Hysteroscopic Curettage Followed by Megestrol Acetate Plus Metformin as a Fertility-Sparing Treatment for Women with Atypical Endometrial Hyperplasia or Well-Differentiated Endometrioid Endometrial Carcinoma

Chu-Yu Jing[1]*(iD), Sheng-Nan Li[2]*, Bo-Er Shan[1], Wei Zhang[1],
Wen-Juan Tian[1], Yu-Lan Ren[1] and Hua-Ying Wang[1]

[1]Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, Shanghai,
China. [2]Department of Gynecology, Longhua Hospital, Shanghai University of Traditional Chinese
Medicine, Shanghai, China.

ABSTRACT

BACKGROUND: In reproductive-aged women, the incidence of atypical endometrial hyperplasia (AEH) or endometrioid endometrial carcinoma (EEC) is rising globally. The study aimed to investigate the effectiveness of hysteroscopic curettage followed by megestrol acetate (MA) plus metformin as conservative treatment in AEH and early EEC.

METHODS: We retrospectively studied AEH and stage IA, grade 1 EEC patients treated with hysteroscopic curettage followed by MA (160 mg/d) plus metformin (1500 mg/d) from January 2010 to December 2020 at Fudan University Shanghai Cancer Center. Treatment outcomes were assessed by complete response (CR) rate, recurrence rate, and pregnancy outcomes. Univariate and multivariate analyses were performed via the logistic regression model.

RESULTS: The study included 79 patients, 31 (39.2%) with AEH and 48 (60.8%) with EEC. The medians of age (years) and follow-up time (months) were 30 and 39.5, respectively. Seventy-six patients (96.2%) finally achieved CR. The median time to CR was 3.6 (3.0-20.6) months. The CR rate after 3 months, 6 months, and 1 year was 55 (69.6%), 67 (84.8%), and 72 (91.1%), respectively. Recurrence occurred in 26 (34.2%) patients. Treatment duration ≥9 months was associated with a lower recurrence rate after CR (P = .012). Fourteen (93.3%) of the 15 recurrent patients who received progestin re-treatment achieved CR again. Finally, 29 patients delivered live births.

CONCLUSIONS: Hysteroscopy followed by MA plus metformin can achieve CR in short time and is overall safe. Consolidation treatment should be prolonged to decrease the recurrence rate, despite a shorter time to CR.

KEYWORDS: Endometroid endometrial cancer, fertility-sparing treatment, hysteroscopy, metformin, megestrol acetate

Introduction

The incidence and mortality of endometrioid endometrial cancer (EEC) and its precursor lesion, atypical endometrial hyperplasia (AEH), are globally on the rise, which is in sharp contrast with many other solid tumors.[1] The unfortunate trend is seen in postmenopausal and premenopausal women, and the onset age is younger and younger. Consequently, oncologists see more reproductive-aged women who desire fertility-preserving treatment rather than definitive surgery as an initial treatment after being diagnosed with EEC or AEH.

The standard treatment for EEC is total hysterectomy and bilateral salpingo-oophorectomy with or without regional lymphadenectomy. A growing literature has suggested that reproductive-aged women with the early

disease can be safely managed with conservative treatment based on progestins.[2-5] The most commonly used progestins are medroxyprogesterone acetate (MPA), megestrol acetate (MA), and levonorgestrel intrauterine device (LNG-IUD).[4-6] The combination of operative hysteroscopy and progestin therapy showed improved effectiveness compared with progestins alone.[7,8] Moreover, the addition of metformin may reinforce the treatment effectiveness of hormonal therapy.[2,9] As data on fertility-sparing strategy are mostly based on small, heterogeneous, retrospective study cohorts, the dose for oral progestins, whether metformin should be added, and the duration of treatment have not been standardized yet.

This study reports the institutional experience of fertility-sparing treatment with hysteroscopic curettage followed by MA plus metformin in AEH and early EEC.

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*C-Y.J. and S-N.L. contributed equally.

Materials and Methods

Patients

This study was retrospective and was approved by the Institutional Ethics Committee of Fudan University Shanghai Cancer Center (approval ID: 2005217-19; approval date: May 11, 2020). All patients have permitted the use of clinical profiles in research without divulging personal data. From January 2010 to December 2020, 97 patients with AEH/EEC were treated with curettage under hysteroscopy followed by MA combined with metformin as fertility-preserving treatment.

Patients eligible for this study must meet the following criteria: (1) strong desire to preserve fertility; (2) below the age of 40; (3) pathologically diagnosed with AEH or well-differentiated EEC (histological grade did not exceed G1); (4) no evidence of myometrial invasion, extrauterine lesions on contrast-enhanced magnetic resonance imaging or computed tomography before treatment initiation; (5) no contraindications for progestins and metformin; (6) no family history of Lynch syndrome or other genetic mutations predisposed to cancer; (7) no concomitant cancer/no history of other cancer; (8) fully informed of risks, follow-up schedules of the conservative treatment.

Patients were excluded if (1) the treatment plan was unfinished or the follow-up period was <6 months, (2) treatment was discontinued against advice, (3) missing critical clinical data or loss of follow-up.

Treatments

Before the first dose of MA and metformin, extensive endometrial resection was performed via hysteroscopy under general anesthesia. Continuous oral MA (160 mg, daily) plus metformin (500 mg, 3 times per day) were prescribed until disease remission. For patients who failed to achieve remission after 6 months, prolonged medical treatment of the same regimen was allowed under careful surveillance. Exercises such as cardio exercises were also encouraged to prevent dramatic weight gain during treatment.

Assessment of treatment effectiveness

Treatment responses were assessed each 2 to 3 months histologically and were classified into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) as reported in the previous studies.[2,10] All histologic specimens obtained from the hysteroscopic evaluation were reviewed by 2 independent gynecological pathologists. Complete response was defined as the reversion of all abnormal endometrial lesions into proliferative or secretory endometrium. Partial response was defined as pathological regression of the disease. Stable disease was defined as no significant improvement compared with pretreatment disease. Progressive disease was defined as the emergence of G2-3 endometrial cancer (EC), myometrial invasion, or extrauterine lesion in patients with well-differentiated EC or the appearance of EC in patients with AEH. Relapse was defined as the emergence of complex hyperplasia, atypical hyperplasia, or cancer after achieving CR. Recurrence-free survival (RFS) was defined as the time interval between the date of CR and the date of recurrence, surgical removal of uterine, or the last follow-up. The last follow-up was censored on October 31, 2021.

Treatment and follow-up strategy after remission

Patients with CR were recommended to receive consolidation treatment with the same regimen for additional 3 months. After CR, if the patient did not have a recent need to conceive, oral contraception or LNG-IUD was recommended to prevent relapse. Follow-up was performed every 3 to 6 months. Transvaginal ultrasonography and endometrial biopsy through dilation and curettage (D&C) or hysteroscopy were conducted to rule out a disease relapse. Enhanced pelvic MR, serological CA-125, and HE4 tests were also recommended to achieve a more comprehensive evaluation. For patients with relapses, either definitive surgery or re-treatment of progestin plus metformin followed by hysteroscopic curettage was recommended. The follow-up interval was calculated from the day when the patient initiated her medical treatment to the last follow-up.

Clinicopathological characteristics of the patients, including age, height, weight, body mass index (BMI), parity, and presence of comorbidities such as impaired glucose tolerance, diabetes mellitus (DM), and polycystic ovary syndrome (PCOS), were obtained from the medical record. Patients were classified as underweight/normal (<25 kg/m²), overweight (25 to <28 kg/m²), and obese (≥28 kg/m²) according to their BMIs.[11]

Statistical analyses

Continuous variables were presented as means or medians. Categorical variables were shown as frequencies with proportions. Variables were compared using the chi-square test, Fisher exact test, Student t test, or Wilcoxon rank sum test as appropriate. Recurrence-free survival was estimated by the Kaplan-Meier method. Univariate and multivariate analyses were conducted based on the logistic regression model. A 2-sided P value <.05 was regarded as statically significant. All statistical analyses were accomplished by SPSS version 23.0 (Chicago, Illinois).

Results

Patient characteristics

The flowchart of the study is shown in Figure 1. Among the 97 screened women, 4 were excluded from the analyses for prior treatment history of AEH/EEC in other hospitals, 8 were excluded for having not achieved treatment outcome, and 6
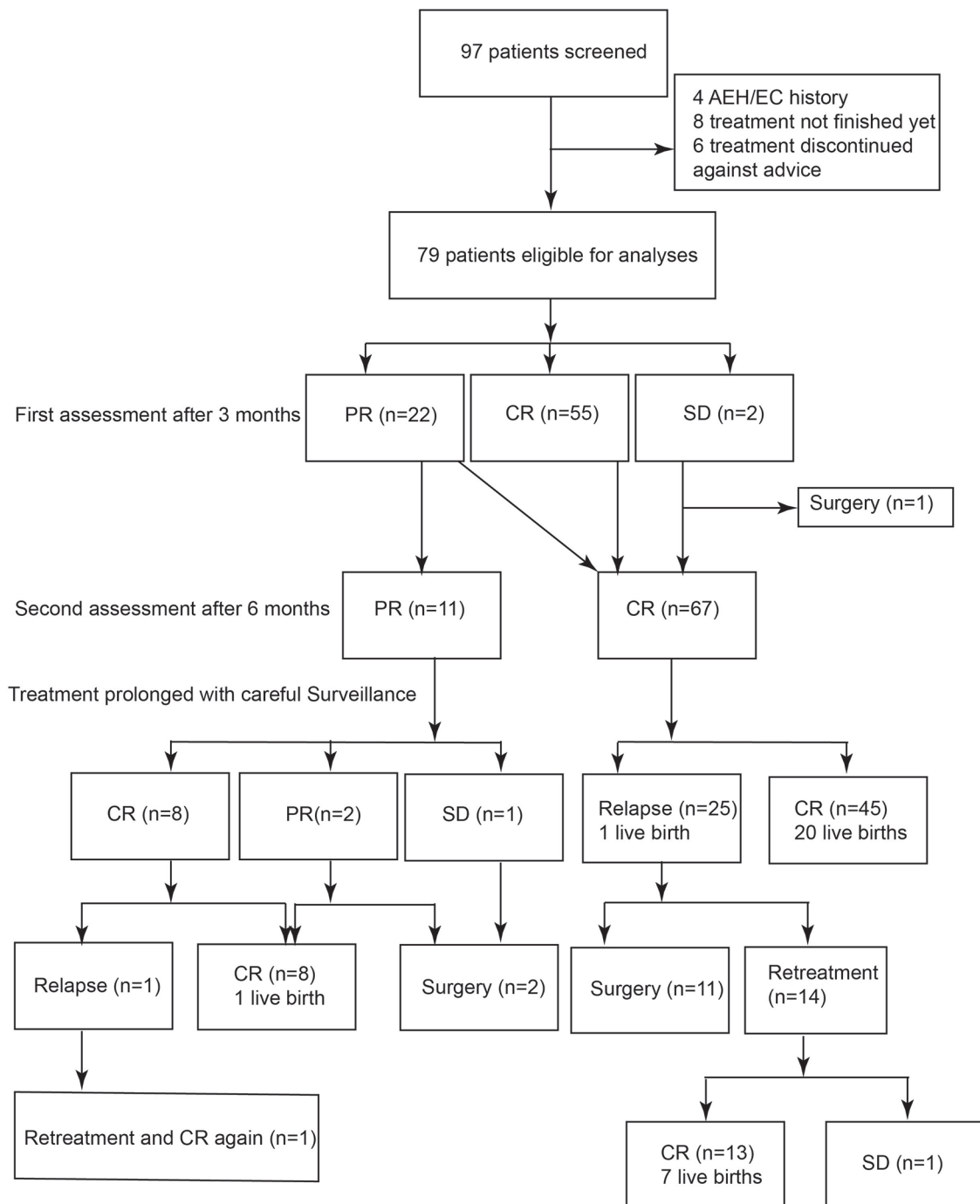
Figure 1. Flowchart of the study.
AEH indicates atypical endometrial hyperplasia; CR, complete response; EC, endometrial carcinoma; PR, partial response; SD, stable disease.

were excluded for discontinuing treatment against doctors' advice. The patients' baseline clinicopathological characteristics are shown in Table 1. Seventy-nine patients were included with a median age at diagnosis of 30.0 (interquartile range [IQR], 27.0-33.0) years and a median follow-up time of 39.5 (IQR, 23.9-60.5) months. The median BMI at initial treatment was 23.4 (IQR, 20.0-27.5) kg/m,^{2} and 32 (40.5%) of the 79 patients were overweight or obese (BMIs ≥25 kg/m^2). Thirty-one (39.2%) women were initially treated for AEH, and 48 (60.8%) were treated for EEC. Of all the patients, 4

(5.1%) showed impaired glucose tolerance, and 2 (2.5%) had DM. Forty-nine of the 77 married patients were nulliparous, and 27 of them complained of infertility. No significant differences were found in baseline clinical characteristics between women with AEH and EEC (Table 1).

Treatment outcomes

The overall CR rate was 96.2% (76/79). Within 18 months, 75 (94.9%) of the included 79 patients achieved CR. The median

Table 1. Baseline clinicopathological characteristics of women who underwent fertility-sparing treatment in our study.

CHARACTERISTICS	OVERALL (N=79)	AEH (N=31)	EEC (N=48)	P VALUE
Age at diagnosis in years, median (IQR)	30.0 (27.0-33.0)	30.0 (28.0-34.0)	29.0 (26.0-32.0)	.415
Follow-up time in months, median (IQR)	39.5 (23.9-60.5)	49.4 (23.9-71.3)	38.3 (23.5-57.9)	.410
Prior live births				.150
None	58 (73.4%)	20 (65.5%)	38 (79.2%)	
One or more	21 (26.6%)	11 (35.5%)	10 (20.8%)	
Initial BMI, median (IQR)	23.4 (20.0-27.5)	23.4 (20.2-26.1)	23.6 (19.9-28.6)	.744
Initial BMI				.155
Underweight/normal	47 (59.5%)	19 (61.3%)	28 (58.3%)	
Overweight	23 (29.1%)	11 (35.5%)	12 (25.0%)	
Obese	9 (11.4%)	1 (3.2%)	8 (16.7%)	
BMI at end of treatment, median (IQR)	24.5 (21.3-28.7)	24.8 (21.3-26.8)	24.1 (21.3-29.3)	.595
Abnormal glucose metabolism				.758
Impaired glucose tolerance	4 (5.1%)	2 (6.4%)	2 (4.2%)	
Diabetes mellitus	2 (2.5%)	1 (3.2%)	1 (2.1%)	
Marital history				.732
Single	9 (11.4%)	4 (12.9%)	5 (10.4%)	
Married	70 (88.6%)	27 (87.1%)	43 (89.6%)	
PCOS	18 (22.8%)	4 (12.9%)	14 (29.6%)	.053
Infertility	28 (35.4%)	9 (29.0%)	19 (39.6%)	.338

Abbreviations: AEH, atypical endometrial hyperplasia; BMI, body mass index; EEC, endometrioid endometrial cancer; IQR, interquartile range; PCOS, polycystic ovarian syndrome.

time to CR from the initiation of treatment was 3.6 (range, 3.0-20.6) months. The number of women who achieved CR at assessments after 3 months, 6 months, and 1 year was 55 (69.6%), 67 (84.8%), and 72 (91.1%), respectively. Twenty-six (34.2%) patients recurred after achieving CR with a median interval to recurrence of 17.9 (IQR, 12.1-35.9) months. Among the 26 patients with recurrent disease, 11 patients finally accepted definitive hysterectomy, and only 1 patient required adjuvant radiotherapy because of pathologically diagnosed deep myometrial invasion. The other 15 patients who strongly desired fertility consented to re-treatment with the same regimen, and 14 of them (93.3%) achieved CR again. At the last follow-up, all enrolled patients were alive and free of disease.

Pregnancy outcomes

Overall, 29 (36.7%) patients successfully got pregnant resulting in live births. Among the 20 parous women following CR, 2 women conceived naturally and finally achieved live births. Fifty-five of the 56 nulliparous women following CR desired to conceive. At the last follow-up, 27 (49.1%) women got live-birth pregnancies, and 20 (74.0%) got pregnant via assisted reproductive technologies. Of note, 7 of the 15 (46.7%) patients

strongly asked for re-treatment after relapse got pregnant and live births after the second disease remission.

Adverse events

The most common adverse event is weight gain. Fifty-four (68.3%) patients underwent weight gain with a median weight gain of 3.0 (range, –17.0 to 20.0) kg during treatment. Severe adverse events (grade 3-4) related to the usage of metformin or MA, such as diarrhea, nausea, lactic acidosis, thrombosis, as well as severe liver and renal dysfunctions, were not observed in this retrospective cohort. Perforation of the uterus, water intoxication, and uterine infection did not occur in this study. Moreover, peritoneal cytology examinations were all negative among the patients who underwent a definitive hysterectomy.

Comparison of treatment outcomes between AEH and EEC

Treatment outcomes for women with AEH or EEC are illustrated separately in Figure 2. The comparison of treatment outcomes in AEH and EEC cohorts is shown in Table 2. The CR rates of AEH and EEC patients were 100% (31/31) and
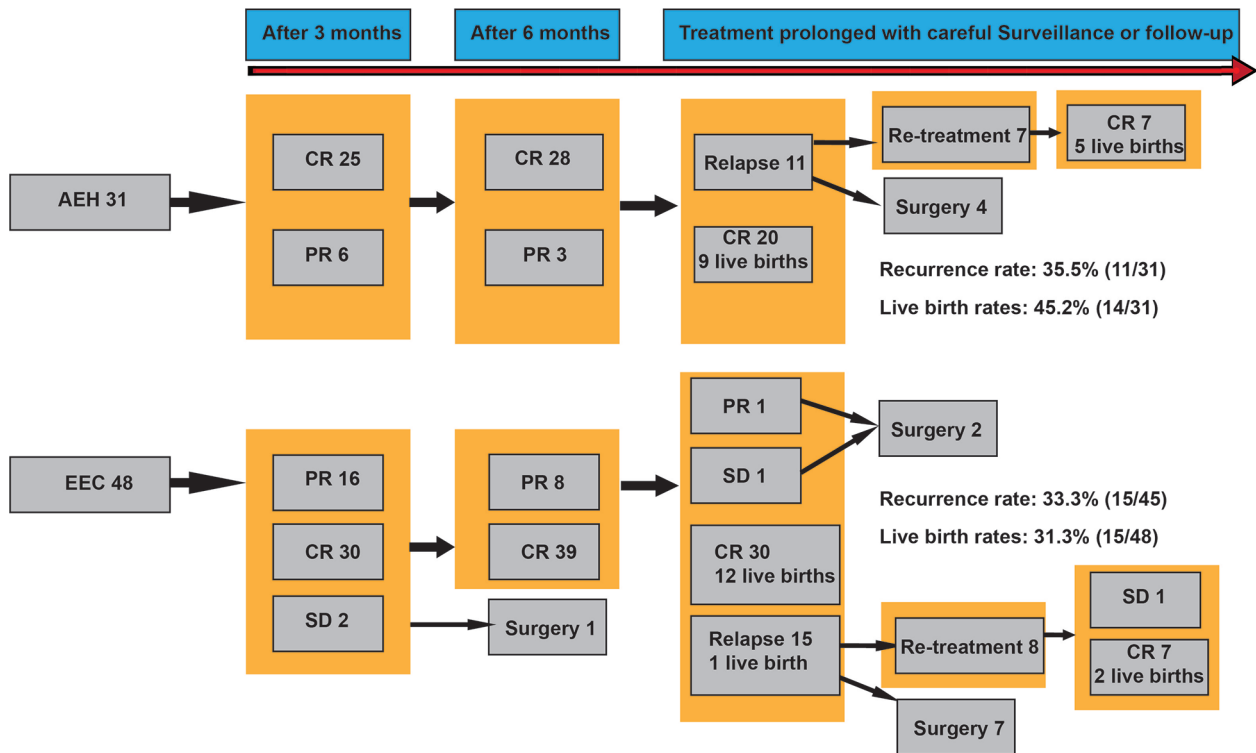
Figure 2. Treatment outcomes of the AEH and EEC subgroups.
AEH indicates atypical endometrial hyperplasia; CR, complete response; EEC, endometrioid endometrial carcinoma; PR, partial response; SD, stable disease.

Table 2. Comparison of treatment outcomes between AEH and EEC.

TREATMENT OUTCOMES	OVERALL (N=79)	AEH (N=31)	EEC (N=48)	P VALUE
CR rate after 3 months, %	69.6 (55/79)	80.6 (25/31)	62.5 (30/48)	.173
CR rate after 6 months, %	84.8 (67/79)	90.3 (28/31)	81.3 (39/48)	.475
CR rate after 1 year, %	91.1 (72/79)	100 (31/31)	85.4 (41/48)	.423
Overall CR rate, %	96.2 (76/79)	100 (31/31)	93.8 (45/48)	.437
Time to CR, median (range)	3.6 (3.0-20.6)	3.4 (3.0-8.9)	3.75 (3.0-20.6)	.057
Initial treatment duration, median (IQR)	7.0 (6.0-9.0)	6.0 (6.0-7.0)	8.0 (6.0-10.0)	**.026**
Time to recurrence, median (IQR)	17.9 (12.1-35.9)	17.6 (14.1-48.7)	18.0 (11.3-35.0)	.659
Recurrence rate after CR, %	34.2 (26/76)	35.5 (11/31)	33.3 (15/45)	.901
RFS in months, median (95% CI)	69.7 (35.8-103.6)	66.7 (42.5-96.2)	87.3 (28.0-146.7)	.773
Remission rate after re-treatment, %	93.3(14/15)	100 (7/7)	87.5 (7/8)	1.000
Live birth rates, %	36.7 (29/79)	45.2 (14/31)	31.3 (15/48)	.332
Live birth rates after re-treatment, %	50.0 (7/15)	71.4 (5/7)	25.0 (2/8)	.132

Abbreviations: AEH, atypical endometrial hyperplasia; CI, confidential interval; CR, complete response; EEC, endometrioid endometrial cancer; IQR, interquartile range; RFS, recurrence-free survival. *P* values <0.05 were marked in bold.

93.8% (45/48), respectively (*P*=.437). The CR rates after 3 months, 6 months, and 1 year were 80.6%, 90.3%, and 100% for AEH and 62.3%, 81.3%, and 85.4% for EEC, respectively. The median time intervals from treatment initiation to CR were 3.4 (range, 3.0-8.9) months in AEH and 3.75 (range, 3.0-20.6) months in EEC (*P*=.057). The median initial treatment

duration, which consisted of time to CR and for consolidation treatment, was 6.0 (IQR, 6.0-7.0) months in AEH and 7.0 (IQR, 6.0-10.0) months in EEC (*P*=.026). Recurrence rates after achieving CR were 35.5% (11/31) in women with AEH and 33.3% (15/45) with EEC (*P*=.901). The median time to recurrence was not significantly different between the 2 cohorts

Table 3. Univariate analyses of predictive factors for relapse after CR in AEH and EEC.

CHARACTERISTICS	AEH			EEC		
	HR	95% CI	*P* VALUE	HR	95% CI	*P* VALUE
Age, y	0.955	0.825-1.105	.534	1.057	0.950-1.176	.309
Initial BMI (≥25 vs <25)	1.283	0.369-4.462	.695	1.518	0.237-1.811	.416
PCOS (– vs +)	0.622	0.077-5.057	.657	0.811	0.339-4.480	.75
Infertility (+ vs –)	1.117	0.288-4.326	.873	1.846	1.023-3.330	**.042**
Abnormal glucose metabolism (– vs +)	0.877	0.109-7.062	.902	0.658	0.303-1.431	.292
Prior live births (≥1 vs none)	0.983	0.505-1.911	.959	0.62	0.358-1.076	.089
Initial treatment duration, months	0.812	0.565-1.165	.258	0.839	0.673-1.046	.118
Initial treatment duration (≥9 months vs <9 months)	0.233	0.036-2.243	.285	0.192	0.043-0.864	**.031**

Abbreviations: AEH, atypical endometrial hyperplasia; BMI, body mass index; CI, confidence interval; EEC, endometrioid endometrial cancer; HR, hazard ratio; PCOS, polycystic ovary syndrome. *P* values <0.05 were marked in bold.
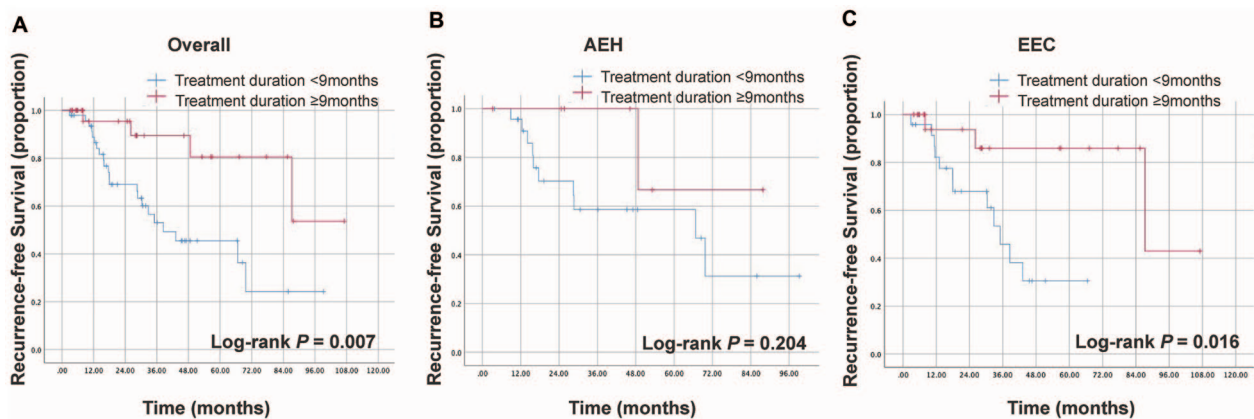

Figure 3. Recurrence-free survival curves of the patients who received conservative treatment shorter or longer than 9 months: (A) the whole cohort, (B) the AEH subgroup, and (C) the EEC subgroup.
AEH indicates atypical endometrial hyperplasia; EEC, endometrioid endometrial carcinoma; *P* values were determined by the log-rank test.

(*P* = .659). Live birth rates were 45.2% (14/31) in the AEH cohort and 31.3% (15/48) in the EEC cohort (*P* = .332). At last, 71.4% (5/7) of women with AEH and 25.0% (2/8) of women with EEC who asked for conservative management after relapses achieved live births (*P* = .132).

Clinical factors predictive of recurrence

Clinical characteristics predictive of recurrence after CR were analyzed through the Cox regression model (Table 3 and Table S1). In univariate analyses, treatment duration as a continuous variable was significantly associated with post-CR recurrence (*P* = .042). Moreover, treatment duration >9 months significantly decreased recurrent risk after CR (*P* = .012; Figure 3A). In AEH, no clinical factors were significantly associated with recurrence. In EEC, history of infertility (hazard ratio [HR] = 1.846, 95% confidential interval [CI], 1.023-3.330, *P* = .042) and initial treatment duration <9 months

(HR = 5.208, 95% CI, 1.157-23.256, *P* = .031) were associated with significant higher risk of recurrence (Figure 3C). In multivariate analyses, the model dropped history of infertility, and initial treatment duration <9 months remained a significant predictor for recurrence.

Discussion

This study reported our institutional retrospective series of AEH and early EEC who received hysteroscopic curettage followed by MA plus metformin as conservative treatment. Our cohort is the largest fertility-preserving cohort with the longest follow-up time treated by the combined strategy reported so far.[2,3,8,12,13] This treatment combination achieved a CR rate of 96.2% (76/29) with a median time to CR of 3.6 (range, 3.0-20.6) months. The treatment strategy also exhibited a recurrence rate of 34.2% (26/76). Fifteen of the 26 recurrent patients asked for progestin re-treatment, and 14 of them (93.3%) achieved CR again. The live birth rate of 55 nulliparous women

who wanted to conceive was 49.1% (27/55). For patients who achieved CR again after recurrence, the live birth rate was 50% (7/14).

Hysteroscopic curettage combined with progestin treatment has been reported to be a safe and effective treatment modality for women with AEH or early EC desiring for fertility.[2,7,8] Compared with blind D&C, hysteroscopy decreases the risk of missing endometrial lesions and damaging the basal layer of the endometrium. Moreover, hysteroscopy-directed lesion removal achieved increased CR rate, shortened CR time, and desirable pregnancy rates ranging from 45% to 61%.[7,8,10] When applying hysteroscopic evaluation in fertility-sparing treatment, the primary concerns are hysteroscopy-specific adverse events such as water intoxication, anesthetic complications, and potential intraperitoneal dissemination of cancer. In this study, adverse events such as water intoxication and anesthetic complications were not observed. Moreover, peritoneal cytology examinations were all negative among patients who finally underwent definitive surgery. A meta-analysis concerning hysteroscopy-related cancer dissemination reported that preoperative hysteroscopy led to increased positive peritoneal cytology but had no impact on prognosis.[14] Altogether, the application of hysteroscopy in fertility conservation treatment is safe when conducted by well-trained doctors.

Metformin is a widely prescribed antihyperglycemic drug for type 2 DM. In recent years, its anticarcinogenic properties have been noticed.[15] Preclinical studies have demonstrated metformin can suppress the growth of various cancer types such as ovarian cancer, EC, and breast cancer via counteracting the PI3K/AKT/mTOR signaling pathway.[15,16] Clinically, metformin has been reported to be associated with improved RFS and overall survival in patients with EC.[9,17] Whether metformin should be added to progestin therapy in fertility-sparing management for AEH and early EC remains controversial. A phase II study in Japan reported that metformin inhibited disease relapse after MPA therapy as fertility-sparing treatment.[13] Moreover, its long-term outcomes demonstrated that combination of metformin with MPA achieved a high CR rate of 97% (61/63) and live birth rates per patient of 45% (14/31).[3] However, retrospective data from the United States indicated that combined progestin and metformin compared with progestin therapy alone failed to improve response rate and live birth rates.[12] A randomized controlled trial in China recently reported that MA plus metformin exhibited higher early CR rate but failed to provide better therapeutic outcomes than MA-only regimen.[2] The long-term outcomes of this study are awaited. Although the addition of metformin to progestin therapy failed to improve outcomes of fertility-preserving treatment substantially, it is still a preferred prescription to countervail the metabolic impact, such as weight gain and glucose intolerance, of systemic progestin therapy.[3]

We reported a relapse rate of 34.2% after CR, which is relatively high compared with previous studies (Table 4).[2,3,5,12] To

explore the reason, we performed univariate analyses to identify clinical factors predictive of recurrence after CR. We found that treatment duration >9 months significantly decreased recurrent risk after CR (*P* = .012). In subgroup analyses, treatment duration >9 months remained a significant predictor for recurrence in the EEC cohort (*P* = .031). So far as we know, the optimal treatment duration of conservative treatment has not been standardized yet.[2-4] Most literature suggested a treatment duration of at least 6 months.[2-4] Alletto et al[5] said that a 9-month treatment period could be effective, and they reported a recurrence rate lower than 10% in their cohort receiving hysteroscopic resection combined with progestins. Recently, Chae et al[18] suggested that 15 months of fertility-sparing treatment could be an optimal treatment duration considering maximizing CR and minimizing PD. However, they did not discuss treatment duration optimal for minimizing post-treatment recurrence. In this study, the median time duration of conservative treatment was 7 (IQR, 6-9) months, slightly shorter than other studies.[4,18] This is mainly because hysteroscopic curettage or metformin could shorten the time to CR.[2,3,7] Thus, the duration of conservative treatment, consisting of time to achieve CR and consolidation treatment, was shortened in our study.[2,3,7] Interestingly, we found that a treatment duration more than 9 months substantially decreased post-CR recurrence, especially in the EEC cohort. Of the patients who firmly asked for progestin re-treatment, 93.3% (14/15) achieved CR again. In subgroup analysis, the remission rates after re-treatment were similar between the AEH and the EEC cohorts (100% vs 87.5%, *P* = 1.00). The live birth rate of the AEH cohort was higher than the EEC cohort, although it failed to reach a statistical significance (71.4% vs 25.8%, *P* = .132). These data indicated that despite a relatively high recurrence rate, most patients can be safely managed with re-treatment with the same regimen and were able to achieve disease remission again. However, post-CR recurrence may affect pregnancy outcomes, especially in women with EEC. Taken together, although prescribing the same regimen for 2 to 3 months was a commonly reported consolidation treatment,[2,8,10] a prolonged consolidation treatment would be preferable despite a high early CR rate when applying hormonal therapy combined with hysteroscopy and metformin.

According to current guidelines, conservative treatments mainly include presumed FIGO stage IA G1 EEC.[19] As the need to preserve fertility increased, several studies attempted to broaden the indications for conservative management.[4,20-22] Growing literature reported that hormonal treatment was safe and feasible in stage IA G2 EC.[4,20-22] So far, the largest series of stage IA G2 EC cohorts receiving conservative treatment was reported by Falcone et al.[4] By adopting systemic or local progestins (74% combined with hysteroscopic resection), they achieved a CR rate of 73.9%, a relapse rate of 41.1%, and a live birth rate of 17.6%.[4] Two studies conducted in China also reported CR rates of 87.5% (7/8) and 75% (3/4) with recurrence rates of

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Table 4. Literature review of AEH and early EC conservatively treated by progestins combined with metformin or with hysteroscopic resection.

STUDY	TREATMENT	STUDY NATURE	NO. OF PATIENTS	MEDIAN FOLLOW-UP TIME, MO	CR RATE	MEDIAN TTCR, MO	RELAPSE RATE	PREGNANCY OUTCOMES
Greggi et al[7]	Hysteroscopic resection + MA or LNG-IUD	Prospective	28 EC	92 (6-172)	89.30%	3 (3-9)	7.70%	Pregnancy rate: 93.3% (14/15); live birth rate: 86.6% (13/15)
Chen et al[8]	Prog + hysteroscopic evaluation	Retrospective	MA 85 (21 EC; 64 AEH); MA-Met 69 (20 EC; 49 AEH)	13 (1-53)	97%	6.7 ± 0.3 (1-18)	5%	Pregnancy rate: 45.0% (27/60); live birth rate 25.0% (15/60)
Mitsuhashi et al[3]	MPA + Met	Retrospective	63 (42 EC; 21 AEH)	57 (13-115)	97%	6 (3-18)	13.10%	Pregnancy rate: 61% (19/31); live birth rate: 45% (14/31)
Chen et al[2]	MA vs MA-Met	RCT	MA 74; MA-Met 76	33.4 (26.0-44.0)	MA 88.9%; MA-Met 91.7%	NA	MA 9.1%; MA + Met 10.7%	Pregnancy rates: MA 48.4%; MA-Met 51.8%; live births rate: MA 17.5%; MA-Met 10.5%
Fader et al[12]	Prog vs Prog-Met	Retrospective	Prog 58; Prog-Met 34	28.4 (IQR 17.2-61.6)	Prog: 69%; Prog-Met: 68%	Prog 4.9 (IQR 3.4-9.7); Prog-Met 6.0 (IQR 3.6-12.1)	Prog:17.2%; Prog-Met:11.7%	Live birth rates: Prog 24%; Prog-Met 6%
Alletto et al[5]	Hysteroscopy + MA	Retrospective	82 (36 EC [5 with MI <3 mm]; 46 AEH)	EC: 30 (24-60); AEH: 36 (24-60)	EC: 94.4%; AEH 100%	NA	EC:8.9% (3/34); AEH:8.7% (4/46)	Live births: EC 14; AEH 21
The present study	Hysteroscopy + MA + Met	Retrospective	79 (48 EC; 31 AEH)	39.5 (IQR 23.9-60.5)	96.20%	3.6 (3.0-20.6)	34.2%	Live birth rate: 49.1% (27/55); overall: 36.7% (29/79)

Abbreviations: AEH, atypical endometrial hyperplasia; CR, complete response; EC, endometrioid carcinoma; IQR, interquartile range; MA, megestrol acetate; Met, metformin; MI, myometrial infiltration; MPA, medroxyprogesterone acetate; NA, not available; Prog, progestins.

42.8% (3/7) and 33.3% (1/3), respectively.[20,21] Concerning a pooled CR rate beyond 70% and an overall good prognosis despite treatment response, conservative treatment is at least a worth-trying option for presumed stage IA G2 ECC who strongly wish to have a baby.[4,20,21]

Myometrium infiltration is often considered one of the exclusion criteria for conservative management.[19] Paradisi et al[23] reported 3 G1, ECC women with minimal myometrial infiltration (<3 mm) who received conservative management of hysteroscopic resection accompanied by progestins. All 3 women achieved CR, and 1 of them successfully achieved a live birth. In 2 women who finally underwent definitive surgery, no evidence of myometrial infiltration was found.[23] In a recent study performed by Alletto et al, conservative management achieved a CR rate of 94.4% in the G1 ECC cohort containing 5 women with minimal myometrial infiltration. With a median follow-up time of 30 (24-60) months, recurrence occurred in 3 of the 5 women.[5] Park et al reported that hormonal treatment yielded a CR rate of 73.9% (17/23) and a recurrence rate of 47.1% (8/17) in G1 EEC with superficial myometrial invasion. Finally, 45% of the women who attempted to conceive achieved live births successfully.[22] Altogether, for EC patients with initial myometrial invasion, conservative treatment is an option for women who firmly want to preserve fertility. Strict follow-up schedules to identify disease progression are indispensable to ensure a good prognosis.

Treatment resistance and disease recurrence are the major obstacles to conservative treatments. Even in strictly selected early-stage patients, a few patients exhibited treatment resistance and were more likely to relapse after disease remission.[3,7,23] Therefore, predictive markers to distinguish these patients are of great importance in optimizing the efficiency of conservative treatment. Several clinical factors such as obesity, PCOS, history of infertility, and menstrual cycle characteristics have been proposed to predict treatment response.[6,24,25] However, their predictive power varied among different studies.[6,22,24,25] A recent study by Raffone et al[6] identified that longer menstrual cycles and infrequent menstrual bleeding served as independent predictors of conservative treatment failure in AEH and EEC. In terms of histological markers, estrogen and progesterone receptors (PRBs) were most extensively validated with conflicting results.[26,27] One of their isoforms, PRB, appeared to be a promising predictor.[6,26] A weak stromal expression of PRB was reported to be a highly sensitive marker in predicting both treatment resistance and recurrence.[28] In addition, a series of biomarkers, such as mismatch repair proteins (MMR), DUSP6, GRP, Ki67, and Bcl2, showed predictive power on treatment response or disease recurrence.[26] Interestingly, MMR deficiency, which was responsible for microsatellite instability, showed a 100% specificity in predicting recurrence in conservatively treated AEH/EEC.[29]

Several studies failed to observe a substantial benefit when adding hysteroscopic resection or metformin into hormonal therapy in patients with strictly selected AEH or early-stage EEC.[2,4,12] However, hysteroscopic resection plus progestins yielded satisfying CR rates when treating patients with risk factors, such as initial myometrial infiltration, G2 grade, and MMR deficiency.[4,23,29] Metformin was reported to exhibit anticancer effects in preclinical studies and was observed to shorten the time to CR and reverse side effects of progestins, such as weight gain.[2,30] As oncologists are also trying to help EC women with risk factors achieve live births, whether adding metformin and hysteroscopic could outweigh progestin alone in EC women with minimal myometrial invasion, a high histological grade, or genetic defects is an interesting issue that is worth further exploration.

Several limitations of the study should be addressed as follows: First, the study is a retrospective, single-centered analysis. Second, we performed extensive endometrial resection via hysteroscopy. Among extensive endometrial resection, 2-step resection (resection of the lesion and a small layer of myometrium below the lesion) and 3-step resection (removal of the endometrium around the lesion in addition to the 2-step resection),[7] which method benefits more remains inconclusive. Despite the limitations, the present study is the largest cohort so far reporting the treatment outcomes of hysteroscopic curettage followed by MA plus metformin as fertility-preserving management.

Conclusions

This retrospective study demonstrated that hysteroscopic curettage followed by MA combined with metformin as fertility-preserving treatment was safe, well-tolerated, and achieved a high response rate and good fertility outcomes. Treatment duration should be prolonged despite a high early CR rate to decrease the post-CR recurrence rate.

Author Contributions

Study design and supervision: H-Y.W, and Y-L.R; Perfrom the study: B-E.S, Y-L.R, W-Z and W-J.T; Data acquisition and analysis: B-E.S, C-Y.J and S-N.L; Manuscript drafting: C-Y.J and S-N.L

ORCID iD

Chu-Yu Jing https://orcid.org/0000-0001-8057-4677

Supplemental Material

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