RESEARCH ARTICLE

Polycystic Ovarian Morphology may be a Positive Prognostic Factor in Patients with Endometrial Cancer who Achieved Complete Remission after Fertility-Sparing Therapy with Progestin

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Abstract

Background: The most studied fertility-sparing therapy for endometrial cancer (EC) is oral progestin therapy. However, complete remission (CR) rate after progestin therapy is not enough ranging from 60 to 80 %, with high recurrence rate. Clinical features that predict treatment efficacy and recurrence after progestin therapy have not yet been revealed in detail. The aim of this study was to investigate prognostic factors in patients with EC who achieved CR after medroxyprogesterone acetate (MPA) therapy. **Methods:** We retrospectively reviewed 35 EC patients treated with MPA at our institution between 2000 and 2016. Following confirmation of endometrioid adenocarcinoma G1, patients orally took 600 mg MPA daily for 26 weeks. Patients with CR periodically took oral contraceptives. The association of recurrence-free survival (RFS) with several clinical features including age, body mass index (BMI), and polycystic ovarian morphology (PCOM) was analyzed. **Results:** Of 35 patients, 25 (71%) achieved CR, whereas 10 (29%) underwent hysterectomy due to failure of MPA therapy. Eleven (44%) of 25 patients with CR successfully gave birth after MPA therapy, whereas 8 (32%) developed recurrence. On univariate analysis, PCOM was significantly associated with better recurrence-free survival (RFS) (P=0.009), and BMI ≥25 kg/m^2 exhibited a nonsignificant trend for longer RFS (P=0.0674). Although multivariate analysis failed to detect any valid hazard ratio (HR), absence of PCOM and non-obesity were both independent risk factors for recurrence (P=0.00293 and P=0.0201, respectively). Notably, none of 10 cases with PCOM experienced recurrence under maintenance with oral contraceptives. **Conclusion:** PCOM might be a good prognostic factor in those achieving CR after MPA therapy for EC.

Keywords: Endometrial cancer- fertility-sparing therapy- medroxyprogesterone acetate- polycystic ovarian morphology

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Introduction

Endometrial cancer (EC) is the most common type of gynecologic malignancy in developed countries (Ferlay et al., 2015; Morice et al., 2016). Although EC is typically thought to be limited to postmenopausal women, 3-10% of women diagnosed with EC are younger than 40 years, of whom 70% are nulliparous (Crissman et al., 1981; Gallop and Stock, 1984; Duska et al., 2001; Simpson et al., 2014; Soliman et al., 2005). The main risk factor of EC is exposure to endogenous and exogenous estrogens associated with obesity, early age at menarche, nulliparity, late-onset menopause, older age (≥55 years), and use of tamoxifen (Morice et al., 2016; Key and Pike, 1988; Pike et al., 1997; Kaaks et al., 2002; Renehan et al., 2008; Grady et al., 1995; Purdie and Green, 2001). Recently, the number of EC patients younger than 40 years is increasing (Duska et al., 2001; Matsuda et al., 2011; Inoue et al., 2016).

As the disease is frequently symptomatic at an early stage, EC is often diagnosed at stage I (Simpson et al., 2014). The standard treatment for EC stage I consists of total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node assessment, depending on the tumor type and grade. Although total hysterectomy is recommended for EC, fertility-sparing therapy is attempted for young patients with early-stage EC. The most studied fertility-sparing therapy for women with stage IA well-differentiated endometrioid adenocarcinoma is oral progestin therapy (Dorais et al., 2011; Fujiwara et al., 2012). However, the complete remission (CR) rate after progestin therapy is not high enough, ranging from 60% to 80%, with high recurrence rate, and some

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deaths have been reported due to disease progression or an undetected synchronous malignancy (Simpson et al., 2014; Fujiwara et al., 2012; Chiva et al., 2008; Ramirez et al., 2004; Park and Nam, 2015; Tangjitgamol et al., 2009; Ushijima K et al., 2007; Koskas et al., 2014; Yasuda et al., 2004; Ferrandina et al., 2005; Ota et al., 2005; Cormio et al., 2006; Ohyagi-Hara et al., 2015). Predictors of treatment efficacy and recurrence after progestin therapy have not been fully elucidated (Simpson et al., 2014).

On the other hand, polycystic ovary syndrome (PCOS) is an endocrine system disorder among women of reproductive age represented by polycystic ovarian morphology (PCOM) with irregular menstruation. PCOS is known as one of the causes of EC, owing to prolonged exposure to estrogen as well as persistent progesterone deficiency (Li et al., 2014; Hardiman et al., 2003; Shao et al., 2014). A previous report demonstrated that EC patients with PCOS were not likely to achieve CR after progestin therapy (Zhou et al., 2015). Another report also demonstrated that there was no association of PCOS history with EC recurrence, whereas obesity was a strong risk factor for relapse of EC (Yang et al., 2015). However, the study did not refer to the maintenance of post-progestin therapy (Yang et al., 2015). PCOM is considered as one of the morphological abnormalities that occurs in ovaries, and its definition is the presence of at least 10 follicles measuring 2–9 mm in diameter in at least one ovary (Miyoshi et al., 2013). Although PCOM does not represent the existence of PCOS, the morphological abnormality is considered as one of the hormonal disorders in premenopausal women (Murphy et al., 2006; Carmina et al., 1997). The association between PCOM and the MPA treatment has not been fully clarified.

In this context, the present study aimed to clarify the association of clinical characteristics, including PCOM with EC recurrence after progestin therapy. It also investigated the management after progestin therapy as well as fertility rate.

Materials and Methods

Patients

Institutional review board approval was obtained for this study. We identified 35 women younger than 40 years with EC who were treated with medroxyprogesterone acetate (MPA) for the purpose of fertility preservation between 2000 and 2016 at our hospital. A retrospective chart review was performed to obtain clinical, pathological, and treatment data. Before initiating MPA, all patients underwent pelvic magnetic resonance imaging (MRI) to assess the presence of myometrial invasion and/or any other uterine and ovary lesions. The presence of PCOM was diagnosed when at least 10 follicles measuring 2–9 mm in diameter was observed in at least one ovary by MRI or transvaginal ultrasonography (TVUS). Almost all the patients were diagnosed as endometrioid adenocarcinoma, grade 1, whereas only two patients were diagnosed as endometrioid adenocarcinoma, grade 2 by total curettage.

MPA treatment

Following confirmation of endometrioid adenocarcinoma G1 by dilation and curettage (D and C), patients orally took 600 mg MPA daily for 26 weeks. Patients diagnosed as endometrioid adenocarcinoma G2 also took the same medication at their own request.

D and C was performed after 8 and 16 weeks from the beginning of the therapy to assess its efficacy. When the pathological findings showed disease progression, hysterectomy was performed even if therapy was underway. Progression of disease was defined as progression to G2 or G3 and myometrial invasion. Hysterectomy was also performed when the diagnosis after 26 weeks of MPA therapy was EC. Complete remission (CR) means that no residual lesion was found after MPA therapy. Patients with CR periodically took oral contraceptives (OCs; containing 1 mg of norethisterone and 0.05 mg of mestranol) daily for 21 days followed by a 7-day period without medication. After 6 months of maintenance with OC, attempt at pregnancy was permitted, because several reports indicate that patients start to develop relapse around 6 months after cessation of therapy (Perri et al., 2011; Ramirez et al., 2004). In vitro fertilization–embryo transfer was performed for most patients who tried to conceive. Endometrial biopsy was performed every 3 or 4 months to assess recurrence. After the diagnosis of relapse of EC, D and C and pelvic MRI were performed.

Endpoints and statistical analysis

The endpoints of this study were the association of clinical characteristics with recurrence-free survival (RFS), CR rate, and birth rate. RFS was measured from the end date of the MPA therapy. Association of RFS with age, body mass index (BMI), and PCOM (defined as the presence of more than 10 follicles in one ovary by MRI or ultrasonography) was analyzed. Survival curves were calculated using the Kaplan-Meier method, and comparison of the curves was performed using log-rank test. The Cox proportional hazards model was used for multivariate analysis. Relation of CR rate to the said parameters was analyzed by Pearson's Chi-square test.

All statistical analyses were performed using JMP software (version 12; SAS Institute, Cary, NC, USA). A value of $P<0.05$ was considered significant.

Results

Patient characteristics

Thirty-five patients met our study criteria. Baseline clinical characteristics were described in Table 1. The

Table 1. Characteristics of all 35 Patients

Parameter	Value
Age at diagnosis, median (range), years	33 (19-39)
BMI, median (range), kg/m^2	21.5 (17.7-34.9)
Parity, n (%)	
Nulliparous	34 (97)
Any parity	1 (3)
PCOM, n (%)	16 (46)

BMI, body mass index; PCOM, polycystic ovarian morphology

Table 2. Chi-Square Test of Variables Associated with Complete Remission (CR)

Characteristics	CR		P-value	OR	95% CI
	Yes	No			
Age at diagnosis			0.28	0.44	0.099-1.986
≥34 years	10	6			
<34 years	15	4			
BMI†			0.39	0.5	0.104-2.395
≥25 kg/m^2	6	4			
<25 kg/m^2	18	6			
PCOM			0.28	0.44	0.099-1.986
Yes	10	6			
No	15	4			

†One patient had no BMI data; CR, complete remission; OR, odds ratio; CI, confidence interval; BMI, body mass index; PCOM, polycystic ovarian morphology.

MPA therapy was performed for the patients who were less than forty years old and whose BMI were less than 35. Twenty-four patients (71%) had normal weight (BMI <25 kg/m^2), whereas 10 patients (29%) were obese (BMI ≥25 kg/m^2) (Table 2). Sixteen out of 35 patients (46%) had PCOM (Table1).

Efficacy of MPA treatment

The median follow-up time from the start of MPA therapy was 89 months (range, 12-193 months). Only two patients continued MPA therapy over 26 weeks: 32weeks and 40weeks, respectively. The patients' outcome was described in Figure 1. Twenty-five patients (71%) achieved CR, while 10 patients (29%) underwent hysterectomy because of the failure of MPA therapy. Eight out of 25 patients with CR (32%) got relapsed during follow up period. Three (37.5%) of them finally avoided hysterectomy, whereas five patients (62.5%) underwent

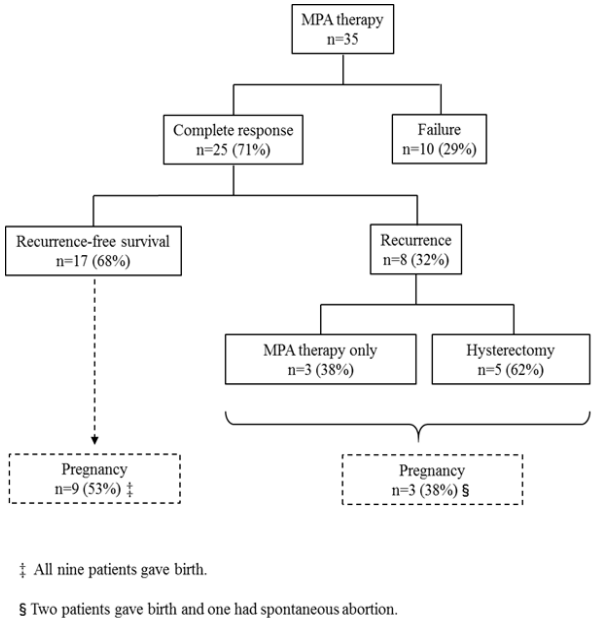

Figure 1. Patients' Outcome after Medroxyprogesterone Acetate (MPA) Therapy and Pregnancy Outcome of Patients with Complete Remission (CR)

Table 3. Univariate and Multivariate Analysis of Recurrence-Free Survival (RFS)

Factors	Univariate analysis	Multivariate analysis	
	P-value	P-value	HR (95% CI)
Age (≥34 years)	0.366	0.431	1.76 (0.41-7.54)
BMI (≥25 kg/m^2)	0.0674	0.0201	n.c.
PCOM	0.009	0.00293	n.c.

HR, hazard ratio; CI, confidence interval; BMI, body mass index; PCOM, polycystic ovarian morphology; n.c., not converged.

hysterectomy. No significant association was observed with any clinical characteristic (Table 2).

Risk factors for recurrence

Eight (32%) of 25 patients with CR relapsed during the follow-up period. Kaplan-Meier curves depicting RFS are shown in Fig. 2A. As shown in Table 3, among several clinical characteristics, presence of PCOM was significantly associated with better recurrence-free survival (RFS) (P=0.009), and BMI ≥25 kg/m^2 exhibited a nonsignificant trend for longer RFS (P=0.0674). Notably, all 16 cases with either PCOM or BMI ≥25 kg/m^2 did not experience recurrence (Figure 2B). Although multivariate analysis failed to detect any valid hazard ratio (HR), absence of PCOM and non-obesity were both independent risk factors for recurrence (P=0.00293 and P=0.0201, respectively) (Table 3). Clinicopathological characteristics were evaluated between patients with PCOM and without PCOM, however there were no significant differences in patients' clinical background (Table S1) or pathological features.

Treatment after relapse

Patients with recurrence are summarized in Table S2. Six of 8 patients developed EC G1, whereas 2 developed EC G2. MPA treatment was conducted in 7 patients. Among them, only 3 (42.8%) did not undergo hysterectomy, whereas 4 patients (57.1%) gave up fertility preservation because of treatment failure or disease recurrence.

Pregnancy after treatment

Twelve (48%) of 25 patients with CR got pregnant and 11 patients (44%) successfully gave birth after MPA

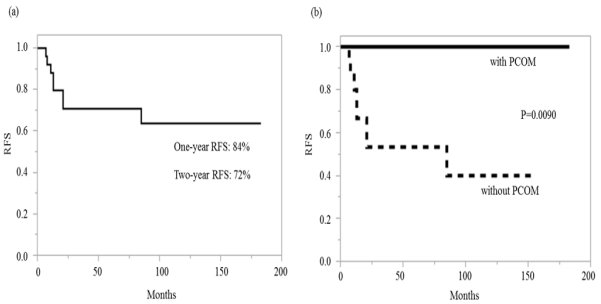

Figure 2. Kaplan-Meier Survival Curve for Recurrence-Free Survival (RFS). (a), Overall; (b), Survival curves according to PCOM (polycystic ovarian morphology)

therapy. Three (37.5%) of 8 patients got pregnant after recurrence and second MPA treatment and 2 (25%) gave birth (Figure 1). Time until pregnancy was measured from the end date of the MPA therapy to last menstrual period. The median time until pregnancy was 20.5 months (range, 1-29 months).

Discussion

In the present study, no clinical parameter was demonstrated to be predictive of achieving CR by MPA therapy, whereas PCOM was identified as a possible good prognostic factor after successful MPA therapy.

In our cohort, once patients with PCOM achieved CR, no one relapsed during the follow-up period. The association of PCOS with MPA therapy has been well investigated (Hardiman et al., 2003; Shao et al., 2014; Pillay et al., 2006). Progesterone resistance was seen in patients with PCOS due to impaired progesterone receptors (Li et al., 2014; Shen et al., 2008; Savaris et al., 2011). Previous reports also demonstrated that patients with PCOS are not likely to achieve remission of EC or atypical hyperplasia of the endometrium (Zhou et al., 2015; Shen et al., 2008). In this study, due to lack of clinical information such as irregular menstruation or hormone findings, our findings do not refer to PCOS but only to the presence of PCOM. The association of PCOM with PCOS has been controversial (Murphy et al., 2006). Although previous studies demonstrated that PCOM is a representative characteristic of PCOS (Pillay et al., 2006; Polson et al., 1988), only around one-third of patients with PCOM have endocrine disturbance similar to patients with PCOS (Carmina et al., 1997). Although the hormonal significance is yet to be identified, we found that patients with PCOM did not relapse under OC maintenance once they achieved CR after progestin therapy. OCs are used for patients with irregular menstruation to achieve regular menstruation as well as to prevent EC by a decrease in unopposed estrogen level. This protective effect of the endometrium from continuous stimulation by unopposed estrogen might be the reason that patients with PCOM tended benefit from OC intake in our cohort.

Regarding the association of obesity with prognosis after progestin therapy for EC, obese patients did not relapse during the follow-up period, whereas 8 (44.4%) of 18 nonobese patients developed recurrence. Contrary to our data, a previous study demonstrated that obesity (BMI >30 kg/m^2) was a risk factor for recurrence after progestin therapy of EC (Yang et al., 2015). The difference might be due to OC use after achieving CR. Obesity is one of the causes of developing EC, due to the hyperestrogenemia by conversion of androstenedione to estrone in the adipose tissue (Kaaks et al., 2002). OC, by reducing exposure to unopposed estrogen, might be important for obese patients to prevent relapse of EC.

In our study, 11 patients with CR (44%) successfully gave birth. Meanwhile, one-third of patients with CR relapsed after fertility-sparing therapy. The disease was progressive at recurrence in two patients. From these results, MPA therapy seems effective and satisfactory for those who want to have a child; however, the risk of recurrence or progression was latent in the therapy. Therefore, sooner infertility treatment is recommended for pregnancy. In addition, hysterectomy might be suggested when family planning is complete or when the patient has given up on having a child (Gotlieb, 2013).

Our study has several limitations. First, patients with PCOM in our study were distributed only by the ovarian morphology and do not meet all the criteria of PCOS. Our study was also limited by its retrospective design and small sample size. Further studies with larger populations are needed to confirm our results.

In conclusion, from our retrospective study, PCOM may be a positive prognostic factor in patients with EC who achieved CR after MPA therapy.

Statement conflict of Interest

None of the authors have any financial support or relationships that may pose a conflict of interest related to this study.

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Table S1. Clinical Characteristics of Patients with and without PCOM (Polycystic Ovarian Morphology) among Patients who Achieved Complete Remission (CR)

Characteristics	PCOM		P-value	OR	95% CI
	Yes	No			
Age at diagnosis			1	1	0.195-5.121
≥34 years	4	6			
<34 years	6	9			
BMI†			0.47	2	0.306-13.062
≥25 kg/m^2	3	3			
<25 kg/m^2	6	12			
Parity					
Yes	0	0			
No	10	15			
Irregular menstruation			0.15	3.6	0.616-21.033
Yes	6	5			
No	3	9			

†One patient had no BMI data; PCOM, polycystic ovarian morphology; OR, odds ratio; CI, confidence interval; BMI, body mass index

Table S2. Oncological Outcomes of Eight Patients who Received Treatments for Recurrence after MPA Ttherapy

Case	Diagnosis at first recurrence	Treatment after recurrence	Final diagnosis	Final TNM
1	Stage IA, EA G1	MPA	No evidence of disease	-
2	Stage IA, EA G1	MPA	No evidence of disease	-
3	Stage IA, EA G1	MPA→recurrence→MPA	No evidence of disease	-
4	Stage IA, EA G1	MPA→recurrence→MPA→recurrence→hyst erectomy	Stage IA, EA G1	T1a, N0, M0
5	Stage IA, EA G2	MPA→recurrence→hysterectomy	Stage IIIC, EA G2	T3a, N1, M0
6	Stage IA, EA G2	MPA→recurrence→hysterectomy	Stage II, EA G3	T2, N0, M0
7	Stage IA, EA G1	MPA→failure→hysterectomy	Stage IA, EA G1	T1a, N0, M0
8	Stage IA, EA G1	Hysterectomy	Stage IA, EA G1	T1a, N0, M0

MPA, medroxyprogesterone acetate; EA, endometrioid adenocarcinoma; TNM, TNM classification.