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Original Article

Fertility-preserving treatment outcome in endometrial cancer or atypical hyperplasia patients with polycystic ovary syndrome

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ABSTRACT

Objective: This study aimed to investigate the impact of polycystic ovary syndrome (PCOS) on fertility-sparing treatment in young patients with atypical endometrial hyperplasia (AEH) or endometrioid endometrial cancer (EEC).
Methods: A total of 285 patients with EEC (n=76, FIGO stage IA, without myometrium invasion) or AEH (n=209) who received progestin-based fertility-sparing treatment were evaluated retrospectively. Among the 285 patients, 103 (36.1%), including 70 AEH cases and 33 EEC cases, were diagnosed with PCOS. General characteristics, cumulative 16- and 32-week complete response (CR) rate, pregnancy outcome and recurrence were compared between patients with or without PCOS.
Results: The cumulative 16-week CR rate was lower in the PCOS group than in the non-PCOS group (18.4% vs. 33.8%, p=0.006). Patients with PCOS took longer treatment duration to achieve CR (7.0 months vs. 5.4 months, p=0.006) and shorter time to relapse after CR (9.6 months vs. 17.6 months, p=0.040) compared with non-PCOS group. After adjusting for patient age, body mass index, PCOS, homeostasis model assessment-insulin resistance index, and serum testosterone levels, we found that body mass index ≥25 kg/m^2 (HR=0.583; 95% CI=0.365–0.932; p=0.024) and PCOS (HR=0.545; 95% CI=0.324–0.917; p=0.022) were significantly correlated with lower 16-week CR rate.
Conclusion: PCOS was associated with lower 16-week CR rate, longer treatment duration and shorter recurrence interval in patients with AEH or EEC receiving fertility-preserving treatment.

Keywords: Endometrial Hyperplasia; Endometrial Neoplasms; Conservative Treatment; Polycystic Ovary Syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disorder in reproductive-aged women. Patients with PCOS are characterized by a classical triad of hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology and are at risk for other conditions, such as obesity or insulin resistance [1]. Chronic anovulation in PCOS patients is generally associated with persistent estrogen exposure and progesterone

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: L.X., C.X.; Formal analysis: W.L., W.Q., L.Q., W.P.; Funding acquisition: L.X., C.X.; Investigation: W.L., W.Q., L.Q., W.P.; Methodology: W.L., W.Q.; Resources: L.Q., L.W.; Validation: W.L., L.Q., L.W.; Supervision: L.X., C.X.; Writing - original draft: W.L., W.Q.; Writing - review & editing: L.X., C.X.

deficiency [2], which results in the elevated risk of developing atypical endometrial hyperplasia (AEH) or endometrial cancer (EC) [3].

Because a majority of the patients with PCOS are young or nulliparous when diagnosed with AEH or EC, fertility-sparing treatment becomes an important priority. High-dose progestin has been widely accepted as the main fertility-sparing treatment for young patients with AEH or well-differentiated endometrioid endometrial cancer (EEC). The reported complete response (CR) rate for high-dose progestin in patients with AEH or EC is approximately 70%–80% [4]. Previous studies reported that higher body mass index and insulin resistance (IR), which are two of the major characteristics of PCOS, negatively affect the outcome of fertility-preserving treatment in AEH and EEC patients [5]. However, whether PCOS specifically has any impact on fertility-sparing treatment in AEH and EEC patients is not clear. Furthermore, whether the status of PCOS affects the pregnancy outcomes in these patients after achieving CR is unknown.

To answer these questions, we carried out a single-centered retrospective study to investigate the prognosis of AEH and EEC patients with PCOS receiving fertility-preserving treatment. The clinical characteristics and oncologic and reproductive outcomes of PCOS patients were analyzed and compared with those of patients without PCOS.

MATERIALS AND METHODS

1. Study population

This retrospective study included 472 consecutive patients (329 AEH and 143 EEC) who received fertility-preserving treatment at the Obstetrics and Gynecology Hospital of Fudan University between January 2017 and August 2019. All patients underwent standardized evaluation and treatment, and the patient information was prospectively collected and recorded during treatment and follow-up. All patients signed informed consent for conservative treatment and for the use of their data for research purposes. The study was approved by the Ethics Committee of Obstetrics and Gynecology Hospital of Fudan University.

The inclusion and exclusion criteria for fertility-sparing treatment followed National Comprehensive Cancer Network guidelines. The inclusion criteria were as follows: 1) histologically-proven AEH or well-differentiated EEC G1 without myometrial invasion; 2) no signs of suspicious extrauterine involvement on enhanced magnetic resonance imaging, enhanced computed tomography or ultrasound, 3) patient age younger than 45 years old; 4) strong willingness to preserve fertility; 5) no contraindications for progestin treatment or pregnancy; 6) not pregnant; and 7) good compliance for treatment. Written informed consent was obtained from all patients before initiating treatment. The exclusion criteria were as follows: 1) use of local or systematic progestins for more than one month before first comprehensive evaluation in our center; 2) incomplete medical records for diagnosis of PCOS; 3) recurrent AEH or EEC; 4) evidence of myometrium invasion; 5) other endocrine diseases, such as hypothyroidism; and 6) loss of follow-up.

2. Pathological diagnosis

All patients were pathologically diagnosed by endometrial biopsy through dilation and curettage with or without hysteroscopy. Pathologic diagnosis was confirmed by two experienced gynecological pathologists according to the World Health Organization

pathological classification (2014). If their opinions differed, a seminar was held in the pathology department to determine the final diagnosis. Another hysteroscopy was performed within 1 month after the initial pathological diagnosis if the patient was diagnosed by dilation and curettage without hysteroscopy.

Diagnosis of PCOS was based on Rotterdam Consensus Criteria [6]. A diagnosis of PCOS was made if at least two of the following criteria were met: 1) oligo/anovulation; 2) signs of hyperandrogenism (i.e., hirsutism and acne) and/or biochemical measurements; or 3) enhanced ovaries (at least 12 discrete follicles of 2–9 mm in diameter in one ovary or an ovarian volume ≥10 cm^3 observed by transvaginal ultrasonography). Patients with other androgen-excess disorders or specific etiologies including congenital adrenal hyperplasia, Cushing's syndrome, thyroid hormone abnormalities, hyperprolactinemia or ovarian/adrenal tumors were excluded.

3. Conservative treatment and evaluation of treatment results

Fertility-preserving treatment was initiated as soon as comprehensive evaluation was completed and a multidisciplinary team determined the patient suitable for fertility-preserving treatment. Therapeutic regimens were decided by doctors. Most patients received oral megestrol acetate (MA) at a dose of 160 mg per day with or without metformin (500 mg, thrice daily). Other patients were treated with a levonorgestrel-releasing intrauterine system (LNG-IUS) only or MA plus LNG-IUS with or without metformin. A comprehensive hysteroscopic evaluation was performed every 3 months during treatment to evaluate therapeutic efficacy. Endometrial lesions were removed under hysteroscopy, and an endometrium biopsy was randomly performed if no obvious lesion was found.

The response to conservative treatment was assessed histologically using specimens obtained during each hysteroscopic evaluation. CR was defined as no hyperplasia or cancerous lesion found. Partial response (PR) was defined as pathological improvement; stable disease (SD) was defined as when the initially diagnosed lesion persisted; and progressive disease (PD) was defined as evidence of EC in patients with AEH or evidence of more severe pathological findings, myometrial invasion or extrauterine metastasis in EEC patients.

Once a patient achieved CR, the same regimen was continued for another 2–3 months for consolidation. Hysteroscopy was performed 3 months after the first CR for confirmation. The duration to achieve CR was calculated from the time of initiating treatment to the time of first pathological CR diagnosis. All patients desiring fertility were encouraged to receive assisted reproductive treatments such as in vitro fertilization after CR. Low-dose progestin, oral contraceptive pills or LNG-IUS were used to prevent recurrences in patients who did not have a parental plan.

Hysterectomy was strongly recommended for patients with SD for 6 months, PR for 9 months or PD at any time during treatment. For patients who refused hysterectomy, alternative treatments including Diane-35 (one pill per day for 21 days out of a 28-day cycle) combined with metformin (500 mg, thrice daily), LNG-IUS insertion or an intramuscular injection of GnRH-a were given according to the recommendations of a multidisciplinary team.

Patients were followed-up every 3 to 6 months after CR. Ultrasound evaluation was done at each follow-up, and an endometrial biopsy using Pipelle was performed every 6 months during follow-up. Patients were followed-up until August 2020. The median follow-up time

from the date of initiating treatment to the last follow up was 22.8 months (range, 3.1–52.7 months). The median follow-up time from the date of achieving CR to the last follow-up was 16.5 months (range, 3.0–44.5 months).

4. Data collection

General information of the patients, including age, weight, height, basic blood pressure and comorbidities (e.g., hypertension or diabetes), was collected before any treatment was given. Blood samples were collected before initiating fertility-preserving treatment, and fasting blood glucose, fasting insulin, lipid profiles, anti-Mullerian hormone (AMH) and sex hormone profiles were evaluated. All blood samples were collected and examined in the laboratory of the Obstetrics and Gynecology Hospital as previously described [7]. Body mass index (BMI) and the homeostasis model assessment-insulin resistance (HOMA-IR) index were calculated. BMI was calculated as weight (kg)/height^2 (m^2). A BMI ≥25 kg/m^2 was considered as overweight [8]. The HOMA-IR index (fasting blood glucose [mmol/L] × fasting insulin [microU/mL]/22.5) was used to evaluate IR status [9]. Patients with HOMA-IR index ≥2.95 were defined as insulin resistant [10]. The diagnostic criteria for metabolic syndrome, diabetes mellitus and hypertension have been previously described [7]. Biochemical hyperandrogenism was diagnosed if total testosterone exceeded 0.51 ng/mL according to the reference value of our laboratory.

5. Statistical analysis

All descriptive data are presented as mean and SD for data with a Gaussian distribution and as median plus range for non-Gaussian distributed data. Categorical variables are presented as frequency with percentage. Continuous variables were analyzed using the Student's t-test or Mann–Whitney U test, as appropriate. The χ^2 test was used to analyze categorical variables except if the expected frequency was <5; in these cases, Fisher's exact test or likelihood-ratio χ^2 was used. Kaplan-Meier method was used to estimate the therapeutic duration; differences between groups were tested using log-rank test. A Cox regression model was used for univariate and multivariate analyses of the relationship between covariates and CR in response to fertility-preserving treatment. Statistical significance was determined as $p<0.05$ in two-sided tests. Statistical analyses were performed using SPSS (version 23.0, IBM, Armonk, NY, USA).

RESULTS

A total of 472 consecutive patients receiving fertility-preserving treatment at the Obstetrics and Gynecology Hospital of Fudan University between January 2017 and August 2019 were retrospectively investigated (**Fig. 1**). Among the total patient group, 187 patients were excluded, including 88 patients who received progestin treatment for more than one month before the first endometrial evaluation at our hospital, 19 patients with recurrent AEH or EEC, 26 patients who were transferred to other hospitals before initiating treatment, 42 patients who quit conservative treatment and required surgery before the first hysteroscopy, 9 patients with insufficient clinical information for the diagnosis of PCOS, and 3 patients with other endocrine diseases. We did not analyze patients with progestin-used history or recurrent AEH/EEC because their previous treatment before transferring to our center might affect the therapeutic efficacy. Ultimately, 285 patients (209 AEH cases and 76 EEC G1 cases) who met all the inclusion criteria were included in this study. Out of the 285 patients, 103 (36.1%) patients, including 70 AEH cases and 33 EEC cases, were diagnosed with PCOS.

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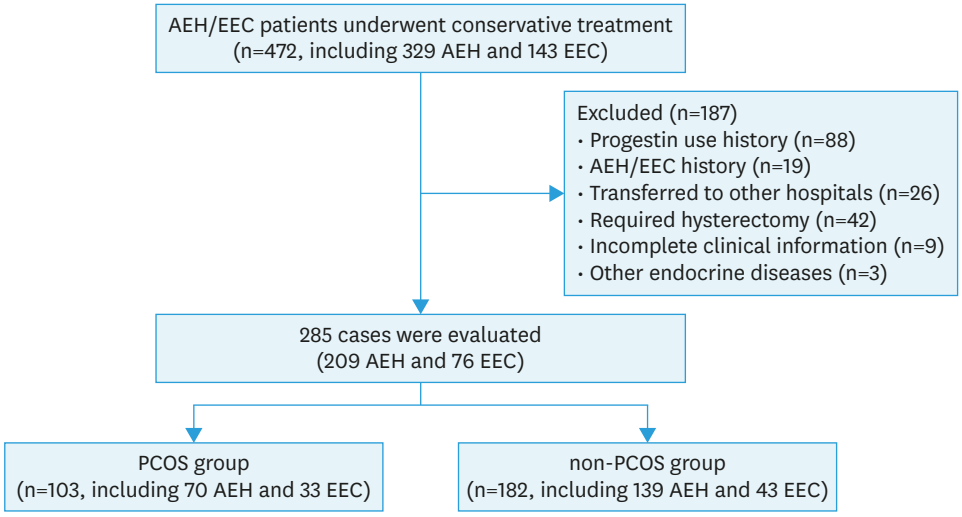

Fig. 1. Flow chart of patient selection.
AEH, atypical endometrial hyperplasia; EEC, endometrioid endometrial cancer; PCOS, polycystic ovary syndrome.

The clinical and pathological characteristics of the patients are summarized in **Table 1**. The median age at diagnosis was 32 years old (range, 20–45 years old) and the median BMI was 24.8 kg/m^2 (range, 16.7–51.6 kg/m^2). Approximately 78.6% of patients were nulliparous when diagnosed with AEH or EEC. The median follow-up time from the date of initiating treatment to the last follow up was 22.8 months (range, 3.1–52.7 months). The median follow-up time from the date of achieving CR to the last follow up was 16.5 months (range, 3.0–44.5 months). A total of 262 patients (262/285, 91.9%) achieved CR with a median treatment duration to CR of 6.5 months (range, 1.0–28.0 months); five patients underwent hysterectomy during treatment, and the remaining 18 patients are still in treatment.

1. Clinical-pathological characteristics of PCOS and non-PCOS patients

Among the total 285 patients, 103 patients were diagnosed with PCOS before initiating progestin therapy. As shown in **Table 1**, compared with the non-PCOS group, the PCOS group was younger (30 years vs. 33 years, p<0.001) and had a higher BMI (26.0 kg/m^2 vs. 24.0 kg/m^2, p<0.001), higher HOMA-IR index (3.1 vs. 2.1, p<0.001), higher serum AMH level (6.3 ng/mL vs. 1.8 ng/mL, p<0.001) and higher serum total testosterone level (0.7 ng/mL vs. 0.3 ng/mL, p<0.001). In addition, patients with PCOS were more likely to show IR (53.4% vs. 26.9%, p<0.001), hypertension (40.8% vs. 28.6%, p=0.035) and diabetes mellitus (16.5% vs. 8.2%, p=0.034) compared with non-PCOS patients. There was no statistical difference in the frequency of AEH or EEC, metabolic syndrome, serum estradiol level or progesterone level between the PCOS and non-PCOS groups. Moreover, no difference was found in the distribution of different progestin treatments between patients with or without PCOS (p=0.824; **Table 1**).

2. Outcome of fertility-sparing treatment

The results of fertility-preserving treatment in patients with or without PCOS are summarized in **Table 2**. Compared with non-PCOS patients, the PCOS group showed a lower cumulative 16-week CR rate (18.4% vs. 33.8%, P=0.006) (**Fig. 2A**). Similar results between PCOS and non-PCOS patients were also found in the subgroups of AEH and EEC patients (**Fig. 2B and C**), although the difference did not reach statistical significance in EEC patients. The median treatment duration to CR was longer in PCOS patients than in non-PCOS

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Table 1. General characteristics of the study population

Variables	All patients	PCOS	Non-PCOS	p-value*
No. of patient	285	103	182	-
Age at diagnosis (yr)	32.0 (20.0–45.0)	30.0 (20.0–40.0)	33.0 (24.0–45.0)	<0.001
BMI (kg/m^2)	24.8 (16.7–51.6)	26.0 (17.5–45.3)	24.0 (16.7–51.6)	<0.001
Overweight	131 (46.0)	61 (59.2)	70 (38.5)	0.001
HOMA-IR index	2.2 (0.2–12.6)	3.1 (0.8–12.6)	2.1 (0.2–12.4)	<0.001
IR	104 (36.5)	55 (53.4)	49 (26.9)	<0.001
MS	111 (38.9)	46 (44.7)	65 (35.8)	0.167
Hypertension	94 (36.7)	42 (40.8)	52 (28.6)	0.035
Diabetes mellitus	32 (11.2)	17 (16.5)	15 (8.2)	0.034
Nulliparous	224 (78.6)	88 (85.4)	136 (74.7)	0.034
Histology at diagnosis				0.123
AEH	209 (73.3)	70 (68.0)	139 (76.4)	-
EEC	76 (26.7)	33 (32.0)	43 (23.6)	-
Progestin therapy				0.824
MA	108 (37.9)	41 (39.8)	67 (36.8)	-
MA+MET	59 (20.7)	18 (17.5)	41 (22.5)	-
LNG-IUS	54 (18.9)	21 (20.4)	33 (18.1)	-
MA+LNG-IUS	56 (19.6)	21 (20.4)	35 (19.2)	-
MA+LNG-IUS+MET	8 (2.8)	2 (1.9)	6 (3.3)	-
AMH (ng/mL)	2.7 (0.02–24.6)	6.3 (0.02–24.6)	1.8 (0.06–7.4)	<0.001
E2 (pg/mL)	56.0 (1.7–762.0)	53.5 (1.7–400.0)	58.5 (2.0–762.0)	0.281
P (ng/mL)	0.5 (0.01–67.5)	0.5 (0.03–65.0)	0.5 (0.01–67.5)	0.759
T (ng/mL)	0.4 (0.01–23.9)	0.7 (0.01–23.9)	0.3 (0.01–1.6)	<0.001
Hyperandrogenism	110 (38.6)	80 (77.7)	30 (16.5)	<0.001
Median follow-up duration (mo)	22.8 (3.1–52.7)	23.4 (3.3–47.7)	22.7 (3.1–52.7)	0.849
Median follow-up duration after CR (mo)	16.5 (3.0–44.5)	15.9 (3.0–44.5)	17.0 (3.0–41.2)	0.398

Data are shown as number (%) or median (range). p-value: comparison between PCOS and non-PCOS group.
AEH, atypical endometrial hyperplasia; AMH, anti-Mullerian hormone; BMI, body mass index; CR, complete response; EEC, endometrioid endometrial cancer; E2, estradiol; HOMA-IR index, homeostasis model assessment-insulin resistance index; IR, insulin resistant; MA, megestrol acetate; MS, metabolic syndrome; LNG-IUS, levonorgestrel intrauterine system; MET, metformin; P, progesterone; T, testosterone.
*All continuous variables were analyzed by Wilcoxon rank sum test. Comparison of distribution of different progestin therapies was analyzed by Fisher's exact test. Comparison of distributions of other categorical variables were all analyzed by Pearson's χ^2 test.

patients (7.0 months vs. 5.4 months, p=0.006; **Table 2**). Because the heterogeneous nature of progestin therapy might interfere with the results, we analyzed the impact of PCOS on treatment results in patients treated with MA only or MA+MET only (**Table S1**). Patients with PCOS showed lower cumulative 16-week CR rate than non-PCOS patients in MA subgroup (12.2% vs. 30.3%, p=0.031). In patients treated with MA+MET, PCOS patients had lower cumulative 16- and 32-week CR rate and longer treatment duration to CR compared with non-PCOS patients (16-week CR rate, 11.1% vs. 36.6%, p=0.048; 32-week CR rate, 33.3% vs. 63.4%, p=0.026; median treatment duration, 9.9 months vs. 6.0 months, p=0.007). These results are consistent with the findings in total sample analysis.

During the median follow-up of 16.5 months (range, 3.0–44.5 months) after achieving CR, recurrence occurred in 10 of the 100 patients in the PCOS group and 17 of the 162 patients in the non-PCOS group. No statistical difference was found in the 24-month cumulative recurrence rate between PCOS patients and non-PCOS patients (27.5% vs. 19.3%, p=0.383). However, patients with PCOS experienced a shorter time to relapse compared with non-PCOS patients (9.6 months vs. 17.6 months, p=0.040). Among those 262 women who achieved CR, only 29 (29/100, 29.0%) PCOS and 55 (55/162, 34.0%) non-PCOS women attempted to conceive. Sixteen (16/29, 55.2%) PCOS and forty-five (45/55, 81.8%) non-PCOS women underwent assisted reproduction technology and the others of the two groups tried to conceive naturally. No significant difference was found in the pregnancy rate (55.2% vs. 45.5%, p=0.397) between PCOS and non-PCOS group. And among patients who achieved

Table 2. Treatment outcomes in PCOS and non-PCOS patients

Variables	All patients	PCOS	Non-PCOS	p-value
No. of patient	285	103	182	-
16-wk CR rate*				
All	28.2	18.4	33.8	0.006
AEH	31.3	21.4	36.3	0.030
EEC	19.9	12.1	26.0	0.134
32-wk CR rate*				
All	62.2	61.2	62.7	0.256
AEH	65.0	67.1	63.7	0.633
EEC	54.6	48.5	59.4	0.257
24-mo CR rate*				
All	97.6	100.0	95.7	0.854
AEH	97.1	100.0	95.6	0.930
EEC	97.7	100.0	94.8	0.839
Median treatment duration to CR (mo)†				
All	6.5 (1.0–28.0)	7.0 (1.0–21.9)	5.4 (1.0–28.0)	0.006
AEH	5.8 (1.0–19.2)	6.6 (1.0–18.5)	4.9 (1.0–19.2)	0.037
EEC	7.1 (1.0–28.0)	7.9 (1.0–21.9)	6.9 (1.0–28.0)	0.133
24-mo recurrence rate*				
All	21.9	27.5	19.3	0.383
AEH	17.1	24.0	14.0	0.388
EEC	124.0	36.1	36.5	0.863
Median duration to recurrence (mo)‡				
All	14.3 (4.4–34.0)	9.6 (4.9–27.1)	17.6 (4.4–34.0)	0.040
AEH	19.8 (6.1–34.0)	12.5 (6.1–27.1)	23.8 (9.1–34.0)	0.056
EEC	10.0 (4.4–17.6)	8.3 (4.9–14.1)	11.0 (4.4–17.6)	0.394
Pregnancy rate§				
All	48.0 (41/84)	55.2 (16/29)	45.5 (25/55)	0.397
AEH	54.4 (31/57)	63.6 (14/22)	48.6 (17/35)	0.266
EEC	37.0 (10/27)	28.6 (2/7)	40.0 (8/20)	0.678
Live birth rate‖				
All	53.7 (22/41)	56.3 (9/16)	52.0 (13/25)	0.790
AEH	51.6 (16/31)	57.1 (8/14)	47.0 (8/17)	0.576
EEC	60.0 (6/10)	50.0 (1/2)	62.5 (5/8)	1.000

Data are shown as % (number) and median (range). p-value: comparison between PCOS and non-PCOS group.
AEH, atypical endometrial hyperplasia; CR, complete response; EEC, endometrioid endometrial cancer; PCOS, polycystic ovary syndrome.
*The 16-week, 32-week and 24-month CR rate and the 24-month recurrence rate were cumulative complete response or recurrence rate at different follow-up points. Cumulative CR/recurrence rates were evaluated with Kaplan-Meier analysis and compared by log-rank test. †The median treatment duration (months) from initiation of conservative treatment to CR. ‡The median duration (months) from achieving CR to recurrence. §Pregnancy rate among patients who attempt to conceive. ‖Live birth rate was calculated among patients who achieved pregnancy.

pregnancy, the live birth rate was 56.3% and 52.0% in PCOS and non-PCOS patients respectively (p=0.790). Pregnancy was lost in 3 out 16 (18.8%) in PCOS group and 6 out of 25 (24.0%) patients in non-PCOS group. Ten (4 PCOS and 6 non-PCOS) women were still in pregnancy till the last follow up.

3. PCOS significantly affected fertility-preserving treatment outcome

To explore whether PCOS affected the outcome of fertility-preserving treatment in AEH and EEC patients, we evaluated possible factors affecting the cumulative 16-week CR rate. Univariate Cox regression analysis showed that age ≥30 years (HR=1.887; 95% CI=1.091–3.264; p=0.023), PCOS (HR=0.496; 95% CI=0.297–0.831; p=0.008), BMI ≥25 kg/m^2 (HR=0.532; 95% CI=0.335–0.845; p=0.008), IR (HR=0.555; 95% CI=0.337–0.914; p=0.021) and hyperandrogenism (HR=0.574; 95% CI=0.354–0.931; p=0.025) were related with a lower 16-week CR rate (**Fig. 3**). Multivariate Cox regression analysis showed that PCOS (HR=0.545; 95% CI=0.324–0.917; p=0.022) and BMI ≥25 kg/m^2 (HR=0.583; 95% CI=0.365–0.932; p=0.024) remained as independent risk factors for lower 16-week CR rate after adjusting for age, PCOS, BMI, IR and hyperandrogenism (**Fig. 3**). Univariate and multivariate Cox

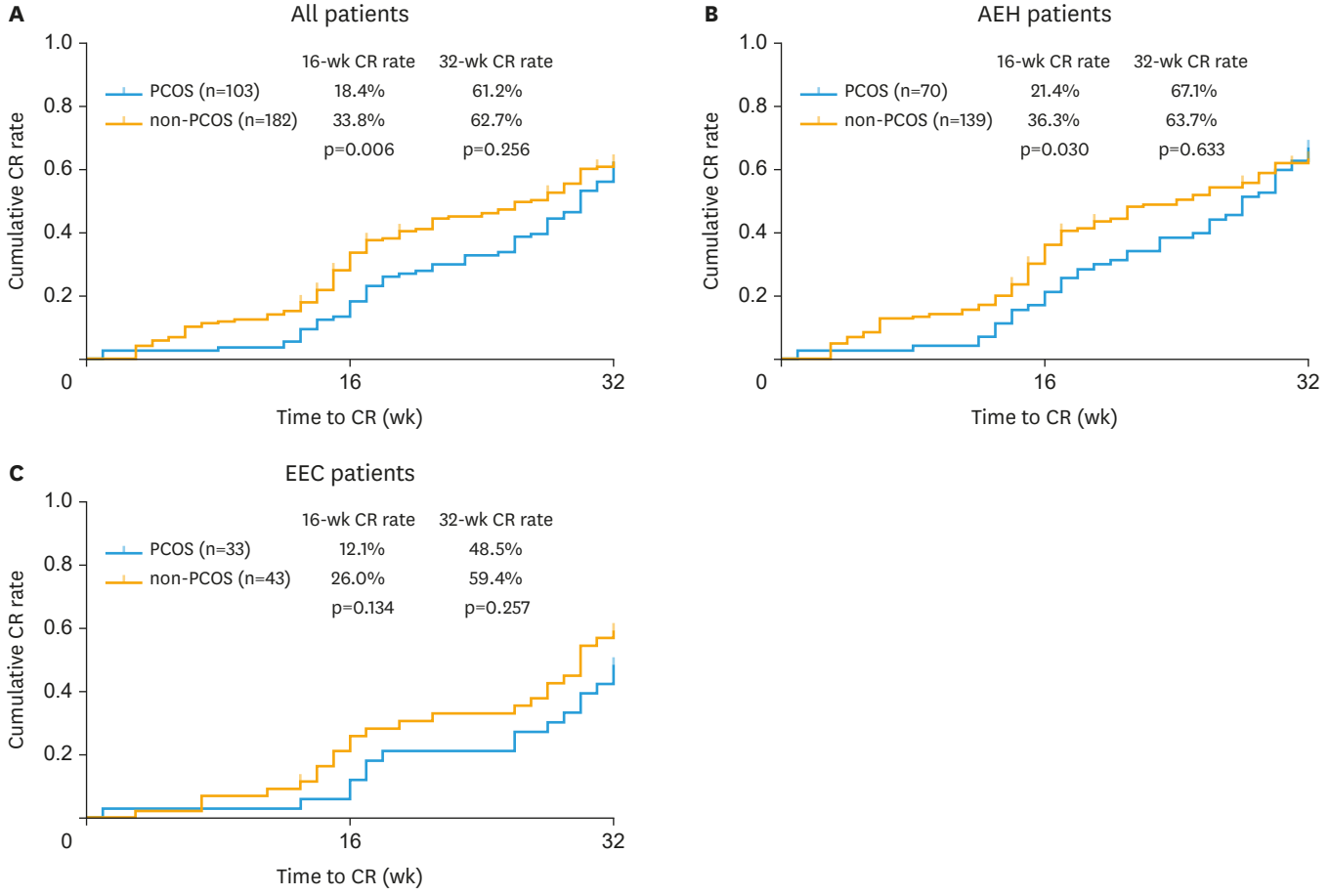

Fig. 2. The 16- and 32-week CR rate in PCOS and non-PCOS group in all patients and subgroups of AEH and EEC patients.
(A) 16- and 32-week CR rate in all patients with or without PCOS; (B) 16- and 32-week CR rate in AEH patients with or without PCOS; (C) 16- and 32-week CR rate in EEC patients with or without PCOS.
AEH, atypical endometrial hyperplasia; CR, complete response; EEC, endometrioid endometrial cancer; PCOS, polycystic ovary syndrome.

regression analysis was also performed in MA and MA+MET subgroups. In MA subgroup, PCOS (HR=0.359; 95% CI=0.135–0.958; p=0.041) remained the independent risk factor of 16-week CR rate in multivariate analysis (**Fig. S1**). PCOS was not found to be an independent risk factor of 16-week CR rate in patients treated with MA+MET (HR=0.537; 95% CI=0.063–1.031; p=0.053), which might be due to limited sample size (**Fig. S2**).

We next stratified PCOS and non-PCOS patients according to BMI (OVWT-, BMI <25 kg/m^2 or OVWT+, BMI ≥25 kg/m^2) in the AEH and EEC subgroups. In the AEH subgroup, PCOS-OVWT-patients (non-PCOS and lean) showed the highest 16-week CR rate (p=0.011) compared with the other three groups (**Fig. 4A**). Similar results were observed in the EEC subgroup, although without statistical significance (**Fig. 4B**).

DISCUSSION

In this single-centered retrospective study, we found that AEH patients with PCOS had a lower 16-week CR rate, longer treatment duration to CR and shorter recurrence interval compared with those without PCOS. We observed similar findings among EEC patients,

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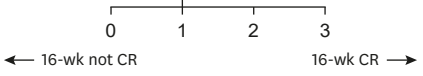
Variables		Univariate analysis		Multivariate analysis	
		HR (95% CI)	p-value	adjusted HR (95% CI)	p-value
Age at diagnosis (yr)	<30	Reference		Reference	
	≥30	1.887 (1.091–3.264)	0.023	1.639 (0.934–2.885)	0.092
PCOS	No	Reference		Reference	
	Yes	0.496 (0.297–0.831)	0.008	0.545 (0.324–0.917)	0.022
Overweight	No	Reference		Reference	
	Yes	0.532 (0.335–0.845)	0.008	0.583 (0.365–0.932)	0.024
IR	No	Reference		Reference	
	Yes	0.555 (0.337–0.914)	0.021	0.735 (0.411–1.315)	0.430
MS	No	Reference			
	Yes	0.858 (0.544–1.353)	0.509		
Hypertension	No	Reference			
	Yes	0.717 (0.439–1.172)	0.184		
Diabetes mellitus	No	Reference			
	Yes	0.709 (0.327–1.541)	0.386		
Nulliparous	No	Reference			
	Yes	0.674 (0.412–1.100)	0.115		
Histology	AEH	Reference			
	EEC	0.588 (0.335–1.031)	0.064		
Progestin therapy	MA	Reference			
	MA+MET	1.213 (0.658–2.235)	0.536		
	LNG-IUS	1.484 (0.822–2.682)	0.191		
	MA+LNG-IUS	1.177 (0.632–2.195)	0.607		
	MA+LNG-IUS+MET	1.150 (0.273–4.847)	0.849		
Hyperandrogenism	No	Reference		Reference	
	Yes	0.574 (0.354–0.931)	0.025	0.743 (0.416–1.330)	0.349



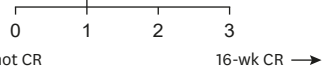
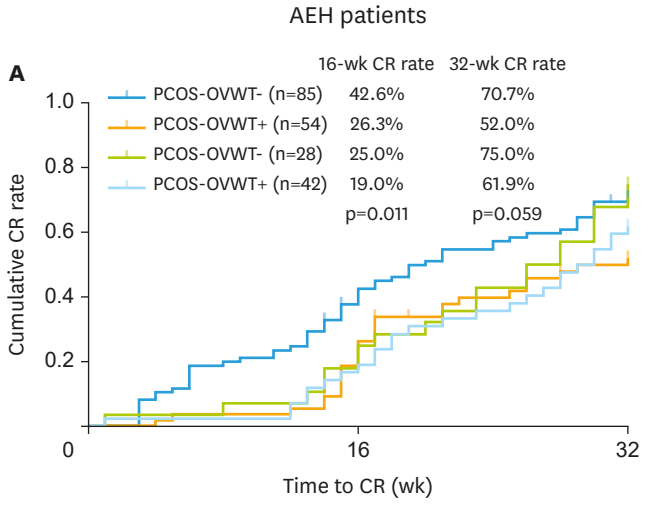


Fig. 3. Risk factor analysis related to cumulative 16-week CR rate.
Univariate and multivariate Cox regression analysis were used to identify risk factors associated with 16-week CR rate.
AEH, atypical endometrial hyperplasia; CI, confidence interval; EEC, endometrioid endometrial cancer; HR, hazard ratio; IR, insulin resistance; MA, megestrol acetate; MET, metformin; MS, metabolic syndrome; LNG-IUS, levonorgestrel intrauterine system.



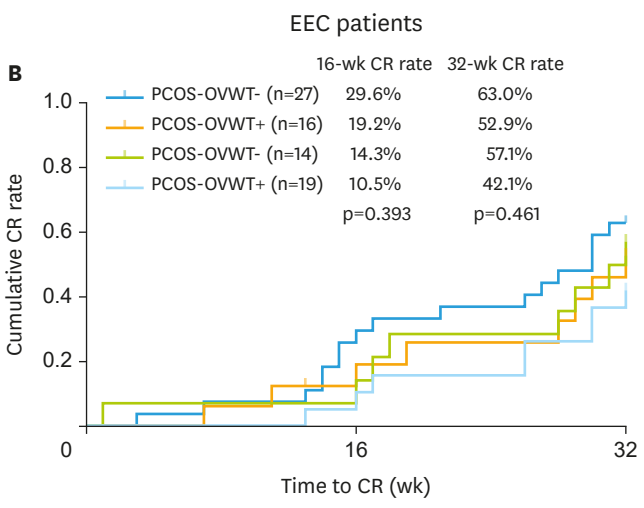


Fig. 4. Differences in 16- and 32-week CR rate between PCOS and non-PCOS group stratified by BMI.
Differences in 16- and 32-week CR rate between PCOS and non-PCOS group stratified by BMI (BMI <25 kg/m^2 or BMI≥25 kg/m^2) in AEH (A) and EEC (B) patients.
AEH, atypical endometrial hyperplasia; BMI, body mass index; CR, complete response; EEC, endometrioid endometrial cancer; OVWT, overweight; PCOS, polycystic ovary syndrome.

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although without statistical significance, which might be due to the limited sample size. Our results identified BMI ≥25 kg/m^2 and PCOS as two independent risk factors for a lower 16-week CR rate.

Endocrine and metabolic factors play an integral part in the development of EC. Obesity, IR and chronic unopposed exposure of endometrium to estrogen, which are considered risk factors of EC, also present in PCOS patients [11-14]. Patients diagnosed with PCOS are three- to four-times more likely to develop EC than the general population [15,16]. Among the patients evaluated in our study, 36.1% (103/285) were diagnosed with PCOS according to the Rotterdam Consensus Criteria. Comparing with <10% PCOS cases in all women of reproductive age [17], the prevalence of PCOS is relatively high in patients with AEH or EEC.

Studies have shown that obesity and IR, both commonly seen in PCOS patients, were associated with poor therapeutic outcome in AEH or EEC patients receiving fertility-sparing treatment [7,18]. However, the impact of PCOS on the outcome of fertility-sparing treatment in AEH or EEC patients has not been reported. A limited number of studies have investigated the impact of PCOS on conservative treatment of AEH or EC, and the results of these reports were not consistent. Okamura et al. [19] reported that medroxyprogesterone acetate treatment was less effective for AEH or EEC patients with PCOS (n=6) compared with non-PCOS patients (n=9). However, another retrospective study conducted by Acosta-Torres et al. suggested that PCOS did not affect the treatment outcomes of AEH or EEC patients (HR=0.66; 95% CI=0.38–1.51; p=0.66) [20]. Our results demonstrated that PCOS status negatively affected the outcome of fertility-preserving treatment in AEH and EEC patients. PCOS and BMI ≥25 kg/m^2 were two independent risk factors that affect fertility-preserving treatment. This is consistent with studies showing that PCOS patients tend to show obesity, IR and higher testosterone levels, which are all thought to negatively affect fertility-preserving treatment outcome [7,21].

One of the main mechanisms causing poor outcome of fertility-preserving treatment in AEH or EEC patients with PCOS might be due to progestin resistance [22,23]. One study showed that the expressions of genes upregulated by progestin, such as MIG6, LIF and GAB1 genes, were significantly lower in endometrium in PCOS patients, whereas cell proliferation–related genes, such as Anillin and cyclin B1 genes, were upregulated [24]. Studies have also shown that chronic inflammation in the endometrium of PCOS patients affects progesterone receptor status. The increased levels of pro-inflammatory cytokines in endometrium, such as tumor necrosis factor-α and interleukin-1β, may directly downregulate progesterone receptor isoforms, possibly via epigenetic modifications [25,26]. In addition, hyperandrogenemia, which is another common metabolic disorder in PCOS, upregulates estrogen receptor in the endometrial epithelium and downregulates progesterone receptor in endometrial stroma cells, leading to progestin resistance in endometrium [27].

We suggest that treatment aiming to alleviate endocrine disorders might be helpful to improve fertility-preserving treatment outcome in AEH or EEC patients with PCOS. Metformin, which is commonly used in PCOS patients, has been shown to improve the 16-week CR rate in AEH patients [28]. One study suggested that metformin along with Diane-35, which has anti-androgenic properties, might be a useful regimen for fertility-preserving treatment in EEC patients [29]. However, after stratifying patients according to different treatment regimens, we found that PCOS patients treated with MA+MET (metformin) (n=18) showed relatively lower 32-week CR rate compared with PCOS patients treated with MA (n=41) (33.3% vs. 56.1%, p=0.117; **Table S1**). This result could be explained by limited

sample size and baseline differences between these two treatment subgroups. There are more EEC patients (9/18, 50.0%) with PCOS in MA+MET group than in MA group (12/41, 29.3%). Moreover, PCOS patients receiving MA+MET showed higher median BMI than those receiving MA (28.4 kg/m^2 vs. 26.0 kg/m^2). These baseline imbalances might lead to relatively lower 32-week CR rate in PCOS patients receiving MA+MET compared with those treated with MA only. Randomized controlled trials with larger sample size and comparable baseline characteristics should be conducted to investigate the effect of metformin on treatment outcomes in PCOS patients with AEH or EEC respectively.

Our results also suggested that the pregnancy rate and live birth rate of patients with PCOS tended to be higher than rates in non-PCOS patients, although without statistical significance. We also found that the serum AMH level in the PCOS group was significantly higher compared with the non-PCOS group. AMH has a high predictive value in assessing the ovarian reserve, and patients with higher AMH have a better pregnancy outcome when receiving in vitro fertilization procedures [30]. Patients with PCOS usually have oligo/anovulation, which is characterized by the arrest of follicle maturation and the disturbed selection of the dominant follicle, and an increased number of early antral follicles secreting high levels of AMH [30,31]. Ovarian aging and age at menopause could be delayed in patients with PCOS [32]. Therefore, we speculate that AEH/EEC patients with PCOS may have higher ovarian reserves and benefit more from assisted reproductive technology.

To the best of our knowledge, this is the first study with a large sample size (n=285) to evaluate the impact of PCOS on AEH or EEC patients receiving fertility-sparing treatment. However, this study has some limitations. The retrospective nature of the study and restricted follow-up duration limits the quality of evidence in this study, especially our conclusions on recurrence and reproductive outcomes. A high-quality prospective study with a larger sample size is needed to clarify the effects of PCOS and relative endocrine disorders on fertility-sparing treatment in AEH and EEC patients.

Our study indicated that PCOS negatively affected the outcome of fertility-sparing treatment in patients with AEH or EEC. Our results identified PCOS and BMI ≥25 kg/m^2 as two independent risk factors related to unfavorable fertility-preserving treatment outcomes in AEH and EEC patients. Our findings suggest that in addition to progestin treatment and body weight management, treatment of PCOS-related metabolic disorders should also be considered for AEH and EEC patients.

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SUPPLEMENTARY MATERIALS

Table S1

Treatment outcomes in PCOS and non-PCOS patients using MA or MA+MET

Click here to view

Fig. S1
Risk factor analysis related to 16-week CR rate in patients receiving megestrol acetate.

Click here to view

Fig. S2
Risk factor analysis related to 16-week CR rate in patients receiving megestrol acetate + metformin.

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