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Original Article

Outcomes of extended progestin therapy in atypical endometrial hyperplasia patients without an initial response to progestin: a retrospective study from two tertiary centers in Korea and Taiwan

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ABSTRACT

Objective: In this study, we evaluated the role of prolonged progestin treatment on atypical endometrial hyperplasia (AEH) patients who did not achieve complete regression (CR) after at least 3 months of progestin treatment. Possible prognostic factors predicting disease regression and recurrence were also assessed.
Methods: We retrospectively identified patients who had histologically confirmed persistent disease after at least 3 months of progestin treatment at two tertiary centers in Korea and Taiwan. Clinicopathologic factors and clinical outcomes were obtained from medical records. Logistic regression was used to analyze the relationship between covariates and the probability of CR and relapse.
Results: Fifty-two patients were included. Thirty-seven of 52 patients (71.2%) achieved CR after prolonged progestin treatment. Median time from starting progestin treatment to CR was 12.0 months. Daily administration of medroxyprogesterone acetate ≥200 mg or megestrol acetate ≥80 mg was associated with higher probability of regression. Nineteen of 37 patients (51.4%) experienced recurrence, with median time from CR to relapse of 15.0 months. Body mass index ≥27 was associated with higher relapse probability. Twelve of 16 patients with disease progression to endometrial carcinoma underwent surgery. The 12 cases had stage I tumors and lived without disease.
Conclusion: Extension of progestin treatment course is feasible for AEH patients without an initial response to progestin. Higher daily progestin dosage was associated with higher probability of CR, and obesity was associated with higher risk of relapse. The patients

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Conflict of Interest
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without an initial response to progestins and whose AEH progressed to endometrial carcinoma had good prognoses.

Keywords: Endometrial Cancer; Endometrial Hyperplasia

Synopsis
This study investigated the effect of prolonged progestin therapy on atypical endometrial hyperplasia (AEH) patients who did not achieve complete regression after at least 3 months of progestin treatment. We found that for AEH patients without an initial response, extending progestin treatment course with higher doses may improve regression rates. Obese patients have a higher probability of recurrence.

INTRODUCTION

Atypical endometrial hyperplasia (AEH) is the precursor lesion of endometrial carcinoma. Previous studies have demonstrated that up to 29% of AEH can progress to endometrial carcinoma if left untreated [1,2]. For patients with AEH, hysterectomy should be recommended to reduce the risk of subsequent carcinoma. However, surgical management may not be suitable for patients who desire to preserve their fertility. Therefore, fertility-sparing alternatives should be considered for these patients.

Clinically, oral progestin, including medroxyprogesterone acetate (MPA) or megestrol acetate (MA), is the most frequently used conservative treatment for AEH and stage IA endometrial carcinoma [3,4]. Other treatment options include gonadotropin-releasing hormone agonists, levonorgestrel-releasing intrauterine system (LNG-IUS), and metformin plus progestin [5-7]. The efficacy and safety of fertility-sparing treatment has been confirmed in several retrospective studies and meta-analyses [4,8-10]. Among these studies, remission rates ranged from 42% to 100% [5,6,11-15]. Most studies have shown that median time to complete regression (CR) from the beginning of progestin treatment is about 3–6 months [16-18]. There is still no consensus on the duration, dosage, and type of progestin treatment. Generally, if no response is achieved after 6 months' conservative treatment, surgical management is recommended.

However, the probability of young women developing AEH and endometrial carcinoma is on the rise [19], and the age at which they are having children is increasing. Therefore, the feasibility of extending the duration of conservative treatment is an urgent issue that needs to be explored in patients without an initial response to progestin treatment but still wish to preserve fertility. This study aimed to investigate the effectiveness of prolonged progestin treatment in women who had histologically confirmed persistent AEH after at least 3 months of progestin therapy. We also identified factors associated with regression and relapse of persistent AEH. Oncologic and reproductive outcomes were also evaluated.

MATERIALS AND METHODS

1. Study population

We retrospectively identified patients with AEH who underwent progestin treatment in the period 2009 to 2022 at Samsung Medical Center in Seoul, Korea, and National Taiwan

University Hospital in Taiwan. A central review of pathologic determination was not included. Patients were included when they met both of these criteria: 1) histologically confirmed AEH or endometrial intraepithelial neoplasia based on World Health Organization definitions [20], and 2) persistent disease confirmed by endometrial biopsy after at least 3 months of progestin therapy. Patients who achieved CR after 3 months of progestin therapy or who underwent hysterectomy before 3 months were excluded. In both institutes, AEH patients who did not achieve regression after three months of progestin therapy would be advised to undergo hysterectomy. Therefore, we defined the duration of initial progestin treatment as the use of progestin for ≤3 months, and extended progestin therapy as the use of progestin for > 3 months. This study was approved by the institutional review boards.

Persistent AEH patients who received extended progestin therapy were classified into two categories: 1) patients with fertility needs, and 2) patients who were unwilling to undergo a hysterectomy. Therefore, if the patient did not experience severe side effects of progestins and the disease did not progress to endometrial carcinoma, the decision to continue progestin treatment primarily would be depended on patients' preference after thorough discussion.

The progestin regimens comprised oral MPA, oral MA, or the LNG-IUS. The LNG-IUS was inserted alone or combined with oral progestin. The clinicians adjusted the progestin dosage to manage the side effects, resulting in a varying range of dosage. Daily doses of MPA ranged from 15 mg to 600 mg, and the dose of MA ranged from 40 mg to 160 mg. For each patient, data of the clinicopathologic characteristics, treatment, and oncologic and fertility outcomes were retrieved form the medical record. Body mass index (BMI) ≥27 was considered obese [21].

2. Follow-up and evaluation of treatment responses

The diagnosis of AEH and response to progestin treatment were assessed by biopsy of endometrial curettage or hysteroscopy. Progestin therapy was initiated within one month after AEH diagnosis. During progestin treatment, the patients underwent regular follow-up in the outpatient clinic. Transvaginal ultrasonography and office hysteroscopy have been used as alternative methods for intrauterine evaluation. Tissue proof would be performed for suspected lesions. Endometrial biopsy for the assessment of treatment response was performed every 3–6 months. The response was classified as follows: 1) regression (CR), defined as the absence of hyperplasia or carcinoma; 2) persistence, the presence of residual hyperplasia; and 3) progression, the progression to endometrial carcinoma.

After achieving CR, the patients were followed every 3–6 months with history taking, transvaginal ultrasonography, and sometimes office hysteroscopy at each visit. Endometrial biopsy was performed if these patients had abnormal symptoms or examination results. Recurrence was defined as subsequent AEH or endometrial carcinoma identified after CR of initial AEH.

Time to regression was calculated from the date of starting progestin treatment to the date of achieving CR. Time to progression was calculated from the date of starting progestin to the date of diagnosis of endometrial carcinoma. Recurrence-free interval (RFI) was defined as the period from the date of achieving CR to the date of disease recurrence or last follow-up. The follow-up period was defined as the interval from the date of AEH diagnosis to the date of the last visit. Safety assessments included recording of adverse events and concomitant medications during the progestin treatment by physical examination, and hematologic and biochemical tests. Adverse events were assessed and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [22].

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3. Statistical analysis

Descriptive statistics were used to summarize clinical characteristics. Categorical variables are expressed as frequencies and percentages, with median and range for continuous variables. Logistic regression analysis was performed to assess association between the clinicopathologic factors and disease status. RFI were estimated by the Kaplan-Meier method. The $p<0.05$ was considered significant. Statistical assessment was performed using MedCalc software 14.12.0 (MedCalc Software bvba, Ostend, Belgium).

4. Ethics statement and informed consent statement

This study was conducted in accordance with ethical principles and approved by the Institutional Review Boards of NTUH (ethical approval number: NTUH-HC REC: 113-070-E) and SMC (ethical approval number: 2022-10-095-002). Patient consent was waived by approval of the ethics committee.

RESULTS

1. Patient characteristics

A total of 52 patients who met the inclusion criteria were included in this study. The baseline characteristics of all patients are presented in **Table 1**. At initial AEH diagnosis, the median age was 35 years (range, 18–52 years). The median BMI was 26.6 kg/m^2 (range, 17.9–46.3 kg/m^2). Forty-three patients (82.7%) were nulliparous. More than 50% (27/52) of the women

Table 1. Clinical characteristics of study population (n=52)

Characteristics	Values
Age at AEH diagnosis (yr), median (range)	35 (15–52)
BMI (kg/m^2), median (range)	26.6 (17.9–46.3)
<24.0	17 (32.7)
≥24.0	29 (55.8)
Unknown	6 (11.5)
Parity (before AEH diagnosis)	
0	43 (82.7)
1	6 (11.5)
2	2 (1.9)
3	1 (3.9)
Medical comorbidities	
None	25 (48.1)
Yes	27 (51.9)
Diabetes	8
PCOS	23
Hypertension	5
Other*	10
Progestin therapy	
MA/MPA	44 (84.6)
MA/MPA + LNG-IUS†	7 (13.5)
LNG-IUS	1 (1.9)
Dosage of progestin treatment	
MPA <200 mg or MA <80 mg daily	8 (15.4)
MPA ≥200 mg or MA ≥80 mg daily	44 (84.6)

Values are presented as median (range) or number (%).
AEH, atypical endometrial hyperplasia; BMI, body mass index; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate; MPA, medroxyprogesterone acetate; PCOS, polycystic ovary syndrome.
*Others included hyperthyroidism, hypothyroidism, thyroid cancer, hepatitis, hyperprolactinemia.
†MA/MPA + LNG-IUS included patients using MA/MPA and LNG-IUS for at least 3 months during the treatment.

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had medical comorbidities, including diabetes (8/27), polycystic ovary syndrome (23/27), hypertension (5/27), and others (10/27). Forty-four patients (84.6%) received oral MPA or MA alone, 7 (13.5%) received oral MPA or MA combined with LNG-IUS, and 1 (1.9%) received LNG-IUS alone during the treatment period.

2. Clinical outcomes of the study population

Table 2 shows the clinical outcomes of patients undergoing prolonged progestin treatment. The median follow-up time was 22.0 months (range, 9.0–122.0 months). The median duration of progestin treatment was 13.0 months (range, 6.0–48.0 months). During the study period, 37 patients (71.2%) had achieved CR at a median interval from beginning progestin treatment to regression of 12.0 months (range, 9.0–58.0 months). Of the remaining 15 patients, 6 had persistent AEH, and 9 progressed to endometrial carcinoma (**Fig. S1**). At the end of follow-up, 21 patients had CR after treatment, and 15 had persistent AEH. The remaining 16 cases had endometrial carcinoma at a median time from starting progestin treatment to cancer diagnosis of 13.0 months (range, 6.0–48.0 months).

In 37 cases with CR of initial AEH after prolonged progestin treatment, 19 of them had subsequent AEH (12 patients) or endometrial carcinoma (7 patients). The RFIs of the 37 cases are exhibited in **Figure 1**. The median time from CR to relapse was 15.0 months. Seventeen out of 52 women received hysterectomy because of disease persistence or progression. Eight women tried to conceive after achieving CR of AEH. Assisted reproductive technologies were applied to help them become pregnant. Seven patients had successful pregnancy and delivered 9 live neonates. Two cases experienced disease progression to endometrial carcinoma after delivery.

During the progestin treatment, abnormal uterine bleeding was the most common adverse event followed by weight gain, headache, depression, abdominal pain, and hypertension (**Table S1**). All the adverse events were grade 1 or grade 2 in severity. Of 52 eligible patients, aspirin was prescribed to 12 (23.1%) of them for the prevention of venous thromboembolism. There were no reports of thromboembolic events in the study population.

Table 2. Clinical outcomes of prolonged progestin treatment

Characteristics	Values
Follow-up time (mo), median (range)	22.0 (9.0–122.0)
Duration of treatment (mo), median (range)	13.0 (6.0–48.0)
Regression rate	37 (71.2)
Median time to regression (mo) (range)	12.0 (9.0–58.0)
Final status of study population*	
Regression (CR)	21 (40.4)
Persistence†	15 (28.8)
Progression	16 (30.8)
Median time to progression (mo) (range)	13.0 (6.0–48.0)
Recurrence‡	19 (36.5)
AEH	12 (23.1)
Endometrial carcinoma	7 (13.5)
Hysterectomy	17 (32.7)
Successful pregnancy after AEH	7 (13.5)

AEH, atypical endometrial hyperplasia; CR, complete remission.
*Final status was based on the pathologic report of the last endometrial biopsy or hysterectomy.
†Persistence was defined as the presence of endometrial hyperplasia in every endometrial biopsy during progestin treatment.
‡Recurrence was considered as subsequent AEH or endometrial carcinoma identified after CR of initial AEH.

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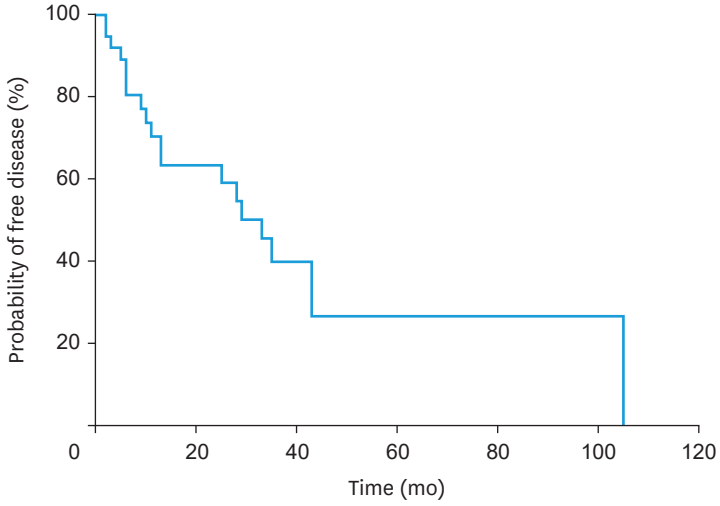

Fig. 1. Relapse-free interval of 37 patients who subsequently progressed to AEH or endometrial carcinoma after complete regression of initial AEH. The median time from complete regression to relapse was 15.0 months. AEH, atypical endometrial hyperplasia.

3. Factors predicting CR and disease relapse

The factors predicting CR after prolonged progestin treatment were further examined (**Table 3**). Daily administration of MPA ≥200 mg or MA ≥80 mg (odds ratio [OR]=0.16; 95% confidence interval [CI]=0.03–0.97, p=0.04) was the only factor associated with higher regression probability. The factors predicting disease relapse after CR were also evaluated (**Table 4**). BMI 27.0 or higher (OR=4.46; 95% CI=1.11–17.90; p=0.03) was associated with higher relapse probability.

4. Clinicopathologic characteristics of patients with endometrial carcinoma

Twelve of 16 patients with disease progression to endometrial carcinoma underwent hysterectomy or staging surgery. The clinicopathologic characteristics of these patients are

Table 3. Factors predicting complete regression of atypical endometrial hyperplasia after prolonged progestin treatment (52 cases)

Factor	Odds ratio	95% CI	p-value
History of diabetes (yes vs. no)	1.53	0.24–5.45	0.86
History of PCOS (yes vs. no)	1.10	0.36–3.35	0.87
BMI (≥27.0 vs. <27.0)	1.34	0.43–4.14	0.61
LNG-IUS insertion during treatment (yes vs. no)	0.31	0.03–2.73	0.29
Dosage of progestin treatment (MPA ≥200 mg or MA ≥80 mg daily vs. MPA <200 mg or MA <80 mg daily)	0.16	0.03–0.97	0.04
Duration of progestin treatment (≥12 mo vs. <12 mo)	0.66	0.21–2.15	0.50

BMI, body mass index; CI, confidence interval; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate; MPA, medroxyprogesterone acetate; PCOS, polycystic ovary syndrome.

Table 4. Factors predicting relapse after complete remission of initial atypical endometrial hyperplasia (37 cases)

Factor	Odds ratio	95% CI	p-value
History of diabetes mellitus (yes vs. no)	0.94	0.16–5.39	0.94
History of PCOS (yes vs. no)	0.84	0.23–3.00	0.79
BMI (≥27.0 vs. <27.0)	4.46	1.11–17.90	0.03
LNG-IUS insertion during treatment (yes vs. no)	0.31	0.05–1.83	0.20
Dosage of progestin treatment (MPA ≥200 mg or MA ≥80 mg daily vs. MPA <200 mg or MA <80 mg daily)	0.19	0.08–4.22	0.29
Duration of progestin treatment (≥12 mo vs. <12 mo)	2.67	0.55–12.88	0.22

BMI, body mass index; CI, confidence interval; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate; MPA, medroxyprogesterone acetate; PCOS, polycystic ovary syndrome.

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Table 5. Characteristics of patients with disease progression to endometrial carcinoma undergoing hysterectomy or staging surgery*

Cases	Age at EC diagnosis	BMI (kg/m²)	FIGO stage†	Histology	LVSI	Preoperative CA-125 (U/mL)	Status at last follow-up
1	49	19.4	IA (confined to endometrium)	Grade 1 endometrioid	Absent	33.4	NED
2	35	29.4	IA (confined to endometrium)	Grade 1 endometrioid	Absent	14.2	NED
3	42	24.3	IA (confined to endometrium)	Grade 1 endometrioid	Absent	22.2	NED
4	33	25.4	IA (5 mm/20 mm)	Grade 1 endometrioid	Absent	10.0	NED
5	40	19.4	IA (confined to endometrium)	Grade 1 endometrioid	Absent	4.9	NED
6	50	18.9	IA (confined to endometrium)	Grade 1 endometrioid	Absent	11.2	NED
7	37	27.1	IA	Grade 1 endometrioid	Absent	5.4	NED
8	33	42.7	IA (confined to endometrium)	Grade 1 endometrioid	Absent	3.6	NED
9	43	23.4	IA (confined to endometrium)	Grade 1 endometrioid	Absent	3.5	NED
10	54	20.1	IA (1 mm/18 mm)	Grade 1 endometrioid	Absent	4.4	NED
11	48	20.8	IA (1 mm/30 mm)	Grade 2 endometrioid	Absent	11.2	NED
12	50‡	21.9	IB (10 mm/15 mm)	Grade 3 endometrioid	Present	5.6	NED

BMI, body mass index; CA-125, cancer antigen 125; EC, endometrial carcinoma; FIGO, The International Federation of Gynecology and Obstetrics; LVSI, lymph-vascular space invasion; NED, no evidence of disease.
*Staging surgery included total hysterectomy with or without bilateral salpingo-oophorectomy, pelvic lymphadenectomy with or without para-aortic lymphadenectomy, resection of any suspicious lesions, omental biopsy, and peritoneal washing cytology.
†2009 FIGO staging system for carcinoma of the endometrium.
‡MMR proteins staining showed loss of PMS2. This patient underwent adjuvant chemoradiation (chemotherapy and radiotherapy).

presented in **Table 5**. Most patients had low-grade endometrioid stage IA tumors without lympho-vascular space invasion. Only one patient had grade 3 endometrioid stage IB endometrial carcinoma. This patient received postoperative adjuvant chemoradiation. The cancer antigen 125 level was within normal range in all patients. During the follow-up period, no recurrence was observed with median disease-free survival of 32.0 months.

DISCUSSION

This study investigated the effectiveness of prolonged progestin treatment in persistent AEH after at least 3 months of progestin therapy. In our cohort, the rate of CR with prolonged progestin treatment was 71.2%. Daily administration of MPA ≥200 mg or MA ≥80 mg was associated with higher probability of CR. Despite the promising regression rate, 51.4% of patients who achieved CR eventually experienced AEH relapse or disease progression to endometrial carcinoma. We found that BMI ≥27 was associated with increased risk of relapse after initial AEH regression. However, the patients with endometrial carcinoma developed as a result of progestin treatment failure had a good prognosis.

In previous studies, the regression rate of AEH or stage IA endometrial cancer under progestin treatment ranged from 42% to 100% [5,6,11-15]. In two meta-analyses, the overall regression rates of AEH were 75% and 85.6%, consistent with our result [4,10]. However, no consensus has been reached regarding the optimal progestin dosage and treatment duration for AEH patients with fertility issues, especially those with an initial poor response to progestins. MPA has been applied with daily doses between 20 and 1,500 mg, and MA between 40 and 480 mg [23].

Baker et al. [24] reviewed 12 studies to investigate the efficacy of progestin treatment in AEH or patients with early endometrial carcinoma receiving 6 or more months of treatment. Overall, 74% of patients with AEH achieved CR. Cho et al. [25] evaluated the efficacy of prolonged progestin treatment for presumed stage IA low-grade endometrioid adenocarcinoma cases having persistent disease after 9 months of progestin therapy. The

CR rate was 72.5% after prolonged progestin treatment (median time from treatment to CR: 17.3 months) with MPA 500 mg daily or MA 650 mg [25]. Our study focused on the AEH patients without an initial response to progestins. Under the extended duration of progestin treatment (median time from treatment to CR: 12.0 months), our study population achieved a CR rate of 71.2%. Daily administration of MPA ≥200 mg or MA ≥80 mg was associated with higher probability of CR.

Despite the acceptable outcomes of progestin treatment for AEH, some patients do not respond to it well, or their disease may recur after an initial regression, demonstrating a risk of progression to endometrial carcinoma. Gallos et al. [4] reported a relapse rate of 26% in AEH patients with fertility-sparing treatment. Yang et al. [26] described a relapse rate of 35.2% in patients with AEH or well-differentiated endometrioid carcinoma treated conservatively. In our cohort, the relapse rate of 51.4% was higher than that in previously published results, possibly due to the relatively progestin-insensitive nature of our study population. Although 19 out of 37 patients relapsed, no severe treatment-related side effects occurred, and there was no increase in disease-specific mortality. Therefore, extending the duration of progestin treatment appears to be a relatively safe approach until we can effectively predict which AEH patients can respond well to progestin. At the end of follow-up, 31 patients ultimately either remained as AEH or progressed to endometrial cancer. This group of poorly-responding AEH might fundamentally differ from the well-responding AEH, potentially due to the differences of progestin resistance [27-30].

Great efforts have been made to identify predictive factors, including clinical, pathologic, and immunohistochemical characteristics, regarding regression and relapse of conservatively treated AEH [26,31-34]. In these studies, certain risk factors, including obesity, have been reported to be associated with treatment response and disease relapse [26,34,35]. In our study, BMI ≥27 was associated with increased risk of relapse after initial AEH regression. A possible obesity-related mechanism of progestin resistance might be excessive estrogen production due to decreased expression of sex hormone-binding globulin and increased synthesis of estrogen in the ovary and surrounding adipose tissue [27,36].

In addition to clinical factors, the identification of biomarkers predicting the response to progestin treatment may help clinicians select the appropriate AEH patients who desire fertility preservation. Raffone *et al.* reported that weak expression of the stromal isoform B progesterone receptor was a highly sensitive marker of both no response and recurrence in conservatively treated AEH [28]. Aberrant signaling of progestin receptor or other pathways, metabolic-immune-tumor microenvironment, and endometrial cancer stem cells are the causes of progestin resistance in endometrial pre-cancer or cancer. Multiple molecules associated with cell proliferation, oxidative stress, metabolism, apoptosis, non-coding RNA, and nucleic acid regulation may be the biomarkers of progestin resistance [27]. It remains unclear whether defective mismatch repair (MMR) is associated with possible response to progestin treatment in AEH and well-differentiated endometrial carcinoma. In two retrospective analyses evaluating the prognostic significance of molecular profiling in AEH and endometrial carcinoma treated with progestins, defective MMR was a predictor of poor response to progestin therapy [29,30].

The strength of our study included the enrollment of a well-defined study population who had persistent AEH after at least 3 months of progestin treatment, and comprehensive patient follow-up information regarding oncologic and reproductive outcomes. Nevertheless,

this study was limited by its retrospective nature and the small number of patients. Other limitations were that we did not include all AEH patients in our analysis to explore the possible mechanisms for their different responses to progestin treatment and the lack of molecular information. These will be the essential issues for our future research.

The results of this study suggest that it may be reasonable for physicians to extend the use of progestin for patients with reproductive concerns or not suitable for hysterectomy who do not have a good response to progestin in the initial stage of treatment. Additionally, on the basis of our findings, outcomes of extending the duration of progestin use beyond 12 months could be investigated in future research. At the same time, to identify predictive factors associated with treatment response, incorporating molecular information into AEH diagnosis could also be considered.

In conclusion, our findings suggest that extending progestin treatment course is feasible for AEH patients without an initial response to progestin. Higher daily progestin dose was associated with higher probability of CR. Obesity was associated with higher risk of AEH relapse and progression. The patients with AEH that progressed to endometrial carcinoma had favorable prognoses. Before receiving fertility-sparing treatment, patients should be informed that conservative treatment is accompanied by risk of disease relapse and progression to endometrial carcinoma.

SUPPLEMENTARY MATERIALS

Table S1

Adverse events* during progestin treatment (n=52)

Fig. S1

Flowchart of clinical outcomes of study population.

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