Outcome of fertility-sparing treatment with medroxyprogesterone acetate for atypical hyperplasia and endometrial carcinoma in young Japanese women

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Summary

Purpose: To review the outcome in patients with atypical endometrial hyperplasia (AEH) and endometrial cancer (EC) who received MPA treatment in the present hospital. *Materials and Methods:* Patients with AEH or EC were administered MPA for 12 weeks followed by endometrial curettage. The rates of effect, recurrence, pregnancy, and complications were evaluated. The changes in progesterone receptors and FOXO-1, known as a target of MPA treatment, were examined by immunostaining. *Results:* Four of seven patients with endometrial cancer and three of three patients with AH had complete response. Four of seven patients had recurred within one year after the treatment and had to undergo hysterectomy. None of the patients showed changes in progesterone receptors. Although six of seven patients were negative for FOXO-1 before and after treatment, all the patients showed increased developments of FOXO-1 during MPA treatment. *Conclusion:* Progestin as a fertility-preserving treatment is expected to be effective for endometrial cancer, but judicious use might be required because it shows high rate of recurrence. Further studies regarding the mechanism may be necessary to achieve high efficacy.

Key words: Medroxyprogesterone acetate; Endometrial carcinoma; FOXO-1; Progesterone receptor; Fertility-preserving treatment.

Introduction

In recent years, the prevalence of endometrial cancer (EC) has continued to increase. There are 142,000 new cases and 42,000 deaths per year all over the world [1]. Most of these endometrial cancer cases occur in postmenopausal women; 25% of these occur in premenopausal women, and 2.5%–14.4% occur in young women of ages less than 40 years. The number of patients with endometrial cancer who desire fertility is predicted to further increase in the future, considering the social trends such as tendency toward late marriage and childbirth in Japan. Progestin, including medroxyprogesterone acetate (MPA), is traditionally administered as therapy for juvenile endometrial cancer to preserve fertility. However, according to the report by Ushijima K *et al.*, the recent rate of effect of MPA therapy is unexpectedly as low as 64%, and the recent rate of recurrence is as high as 57% [2], which indicates that there are many issues to be improved. It is considered that the mechanism of progestin must be clearly understood to improve the rate of effect and to decrease the rate of recurrence. The authors retrospectively reviewed the treatment outcome in ten patients with atypical endometrial hyperplasia and endometrial cancer who received MPA therapy in the present hospital to preserve fertility.

Materials and Methods

The authors studied patients who received primary treatment for atypical endometrial hyperplasia and endometrial cancer in the present hospital in the last 15 years. The following patients were considered eligible before the initiation of MPA therapy: (1) patients with endometrial cancer (EC) that was diagnosed as grade 1 by curettage of the entire endometrium or atypical endometrial hyperplasia (AEH); (2) with lesion confined to the endometrium and confirmed by diagnostic imaging; (3) women of a reproductive age; (4) body mass index (BMI) < 35; (5) without prior thrombosis; and (6) with strong desire to receive therapy to preserve fertility. Before performing the study, the authors informed the patients that the standard treatment is total hysterectomy, and therefore, the therapy to preserve fertility is merely palliative treatment, and obtained their consent. The authors studied the effect of the treatment protocol consisting of administration of 400–600 mg/day of MPA for 12 weeks followed by curettage of the entire endometrium. The patients without complete response (CR) received 400–600 mg/day of MPA for an additional 12 weeks and then underwent curettage of the entire endometrium to evaluate the efficacy. The patients with CR who desired immediate pregnancy began receiving timed therapy. The patients without CR by the secondary treatment above (Not CR) continued receiving MPA and underwent curettage of the entire endometrium regularly, along with examination to confirm the absence of disease extension; total abdominal hysterectomy and bilateral oophorectomy were performed once malignant cells were detected.

Endometrial thickness was measured by transvaginal ultrasound (TVUS) at every 12 weeks before curettage of the entire endometrium. The specimen obtained from the curettage was evaluated by three pathologists and classified into the following classes: complete response (CR), partial response (PR), no change (NC), and progressive disease (PD). CR was defined as the time when the carcinoma and atypical lesion completely dis-

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Table 1. — *Patient characteristics.*

Age (years)	Median	34
	Range	21-42
Histology	AEH	3 (30.0%)
	EC G1	7 (70.0%)
BMI	Median	21.8
	Range	17.0-28.8
Gravida	0	8 (80.0%)
	1	2 (20.0%)
	> 2	0 (0.0%)
Para	0	9(90.0%)
	1	1 (10.0%)
	> 2	0 (0.0%)
PCOS		3 (30.0%)
Irregularity of period		6 (60.0%)

AEH: atypical endometrial hyperplasia; EC: endometrial carcinoma; PCOS: polycystic ovary syndrome.

Table 2. — *Response to MPA.*

Response	AEH (n = 3)	EC (n = 7)	Total (n = 10)
CR	3 (100%)	4 (57.1%)	7 (70.0%)
Not CR	0 (0.0%)	3 (33.3%)	3 (30.0%)

appeared. PR was defined as observation of atrophy or regression of the secretory epithelium but no residual atypical cells. NC was defined as no atrophy or regression but presence of residual atypical cells. PD was defined as the presence of lesion (grade 2 or 3 and higher) was observed. The side-effect was evaluated on the basis of the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2. The efficacy rate was defined as a ratio of CR and PR accounting for the percentage of all cases. The authors examined this treatment in terms of the rates of effect, recurrence, pregnancy, and complication.

Results

Patient characteristics are shown in Table 1. The mean age of ten patients with AEH and EC was 31.5 ± 10.5. The average BMI was 22.9 ± 5.9. Six of 10 patients (60.0%) had menstrual irregularity. Three of ten patients (30.0%) were diagnosed with polycystic ovary syndrome (PCOS). Because of MPA therapy, the lesions disappeared in 57.1% of patients with endometrial cancer (four of seven patients) and in all patients with AEH (three of three patients) (Table 2). The rate of recurrence was 57.1% (four of seven patients) and all cases relapsed within one year. All patients with AEH (three patients) were classified into CR and showed no recurrence. Three of seven patients with EC who were classified into CR showed aggravation during the period of the treatment and recurrence; all of these patients had to undergo total abdominal hysterectomy (Table 3). Concurrence of ovarian cancer was found in one patient. None of the patients experienced MPA-specific side-effects such as thromboembolism, significant weight gain, and liver function abnormalities.

One of the evaluations before and after treatment was measuring the endometrial thickness by TVUS. In the CR group and the Not CR group, there was no significant difference in endometrial thickness before and after treatment (data not shown). The changes in the development of progesterone receptors (PR-A and PR-B) and FOXO-1, considered as a target of MPA treatment was examined by immunostaining. All patients were positive for PR-A and PR-B. None of the patients showed changes in development of PR-A and PR-B and in the PR-B/PR-A ratio (Figure 1A). Although six of seven patients were negative for forkhead box protein O1 (FOXO-1) immunostaining before and after treatment, all the patients showed increased development of FOXO-1 in the nucleus and cytoplasm during MPA treatment (Figure 1B).

In this study, the pregnancy rate was 10.0% (one of ten patients). One woman who had AEH became pregnant after receiving clomiphene for inducing ovulation and delivered single well-being baby at 39 weeks. The other patients with EC received MPA therapy followed by infertility treatment with an ovulation-inducing agent, but it did not result in pregnancy and they underwent total abdominal hysterectomy.

Table 3. — *All cases of MPA therapy in the present hospital.*

No	Age	Histology	Response	Ovulation induction	Outcome	Time to recurrence
1	42	AEH	CR	Free	–	No recurrence
2	30	AEH	CR	IVF-ET	–	No recurrence
3	30	AEH	CR	Clomiphene citrate	NVD (39wd)	No recurrence
4	34	EC G1	CR	Clomiphene citrate	TAH+BSO	3 months, with ovarian cancer
5	21	EC G1	PD	–	TAH+BSO	PD
6	33	EC G1	CR	Free	TAH+BSO	6 months
7	33	EC G1	CR	Clomiphene citrate	TAH+BSO	12 months
8	38	EC G1	CR	Clomiphene citrate	TAH+BSO	12 months
9	32	EC G1	PD	–	TAH+BSO	PD
10	37	EC G1	PD	–	TAH+BSO	PD

IVF-ET: in vitro fertilization and embryo transplantation; NVD: normal vaginal delivery; TAH: total abdominal hysterectomy; BSO: bilateral salpingo oophorectomy.

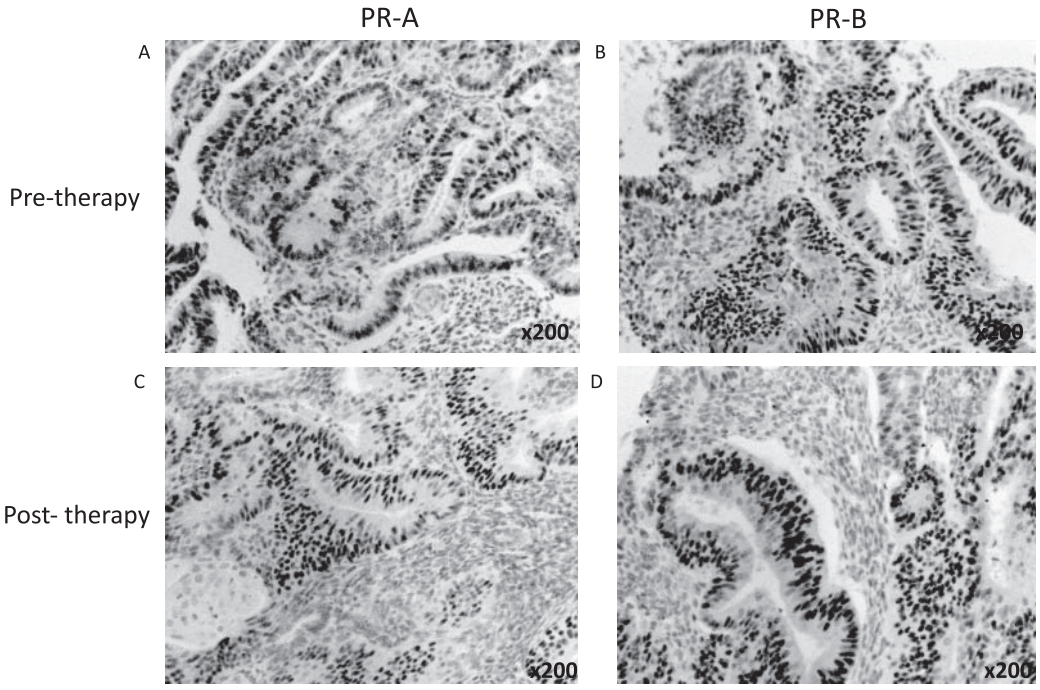

Figure 1A. — Immunohistological analysis was performed according to Saito's protocol [15] using primary antibody hPRa7 for PR-A and hPR2 for PR-B. All patients were positive for PR-A and PR-B. None of the patients showed changes in development of PR-A and PR-B and in the PR-B/PR-A ratio (A vs. C, B vs. D).

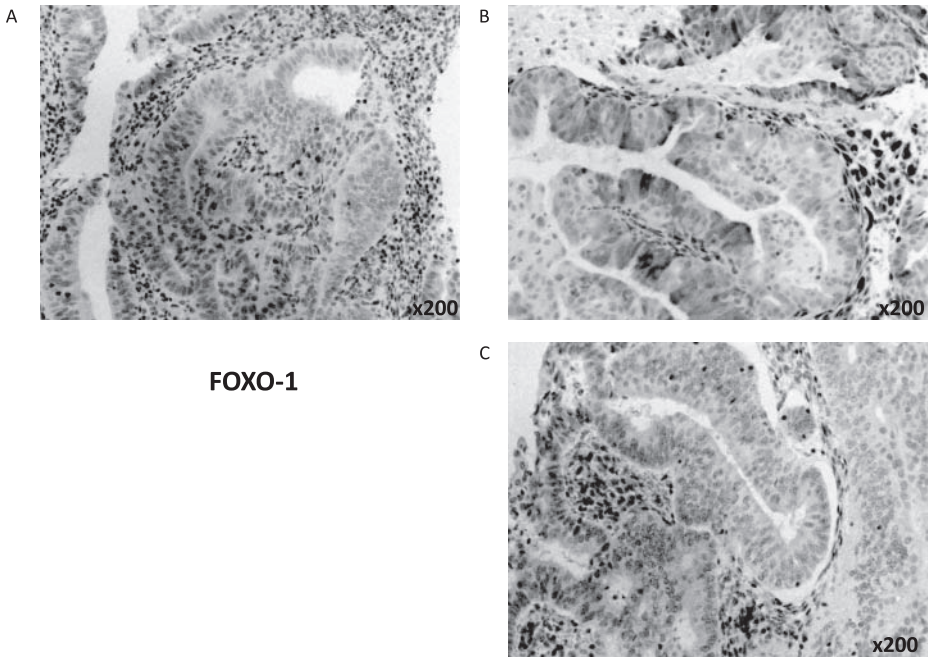

Figure 1B. — Immunohistological analysis was performed using primary monoclonal antibody FOXO-1 (C29H4). Six of seven patients were negative for FOXO-1 immunostaining before and after treatment (A and C). All the patients showed increased development of FOXO-1 in the nucleus and cytoplasm during MPA therapy (B). Of these, the results of Case 10 are shown.

Discussion

In the present study, the efficacy rate of MPA for all the cases of AEH were classified into CR, whereas the efficacy rate for EC was 57.1%, which indicated a result that was not good as that shown in previous studies [3–8]. All the four patients with endometrial cancer who were classified into CR showed relapse (100%) and had to undergo total abdominal hysterectomy. The results of the prospective study by Ushijima K *et al.* were also disappointing in that the efficacy rate of MPA was 64% and the rate of recurrence was 57% [2]. However, the present study results showed an approximately similar rate of effect to the study by Ushijima K *et al.* To improve the rate of pregnancy, it is important to prevent recurrence. Ushijima K *et al.* reported that patients who did not receive any treatment after successful study treatment showed higher rate

of recurrence (69%) than patients who received periodical EP (estrogen + progestin) therapy [2]. Similar findings were obtained in the present study, which suggested that no periodical hormone administration after the study treatment might cause a high rate of recurrence. In addition, all patients showed disease relapse within 12 months after the study treatment, and therefore, patients who desired fertility should receive infertility treatment as early as possible. Regarding infertility treatment, Elizur SE *et al.* reported that 64% of patients who received successful fertility-preserving treatment had to also receive infertility treatment; further, their study showed that six of eight patients (75.0%) became pregnant by aggressive in-vitro fertilization (IVF) and four of eight patients (50.0%) had babies [9]. Han AR *et al.* reported that ten of 11 patients treated with progestin as primary fertility-preserving therapies had received assisted reproductive technology (ART) and six patients became pregnant [10]. It is believed that more aggressive intervention than timing the treatment is required for successful pregnancy and delivery. It might be important to inform patients of the usefulness of aggressive infertility treatments such as in vitro fertilization (IVF) after successful fertility-preserving treatment. A study demonstrated that levonorgestrel intrauterine device (IUD) leads to regression of endometrial hyperplasia and reduce cancer incidence [11]. This might be considered prior to levonorgestrel IUD use in patients who do not desire immediate pregnancy.

In the present study, treatment was performed by using MPA alone, without a combination drug such as aspirin for thrombosis prophylaxis. However, no patient had serious complications such as thrombosis, significant obesity, and liver function abnormalities. One patient presented complications of ovarian cancer during the course of study (10.0%). Evans-Metcalf ER *et al.* reported that 11% of young patients with EC show complications of ovarian cancer [12], and the present study results were similar to that shown in their study.

Recently, MPA was shown to be associated with cytostatic effects mainly via PR-B [13]. Jongen V *et al.* reported that patients with PR-B/PR-A < 1 had a poor prognosis factor [14]. In the present study, pretreatment development of PR-B and PR-A was examined, but the relationship between PR-B/PR-A ratio and prognosis remains unclear. Conversely, there is a report of decreased development of PR-B in progestin-resistant EC cell line [15]. None of the patients who were classified into recurrence or PD showed decreased development of PR-B before and after treatment, which suggested that development of PR-B was not effective in predicting successful MPA treatment (Figure 1A). MPA increases development of FOXO-1 through PR-B and leads to apoptosis in *vitro* experiment [16]. In the present study, immunostaining showed increased development of FOXO-1 in the nucleus and cytoplasm during MPA treatment, which suggested that FOXO-1 was a target of MPA treatment. However, increased development of FOXO-1 was found in all cases, including the failure-free and aggravated cases; therefore, further studies are required to confirm if FOXO-1 is a biomarker of successful treatment.

Although TVUS was used for monitoring the endometrial thickness, it is not confirmed whether it is useful as one of indexes to judge the effect of treatment, because no significant difference in endometrial thickness was observed between the CR and Not CR group. Thus, the authors considered that monitoring endometrial thickness was not useful to determine the effect of MPA treatment.

Progestin as a fertility-preserving treatment is expected to be effective for endometrial cancer, but judicious use might be necessary because it shows high rate of recurrence as well as the risk of concurrence of ovarian cancer. Once confirmed that the lesions have disappeared, the patients' therapy should be shifted to an aggressive infertility treatment immediately to help improve the pregnancy rate. Further studies regarding the mechanism may be necessary to achieve high and effective treatment because administering progestin alone for EC has limitations.

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