Treatment for complex atypical hyperplasia of the endometrium

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Summary

Objective: To clarify the clinical outcome of women with complex atypical hyperplasia of the endometrium who were treated either by hysterectomy or a non-surgical treatment with medroxyprogesterone acetate (MPA).

Study design: Thirty of the 53 patients with complex atypical hyperplasia of the endometrium were treated by undergoing hysterectomy and 20 were treated with MPA alone as the primary therapy. Their clinical features and outcomes were evaluated.

Results: The ages of the 53 patients ranged from 28 to 62 years (mean 46.2). Fifteen (75%) of the 20 patients (8 of 12 with low-dose MPA and 6 of 8 with high-dose MPA) responded initially to MPA therapy. Two of the 12 patients who were treated with low-dose MPA progressed to endometrial adenocarcinoma. Three patients treated with high-dose MPA conceived after treatment having three healthy infants.

Conclusion: Primary treatment with high-dose MPA is a safe and effective therapy for women with complex atypical hyperplasia of the endometrium who wish to preserve their fertility.

Key words: Atypical endometrial hyperplasia; Medroxyprogesterone acetate; Function-retaining therapy; Surgery, and fertility.

Introduction

Endometrial carcinoma is the second most frequent malignant tumor of the female genital tract and its incidence has been increasing steadily in Japan [1]. The carcinogenesis of endometrial carcinoma has not been clarified yet. Complex atypical hyperplasia (CAH), however, is recognized as the immediate precursor of endometrial cancer [2-9] with a progression rate of 14.6-75.0%. In our series [10], 21.4% of CAH have a risk of progressing to carcinoma. Elderly patients with CAH are usually treated by hysterectomy, which can prevent development of endometrial cancer. However, hysterectomy sacrifices childbearing ability. For younger women with endometrial carcinoma who desire to preserve their fertility, a function-retaining treatment with progestin is desirable and could be applied. Progestin therapy is based on the mechanism that endometrial hyperplasia is caused by prolonged unopposed estrogen stimulation to the endometrium. Therefore, cyclic or continuous stimulation by progestin would be an appropriate function-retaining therapy; extensive studies with progestins support such a treatment for various endometrial hyperplasias [7, 8, 10-12].

We undertook a retrospective study on the outcome of women with CAH. The objectives were: 1) to clarify clinical features and outcome of treatment for women with CAH, 2) to determine whether progestin therapy was effective in CAH, and 3) to determine whether these women were able to bear children if progestin therapy was successful.

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Materials and Methods

Between January 1974 and December 1997, 53 patients were diagnosed as having CAH by specimens of either endometrial four-direction curettage biopsy or dilatation and curettage at the Department of Gynecology, Kitasato University Hospital. Assessment of histological diagnosis of CAH was conducted using the histological classification of tumors of the female genital tract (WHO, 1994) [13]. Patients' clinical history and their subsequent histories up to December 1999 were obtained by reviewing the records at Kitasato University Hospital. The authors of this paper reviewed all available slide specimens from endometrial biopsies, total dilatation and curettage, and hysterectomy.

Progestin therapy was given in the regimens of either medroxyprogesterone acetate (MPA) 400 mg daily per os continuously (high-dose MPA group) or cyclic therapy that consisted of 10 mg daily for 14 consecutive days followed by 14 non-prescription days for 6 cycles (low-dose MPA group). Endometrial biopsy and cytology were conducted to detect the effect of MPA at 4 to 12 week intervals. Lesions were defined as having regressed, persisted, or progressed based on the available specimens during or after completion of treatment according to the following criteria: Regression was indicated if the last endometrial sample obtained by dilatation and curettage following hysteroscopy or the hysterectomy specimen showed a normal endometrium. Persistence was indicated if the last biopsy showed the same findings as the entry biopsy. Progression was indicated if a carcinomatous lesion appeared. Recurrence was indicated if any lesion that initially regressed after treatment appeared again.

Results

Fifty-three patients with CAH comprised 10.8% of the 489 patients with endometrial carcinoma or CAH who were admitted to the hospital during the same period.

Three women refused any treatment after the initial diagnosis was made, although two of them accepted follow-up monitoring, and were not excluded from the analysis. Twenty patients were treated with MPA (8 with high-dose and 12 with low-dose). Thirty women underwent hysterectomy within six months after diagnosis.

Table 1. — *Clinical characteristics of 53 women with complex atypical hyperplasia of the endometrium.*

	Hysterectomy	High-dose MPA	Low-dose MPA	No therapy
Case	30	8	12	3
Age (mean)	34-62 (49.6)	28-53 (37.6)	29-52 (41.8)	36-73 (52.7)
Nulligravida (%)	2 (6.7)	5 (62.5)	3 (25.0)	0
Menometrorrhagia (%)	23 (76.7)	5 (62.5)	12 (100)	3 (100)

Clinical information was available for all patients (Table 1). The age of the patients treated by hysterectomy, high-dose MPA and low-dose MPA ranged from 34 to 62 years (mean 49.6), from 28 to 53 years (37.6) and from 29 to 52 years (41.8), respectively. CAH was seen most often among patients in their 40s (22 cases, 41.5%). The age of the patients treated non-surgically was significantly younger than that of the patients treated by surgery ($p < 0.0005$). Ten patients (18.9%) were nulligravida and three at first had requested treatment for infertility. The age of the nulligravidous patients ranged from 28 to 53 years with an average of 35.4 years. The ages of 43 gravidous patients ranged from 31 to 73 years with an average of 48.7 years. Nulligravidous patients were significantly younger ($p < 0.0005$). Metrorrhagia was a chief complaint in 43 cases (81.1%). Seven patients (13.2%) were postmenopausal, and 24 (52.2%) of 46 premenopausal patients had regular menstrual cycles. Among the 21 patients who recorded their basal body temperature, cyclic ovulation was seen in only four cases (19.0%). Follow-up tracking for the 22 patients who did not undergo hysterectomy initially ranged from 8 to 281 months, with a mean of 66 months.

Fifty-two of 53 patients received endometrial cytology and 19 (36.5%) were diagnosed as negative, 29 (55.8%) as suspicious and four (7.7%) as positive for malignant cells. Dilatation and curettage was used to make the diagnosis of CAH in 48 cases (90.6%), whereas in five cases (9.4%) four-direction endometrial curettage was used.

Among those patients treated with high-dose or low-dose MPA for CAH, complete regression was achieved in 75% of both groups. Median length of the treatment required for regression was 10.8 weeks with a range of 4-30 weeks in the case of the high-dose MPA group. The median number of cycles of treatment required for regression was 7.3 with a range of 3-15 cycles in the case of the low-dose MPA group. There was no recurrence in six patients who had complete regression by high-dose MPA therapy, whereas one of the nine women who had completely regressed by low-dose MPA developed recurrence of her lesion 29 weeks after discontinuation of therapy. However, two patients (25%) who were treated with high-dose MPA and one (17%) with low-dose MPA revealed persistent CAH despite 7-10 months of treatment.

Table 2. — *Follow-up of the patients with complex atypical hyperplasia treated with MPA.*

	Total	Regression (%)	Persistent (%)	Progression (%)
High-dose MPA	8	6 (75.0)	2 (25.0)	0
Low-dose MPA	12	9* (75.0)	1 (8.3)	2 (16.7)

*: One case had recurrent disease.

Table 3. — *Clinical and pathological features in patients who progressed to endometrial carcinoma.*

Case	Age	Interval to cancer	Therapy for CAH*	Stage	Histology
1	45	32 months	Low-dose MPA	Ib	G2
2	29	73 months	Low-dose MPA	Ia	Adenocanthoma G1
3	36	28 months	No therapy	Ib	G2

*CAH: complex atypical hyperplasia.

No woman who received MPA therapy for CAH developed histologically documented progression to endometrial carcinoma during MPA treatment. However, two of 12 patients who were treated with low-dose MPA progressed to endometrial adenocarcinoma 73 and 32 months after their initial diagnosis of CAH (Table 3) (cases 1, 2). Case 2 received other hormone therapy to induce ovulation after the failure of low-dose MPA treatment. This also failed to induce ovulation or to control metrorrhagia. One patient who had declined all treatment developed endometrial carcinoma 28 months after her initial diagnosis (case 3). Sporadic ovulation was observed by monitoring basal body temperature in cases 1 and 3 and case 2 appeared monophasic. Two tumors were G2 endometrioid adenocarcinoma and one was G1 endometrioid adenocarcinoma with benign squamous differentiation with all cases having coexistence of hyperplasia adjacent to the carcinoma. The surgical stage of the carcinomas was Ia in two cases and Ib in one case. They underwent surgery for endometrial carcinoma and are without evidence of recurrence 143-281 months after their initial diagnosis.

Five of 20 patients treated non-surgically desired children. Three women treated with high-dose MPA who had been nulliparous and had complained of infertility or irregular menstrual cycles became pregnant. Their basal body temperature was monophasic before and after MPA treatment. Following regression of their endometrial lesions, they were treated in order to induce ovulation. Intact pregnancies were diagnosed 22 months, seven months and 30 months after completion of MPA treatment, respectively. The patients delivered full-term babies who appeared normal and healthy, and no evidence of recurrent carcinoma was revealed after delivery.

Discussion

In this series, 15 of 20 women with CAH achieved regression of their lesions by MPA treatment and 30 patients were cured of CAH by simple hysterectomy. No patients on whom follow-up was available died. Because they are frequently nulliparous, the women are often

willing to assume some risk to preserve their fertility. Three women in our series have achieved successful full-term pregnancies and normal deliveries following MPA treatment. Our results of MPA therapy are consistent with those of recent case studies [11] for young women under age 40, in which 17 (89.5%) of 19 cases showed an initial regression by using progestin therapy.

CAH was seen most often among patients in their 40s, whose ages were approximately a decade younger than those with endometrial carcinoma in our series (data not shown), as well as other studies [5, 10, 14-16]. The most common symptom reported was metrorrhagia with frequent irregular menstrual cycles [5]. Similar results were found in our study and ovulatory disturbances were found frequently in patients with CAH. These data suggest that endometrial hyperplasia is the result of persistent and prolonged unopposed estrogen stimulation to the endometrium. Notably, one patient who refused treatment for CAH and two patients who discontinued low-dose MPA therapy were found to develop endometrial carcinoma. Clearly, CAH may not remain as a benign lesion when left untreated.

Progestin therapy for endometrial hyperplasia has been reported in the literature [7, 8, 10-12]. Kurman, *et al.* [5] performed hormonal therapy, either by progestins or inducing ovulation in young patients who wished to retain their fertility. They concluded that a conservative plan of management was justified because none of the patients with endometrial hyperplasia who progressed to carcinoma died from their tumors and nearly one-fourth of those younger than 40 years had successful normal-term deliveries. DiSaia and Creasman [17] argue that the patient's age should be reflected in the treatment method. That is, for patients in their teens or in process of sexual maturity, at least six months of artificial cycles must be provided using both estrogen and progestin. In those patients who desire childbearing, three months of artificial cycles should be prescribed, followed by the induction of ovulation. In perimenopausal patients the recommendation is for a cyclic prescription of MPA (20 mg/day) that should be continued for six months, or a hysterectomy. Hysterectomy is recommended for post-menopausal patients. Randall and Kurman [11] stated that hysterectomy is the treatment of choice for women over 55 with CAH.

The effect of low-dose MPA was equal to that of high-dose MPA as far as initial regression rate observed in our series. However, two cases progressed to endometrial carcinoma, although they initially responded well to low-dose MPA treatment and were under observation. In contrast to low-dose MPA therapy, none of the eight cases treated with high-dose MPA therapy developed recurrent or progressive lesions. Although the results of this study cannot always recommend the exact regimen of MPA therapy for CAH, it seems to be reasonable to begin with 200 mg twice a day and to continue for more than four months according to subsequent biopsy and cytology findings. Endometrial sampling, either biopsy or cytology, was performed every 1-3 months in our cases, and this appears to be an adequate level of monitoring. We had two patients who developed endometrial carcinoma after completion of MPA therapy. Both these patients had a history of anovulation or sporadic ovulation. The findings suggest that the physician must ensure that the endometrium is kept in an ovulatory cycle either spontaneously or by exogenous hormone therapy. Indefinite follow-up seems to be necessary for patients who have achieved regression of CAH. DiSaia and Creasman [17] also indicated that a close follow-up, once every three months, is required for patients who undergo hormonal therapy.

In the literature, a variety of progestins, dosages and schedules have been prescribed for patients with CAH [7, 8, 10-12]. Randall & Kurman [11] treated 19 patients with atypical hyperplasia by using megesterol, MPA, or ovulation induction. Both megesterol and MPA were effective with a variety of dosages and their regression rate was 94.1%. They concluded that 40 mg/day megesterol acetate was reasonable to begin the treatment.

Recently, an application of gonadotrophin-releasing hormone analogue (GnRHa) for endometrial hyperplasia has been reported [15]. Grimbizis, *et al.* [15] reported that simple or complex hyperplasia responded well to GnRHa with high regression rates (86.5%, 85.7%, respectively), while it was not effective for CAH.

In conclusion, our case series supports that primary treatment with high-dose MPA is a safe and effective therapy for women with atypical hyperplasia who wish to preserve their fertility. The patient must be prepared to comply with prolonged treatment and multiple endometrial samplings. With careful monitoring, these patients are at minimal risk of developing carcinoma and have a chance of conceiving and carrying a full-term delivery.

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