

# Pregnancy outcomes of women who received conservative therapy for endometrial carcinoma or atypical endometrial hyperplasia

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## Abstract

**Case:** Approximately 3%-25% of cases of endometrial carcinoma (EC) or atypical endometrial hyperplasia (AH) occur in women aged <40 years and conservative treatment with high-dose medroxyprogesterone acetate (MPA) is administered to women who wish to preserve their fertility. Here is reported the pregnancy outcomes of patients with EC or AH who received MPA therapy at Tokushima University Hospital, Tokushima, Japan. The frequency of pregnancy and live births among the patients with EC or AH who received conservative treatment, followed by fertility treatment, were analyzed retrospectively.

**Outcome:** Twelve patients underwent fertility examinations and received fertility treatment immediately after the completion of conservative treatment for EC or AH. One patient had the complication of severe diabetes and total embryo cryopreservation was performed before her diabetes was treated. Among the other 11 patients, 8 (72.7%) became pregnant at least once and 6 (54.5%) experienced at least 1 live birth. Three patients (25.0%) suffered disease recurrence during or after the infertility treatment and all of the recurrences occurred in the EC cohort.

**Conclusion:** When patients with EC or AH wish to preserve their fertility, it is recommended that prompt and effective fertility treatment, including assisted reproductive technology, should be initiated just after conservative treatment because EC and AH exhibit relatively high recurrence rates among conservatively treated patients.

## KEYWORDS

assisted reproductive technology, atypical endometrial hyperplasia, conservative treatment, endometrial carcinoma, medroxyprogesterone acetate

## 1 | INTRODUCTION

It has been reported that ~5%-25% of cases of endometrial carcinoma (EC) or atypical endometrial hyperplasia (AH) occur in women

aged <40 years.<sup>1-3</sup> Essentially, the standard treatment for EC and AH is a total hysterectomy<sup>4</sup>; however, conservative treatment with high-dose medroxyprogesterone acetate (MPA) is administered to women with EC or AH who wish to preserve their fertility (after

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adequate informed consent has been obtained). The regression rates that are associated with conservative treatment range from 70% to 80%; thus, it seems to be a feasible approach for EC and AH. However, it also has been reported that ~30% of patients suffer a recurrence after the achievement of a complete response (CR).<sup>5,6</sup> In addition, most patients with EC or AH have disease-associated ovulation disorders. Therefore, prompt and effective fertility treatment should be initiated just after conservative treatment in patients with EC or AH who wish to get pregnant immediately. The authors recommend that such patients should undergo fertility examinations and treatment as soon as possible after MPA therapy. Various studies have reported successful deliveries after conservative treatment.<sup>5-12</sup> In addition, some studies have indicated that fertility treatment after conservative treatment for EC or AH results in better pregnancy outcomes, compared with expectant management<sup>5-10</sup>; however, the sample sizes of these studies were small and the accumulation of further studies is needed in order to allow firm conclusions to be drawn. Here is reported the pregnancy outcomes of patients with EC or AH that underwent MPA therapy, followed by fertility treatment at Tokushima University Hospital, Tokushima, Japan.

## 2 | CASE REPORTS

The Institutional Review Board of Tokushima University, Tokushima, Japan, approved this retrospective study (approval no.: #2814). The clinical and pregnancy outcomes of the patients that had been diagnosed with EC or AH and who underwent conservative treatment at Tokushima University Hospital between January, 2002 and March, 2017 were evaluated.

The initial pathological diagnosis and EC or AH lesion removal were performed using endometrial curettage. If needed, a hysteroscopy, magnetic resonance imaging, and/or computed tomography were added to rule out myometrial invasion and distant metastasis. The increased risk of disease progression and recurrence that is associated with choosing conservative therapy, instead of the standard surgical treatment, was explained to all the patients. Most of them received conservative treatment based on the same protocol. An endometrial curettage was performed every 3 months after the initiation of MPA (600 mg/d) therapy. After achieving a CR or partial response (PR), additional MPA treatment was administered for 3 months and an endometrial curettage was carried out again. If no residual lesion was detected, the MPA therapy was discontinued and pregnancy was permitted. When MPA was administered, aspirin also was used to prevent a thrombosis. It is recommended that the patients who want to become pregnant immediately should undergo fertility examinations and treatment as soon as possible after the MPA therapy. Holmstrom therapy that involves the oral administration of progestin was recommended for the patients who did not wish to get pregnant. After the fertility examination, conventional fertility treatments (timed intercourse, ovulation induction or controlled ovarian stimulation, and/or intrauterine insemination) or assisted reproductive technology (ART) were used, according to the

status of the primary disease, the patient's history of infertility, and infertility factors. Clinical pregnancy was defined as the detection of an intrauterine gestational sac by ultrasound. Twelve patients underwent fertility examinations and treatment immediately after the completion of the conservative treatment for EC and AH. Although a CR was not achieved in 2 patients (No. 1 and 8) (ie, they were diagnosed with non-atypical hyperplasia even after treatment), these atypia were mild and they were allowed to receive treatment for pregnancy. The patients' characteristics and treatment outcomes are summarized in Table 1. Ten out of 12 (83.3%) patients had menstrual disorders and 6 (50.5%) patients received fertility treatment. One patient (No. 4) had the complication of severe diabetes and total embryo cryopreservation was conducted before her diabetes mellitus was treated. Among the other 11 patients, 8 (72.7%) became pregnant at least once and 6 (54.5%) experienced at least 1 live birth. Three (25.0%) patients suffered disease recurrence during or after the fertility treatment and all cases of recurrence occurred in the EC cohort. Although a hysterectomy was recommended after delivery in most cases, especially for the patients with EC, none of this cohort agreed to surgery and conservative cytological and histological examinations were continued.

## 3 | DISCUSSION

As mentioned above, some studies have suggested that administering fertility treatment after conservative treatment improves the pregnancy outcomes of patients with EC or AH.<sup>5-10</sup> For example, 1 study found that the live birth rate of patients who received fertility treatment was 39.4%, whereas that of patients who tried to spontaneously conceive was 14.9%.<sup>5</sup> Similarly, another study showed that 11 out of 20 patients conceived after conservative treatment and 10 out of these 11 patients received fertility treatment.<sup>6</sup> However, as far as the authors know, there is no consistent evidence about which kinds of fertility treatment are most advantageous after conservative treatment for EC and AH, although some studies have suggested that ART is especially beneficial for such patients.<sup>8-10</sup> For instance, 1 group reported that the pregnancy rate that is associated with ART is as high as 80% among conservatively treated patients with EC or AH.<sup>10</sup> As noted above, 72.7% of this study's patients were able to conceive after fertility treatment, indicating that the pregnancy rate at the current institution was equal to or greater than those that have been reported in previous studies. It should be noted that although the sample size of the present study was small, all of the patients that received ART conceived and delivered at least 1 child. In contrast, the primary disease relapsed in 25% of these patients and this recurrence rate was similar to those that have been described in previous studies.<sup>5,6</sup> Therefore, it is recommended that prompt and effective fertility treatment, including ART, should be initiated just after conservative treatment in patients with EC or AH who want to become pregnant. In addition, the relatively high recurrence rate of EC and AH always must be taken into account when conservative treatment is considered.

**TABLE 1** Reproductive outcomes of fertility treatments for patient received conservative treatment

Patient	Histology (grade)	Age (years)	Gravida/para	Menstruation	Response to MPA therapy	Relapse (months after CR)	History of fertility treatment	Cause of infertility	Fertility treatment	Result of treatment	
										Pregnancy	Live birth
1	AH	34	0/0	Regular	PR	—	—	Male factor Tubal factor	IVF-ET	3	1
2	AH	31	0/0	Irregular	CR	—	—	PCOS	CC, hMG	0	0
3	AH	40	0/0	Irregular	CR	—	—	Male factor Anovulation	CC, IUI	0	0
4	AH	38	0/0	Amenorrhea	CR	—	CC	Anovulation	Embryo cryopreservation (before DM treatment)	—	—
5	EC (1)	26	0/0	Irregular	CR	48	—	—	CC, IUI	2	2
6	EC (1)	35	0/0	Regular	CR	—	IUI	Luteal insufficiency	IVF-ET	1	1
7	EC (2)	35	0/0	Irregular	CR	18, 11	Timed intercourse	Hyperprolactinemia Anovulation	ICSI-ET	1	1
8	EC (1)	35	5/0	Irregular	PR	16	CC	—	CC, hMG	1	0
9	EC (1)	30	0/0	Irregular	CR	—	—	Delayed ovulation Luteal insufficiency	CC, hMG, IUI	4	2
10	AH	31	0/0	Irregular	CR	—	CC	PCOS Tubal factor	CC, rFSH	1, ongoing	0
11	EC (1)	33	0/0	Irregular	CR	—	—	Anovulation	Embryo cryopreservation (high risk of OHSS)	—	—
12	AH	39	0/0	Irregular	CR	—	CC	PCOS	IVF-ET	1	1

AH, atypical hyperplasia; CC, clomiphene citrate; CR, complete response; DM, diabetes mellitus; EC, endometrial carcinoma; ET, embryo transfer; hMG, human menopausal gonadotropin; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; MPA, medroxyprogesterone acetate; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome; PR, partial response; rFSH, recombinant follicle-stimulating hormone.

## DISCLOSURES

**Conflict of interest:** The authors declare no conflict of interest.  
**Human rights statement and informed consent:** This study was approved by the Institutional Review Board of Tokushima University, Tokushima, Japan. Informed consent to be included in this study was obtained from all the patients. All the procedures that were followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments.  
**Animal studies:** This article does not contain any study with animal participants that were performed by any of the authors.

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