulative complete response (CR) rate in EAH and EC patients. B. The cumulative CR rate in patients with different body mass index (BMI). Patients with BMI ≥ 25 kg/m² needed longer time to achieve CR compared with those with BMI < 25 kg/m². C. The cumulative CR rate in patients with different lesion size. Patients with lesion size > 2 cm needed longer time to achieve CR compared with those with lesion size ≤ 2 cm.

Table 2
Factors associated with result of conservative treatment at 18 months of treatment.

Characteristics	Total, n	CR, n (%)	P value	Length of treatment (months)	P value	Univariate Cox P	OR, 95% CI	Multivariate Cox P	OR, 95% CI
	152	148 (97.4)	–	6.7 ± 0.3	–				
Pathological diagnosis									
EAH	115	112 (97.4)	1.00	6.8 ± 0.4	0.51				
EEC	37	36 (97.3)	–	6.4 ± 0.6	–				
Age at diagnosis (years)	50	50 (100.0)	0.30	6.4 ± 0.5	0.60	0.64	0.921 (0.654–1.297)		
≥30 years	102	98 (96.1)	–	6.8 ± 0.4	–				
BMI	84	83 (98.8)	–	6.0 ± 0.4	0.012	0.025	0.687 (0.496–0.954)	0.029	0.683 (0.484–0.963)
<25 kg/m ²									
Insulin resistance									
≥25.0 kg/m ²	68	65 (95.6)	0.33	7.6 ± 0.5	–				
Yes	65	62 (95.4)	0.31	7.4 ± 0.5	0.082	0.120	0.771 (0.555–1.071)		
Metabolic syndrome									
Yes	57	56 (98.2)	1.00	7.3 ± 0.5	0.18				
Hypertension									
Yes	9	9 (100.0)	1.00	8.2 ± 1.4	0.29				
Diabetes mellitus									
Yes	6	6 (100.0)	1.00	7.5 ± 1.9	0.63				
Nulliparous									
No	126	122 (96.8)	1.00	6.5 ± 0.4	0.33				
Lesion location									
No obvious lesions	152	148 (97.4)	–	7.0 ± 0.3	–				
Close to the orifice of fallopian tubes ^a	60	58 (96.7)	1.00*	6.5 ± 0.5	0.73*				
Lower segment ^b	55	53 (96.4)	0.63**	6.7 ± 0.6	0.79**				
Unavailable	47	45 (95.7)	0.60**	7.2 ± 0.7	0.29**				
Lesion size ^c									
≤2 cm	5	5	–	–	–				
>2 cm	58	58 (100.0)	0.14	5.9 ± 0.4	0.024	0.043	0.701 (0.496–0.989)	0.045	0.701 (0.496–0.991)
Unavailable	82	78 (95.2)	–	7.4 ± 0.5	–				
Single lesion ^d									
Yes	12	12 (100.0)	–	–	–				
No	62	60 (96.8)	1.00	6.5 ± 0.5	0.59				
Unavailable	87	85 (97.7)	–	6.9 ± 0.4	–				
	3	3 (100.0)	–	–	–				

EEC, early-stage endometrioid endometrial cancer; EAH, endometrial atypical hyperplasia; BMI, body mass index; CR, complete response.

* Compared to patients with obvious lesions in endometrium.

** Compared to patients without lesions in corresponding location.

^a Lesions' distance is <5 mm from the orifice of fallopian tubes.

^b Lesions located the lower segment near internal orifice of cervix.

^c Size of punctiform or polypoidal lesion was evaluated by basal diameter but not the diameter of lesions. The size of cluster or sheet-like lesion was evaluated with the maximum diameter.

^d Only one punctiform or polypoidal lesion.

4. Discussion

In this study, we reported our institutional retrospective series of EAH and early-stage EC patients who were eligible for conservative treatment and treated by combined comprehensive hysteroscopic evaluation and progestin therapy. The mean treatment duration for achieving CR was 6.8 ± 0.4 months for EAH, and 6.4 ± 0.6 for EEC separately, with both CR rates > 90%. The high response rates in our study might result from strict patient-selection, which followed NCCN guideline for conservative therapy. Comprehensive hysteroscopic evaluation and complete removal of lesions might also improve the treatment outcome of progestin.

Hysteroscopic biopsy has been applied more commonly into conservative treatment for a higher CR rate. The first case series published were from Mazzon et al. in 2010, with 6 cases all resulted in CR [16]. Shan et al. carried out a prospective observational study in which 14 cases of endometrial cancer and 12 cases of atypical hyperplasia were included [17]. Complete hysteroscopic curettage was done for each patient and these patients were later treated with hormone therapy, and 21 (80.8%) patients responded well to treatment. Recently researches of EAH or EEC patients treated with hysteroscopy combined with systematic progestin therapy or LNG-IUS further proved the efficiency of hysteroscopy [8,12,18]. With 120 EAH and 40 EC patients, our study provides further evidence that hysteroscopy treatment is an

effective choice to improve conservative treatment efficiency for these patients.

Because the goal of our study is to evaluate hysteroscopy as the first line treatment for EAH and EC patient, we excluded 66 patients who had >1 month of progestin treatment before transferring to our hospital. These 66 excluded patients had similar CR rate (93.9% for excluded group vs 97.4% for included group) and treatment duration to achieve CR (5.8 ± 0.7 m vs 6.7 ± 0.3 m) after initiating our hysteroscopy combined with progestin regimen. The therapeutic effects in these excluded patients further support the value of hysteroscopy in fertility preserving treatment in EEC and EAH patients. The reason that the recurrence rate is higher in the excluded group than included group (14.5% vs 5.4%) might be because that most of the patients in the excluded group were transferred from other hospital because of poor response rate.

There are several advantages using hysteroscopy as part of the first line fertility preserving treatment for EEC and EAH patients.

Firstly, image guided lesion biopsy under hysteroscopy can be used to differentiated myometrial invasion. Conservative treatment is usually reserved for EEC with no evidence of myometrial invasion, but image study is sometimes confusing when junction zone are blurred which might be caused by myometrial invasion, mechanical disruption of endometrial basal layer after D&C, or other conditions like adenomyoma, etc. Hysteroscopic resection of the suspected lesion and myometrium beneath under the guidance of imaging study allows for both a clearer

pathologic diagnosis of myometrial invasion and an added benefit of therapeutic effects [16].

Comprehensive evaluation and resection of lesion is another obvious advantage of hysteroscopy. With direct visualization, hysteroscopy can find and resect all possible lesions, especially those near fallopian tube orifice or internal cervical orifice which are easily missed by blind D&C. Complete resection of endometrial lesion might be helpful to improve progestin effect in EAH and EC patients. For the patients treated with the hysteroscopic resection plus progestins, De Marzi et al. [10] observed a 100% response rate in 23 EEC patients, and Falcone et al. [12] observed a 92.9% response rate in 28 EEC patients after 6 months of progestin treatment. For patients using D&C only, which could only remove about 50% of endometrium [19], studies reported a CR rate at 60% to 80% within 12 month of progestin treatment [20,21].

The third advantage of hysteroscopy is to preserve normal endometrium as much as possible, which is ultra-important for patients desiring fertility. In our practice, suspected lesions are dissected by cold knife individually and background endometrium is randomly biopsied for pathological diagnosis. Electronic resection is only reserved for cases with suspected myometrium invasion. We reported a 45% pregnant rate in patients desiring fertility, which is similar to previous reports [8,22,23].

However, there are still several concerns about hysteroscopy usage in EEC and EAH patients. Anesthetic complication, water intoxication, uterine wall perforation, infection are the common side effects of hysteroscopy which can be minimized or avoided by professional performance. Relatively high cost is another disadvantage of hysteroscopy. Doctors might discuss with the patient to choose either hysteroscopy or D&C.

Another major concern of repeated hysteroscopy for EC is the potential risk of intraperitoneal dissemination of cancer cells during hysteroscopic performance [24]. In a recent meta-analysis, although preoperative hysteroscopy resulted in a significant increase of positive peritoneal cytology, no impact on prognosis was observed [25]. Because dissemination of malignant cells does not seem to impact prognosis in early-stage low grade endometrial cancer [26,27] and only women with endometrioid cancer confined to endometrium should be considered as candidates for conservative management of endometrial cancer, we suggest that the addition of hysteroscopy to progestin treatment might still be a safe treatment choice for these patients. However, caution should still be taken to prevent intraperitoneal dissemination and detect possible extrauterine metastasis as much as possible. In our practice, we control effective distention pressure during hysteroscopy as low as possible, which is preferred as under 13–15 kPa, to minimize possible intraabdominal cancer cell dissemination. And we perform enhanced MRI every 6 month during progestin therapy to detect possible extrauterine involvement. No metastasis was found in EEC patients after hysteroscopy in our study. We suggest that for the sake of patient safety, comprehensive hysteroscopic evaluation and lesion resection for EAH and EC patients should be conducted by well-trained doctors in qualified centers.

Many studies have evaluated possible factors which might affect the result of conservative treatment in EAH and EC patients, such as increased BMI [20,23,28], insulin resistance [14], tumor pathological grade [29] or different therapeutic regimen used [30,31]. Our study also confirmed that BMI <25 kg/m² positively affects therapeutic effects. However, as a possible major factor affecting treatment effects, the impact of intrauterine endometrial lesion condition on therapeutic effects has not been well studied. In our study, we found that endometrial lesion size > 2 cm in the initial assessment affected the treatment duration. As some patients were initially diagnosed by D&C, lesions under hysteroscopic evaluation may be smaller than its initial status. But at least our results showed patients with smaller lesion size presented with shorter treatment duration.

Our study still has some limitations. The retrospective nature of the study and restricted follow-up duration limits the quality of evidence in this study. A prospective well designed study for both EAH and EC

patients with a standard evaluation and treatment protocol might provide more convincing information about the effects of comprehensive hysteroscopic evaluation and treatment on conservative treatment.

In conclusion, we found an average of 6 months to CR could be achieved by comprehensive hysteroscopic evaluation and lesion resection plus progestin therapy in young patients with EAH and EEC. BMI <25 kg/m² and initial lesion size ≤2 cm were correlated with shorter treatment duration for achieving CR. Comprehensive hysteroscopic evaluation and lesion resection may lead to better treatment effect and less endometrial damage. For the sake of patient safety, EAH and EEC patients seeking for fertility preserving treatment should be carefully evaluated and appropriately selected. Comprehensive hysteroscopic evaluation and lesion resection should be conducted by well-trained doctors in qualified centers. Larger prospective studies are further needed to verify the benefits of including standardized hysteroscopy into conservative therapeutic regimens.

Conflict of interest

No potential conflicts of interest were disclosed.

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Author contribution

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Chengcheng Ning, Yue Shi and Xuezhen Luo: Investigation - supporting

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