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CLINICAL ARTICLE

Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer

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ABSTRACT

Objective: To investigate the oncologic and reproductive outcomes after progestin treatment of complex endometrial hyperplasia (CEH) and grade 1 endometrial carcinoma (EC). *Methods:* In a retrospective study, data were obtained for patients aged 20–42 years with CEH or grade 1 EC at presumed stage IA (without myometrial invasion) who wished to preserve fertility and were treated at the Peking Union Medical College Hospital, China, between January 1, 2000, and December 31, 2011. Patients had received oral medroxyprogesterone acetate (250–500 mg/day) or megestrol acetate (160–480 mg/day) for at least 6 months. Response to progestin treatment was assessed histologically. *Results:* Among 53 included patients, 39 (74%) achieved complete response after a median period of 6 (3–24) months. Complete response was less frequent among obese than nonobese patients (4/12 [33%] vs 35/41 [85%]; $P = 0.001$). Disease recurrence was recorded in 10 (26%) patients with complete response; the 5-year recurrence-free survival rate was 71%. Among the 33 patients who retained a desire to conceive, 17 (52%) became pregnant. *Conclusion:* Fertility-sparing management with oral progestin is effective. Obesity is associated with a lower probability of long-term success.

1. Introduction

Endometrial carcinoma (EC) is the most common cancer of the female genital tract in high-income countries [1,2], and is also becoming increasingly frequent in China [3]. Its precursor, complex endometrial hyperplasia (CEH), is found in 5%–10% of all premenopausal women presenting with abnormal uterine bleeding worldwide [4,5]. For patients with EC or CEH, hysterectomy with or without bilateral salpingo-oophorectomy is the gold-standard treatment. Nevertheless, this treatment can be unacceptable to patients who still wish to conceive; a conservative, fertility-sparing approach should therefore be considered in this population.

EC and CEH usually occur due to unopposed estrogen stimulation [6]. Because well-differentiated EC tends to retain estrogen and progesterone receptors [7], hormone (progestin) therapies have been previously used in the treatment of this disease [8]. However, it has been reported that some patients show little response to progestin and can even progress during treatment [9–11]. Thus, a re-evaluation of the safety of progestin therapy and the identification of features that predict treatment success would greatly benefit this population.

The objective of the present study was to assess the efficacy and relevant prognostic factors of progestin treatment in Chinese patients with a diagnosis of CEH or grade 1 EC at presumed stage IA (without myometrial invasion).

2. Materials and methods

A retrospective study was undertaken using data for patients with EC or CEH and of childbearing age who were managed with oral progestin fertility-sparing treatment between January 1, 2000, and December 31, 2011, at the Peking Union Medical College Hospital, China. Patients' eligibility for oral progestin treatment included: age of 20–42 years, with a strong desire for fertility preservation and pathologic endometrium results of grade 1 EC or CEH; expression of progestin receptors (PgRs) in the endometrium; no evidence of myometrial invasion (evaluated by transvaginal ultrasonography and pelvic magnetic resonance imaging [MRI]); and presumed stage IA disease on the basis of the 1988 staging system of the International Federation of Gynecology and Obstetrics. All the patients treated with oral progestin during this time period were included in the present study except four cases lost to follow-up. The body mass index (BMI, calculated as weight in

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kilograms divided by the square of height in meters) cut-off point was set at 30 according to the current international classification of WHO Health Organization [12]. Patients were considered to be obese if the BMI was over 30. All pathology slides were re-reviewed by two pathologists specializing in gynecologic oncology. Informed consent, both for treatment and future study participation, were obtained from every patient at the time of treatment. Study approval was obtained from the Institutional Review Board of the study center.

All eligible patients were provided extensive counseling regarding fertility-preserving options, including the potential risks of disease recurrence or progression. Progestin therapy consisted of oral medroxyprogesterone acetate (MPA) at doses of 250–500 mg/day or megestrol acetate (MA) at doses of 160–480 mg/day. Patients were scheduled to receive progestin therapy for at least 6 months. Gonadotropin-releasing hormone agonists (GnRH-a) were administered for three to six cycles (leuprolide acetate depot 3.75 mg/28 days as one cycle), depending on the treatment response. A levonorgestrel-releasing intrauterine system (LNG-IUS) was placed in those who had no immediate childbearing plan. Following initiation of oral progestin treatment, all patients underwent a pelvic examination as well as biochemical assays for the detection of tumor markers and imaging studies every 3 months, including a transvaginal ultrasonography or MRI.

Response to progestin treatment was assessed histologically using specimens obtained via hysteroscopic biopsies or dilatation and curettage, on the basis of the doctors' discretion and affordability. The histological evaluation was performed every 3 months, except for patients who received progestin treatment for more than 12 months, in which case the interval could be extended to 4–6 months during the second year. A complete response (CR) was defined as the absence of hyperplasia or carcinoma. Once patients achieved a CR, a maintenance therapy was administered for 3–6 months. Low-dose cyclic progestin, oral contraceptives, or a LNG-IUS were administered to patients with no immediate childbearing plans. Survival was censored according to the final follow-up date (July 1, 2014).

The frequency distributions of the baseline characteristics were compared with Fisher exact tests when the expected frequency was less than five; otherwise, the Pearson χ^2 test was used. The recurrence-free survival rate was defined as the time (in months) from the date of achieving a CR to the date of relapse or end of follow-up. The survival curve was constructed with the Kaplan–Meier method. Statistical analyses were performed with SPSS 20.0 software (IBM, Armonk, NY, USA). $P < 0.05$ were considered significant.

Table 1
Characteristics, treatment, and follow-up of patients treated with progestin[a].

Variable	Total (n = 53)	CEH (n = 16)	EC (n = 37)	*P* value
Baseline characteristics				
Age, y				0.103
≥35	16 (30)	2 (13)	14 (38)	
<35	37 (70)	14 (88)	23 (61)	
Body mass index[b]				>0.99
≥30	12 (23)	4 (25)	8 (22)	
<30	41 (77)	12 (75)	29 (78)	
Previous pregnancy				0.480
Yes	5 (9)	2 (13)	3 (8)	
No	48 (91)	14 (88)	34 (92)	
Associated risk factor for endometrial disease				
Abnormal menstruation	50 (94)	15 (94)	35 (95)	0.668
Polycystic ovary syndrome	18 (34)	7 (44)	11 (30)	0.322
Diabetes mellitus	6 (11)	2 (13)	4 (11)	0.595
Family history of cancer	5 (9)	1 (6)	4 (11)	0.520
Treatment				
Oral progestin	53 (100)	16 (100)	37 (100)	–
Oral progestin and GnRH-a	9 (17)	3 (19)	6 (16)	0.554
Oral progestin and LNG-IUS	2 (4)	1 (6)	1 (3)	0.517
Follow-up				
Treatment response				0.650
Complete response	39 (74)	12 (75)	27 (73)	
Partial response	4 (8)	1 (6)	3 (8)	
Stable disease	6 (11)	1 (6)	5 (14)	
Progressive disease	4 (8)	2 (13)	2 (5)	
Time to complete response, mo				0.528
≤6	24 (45)	7 (44)	17 (46)	
>6	15 (28)	5 (31)	10 (27)	
Recurrence				0.813
Yes	11 (21)	3 (19)	8 (22)	
No	42 (79)	13 (81)	29 (78)	
Pregnancy				0.023
Yes	17 (32)	9 (56)	8 (22)	
Live birth	11 (20)	6 (38)	5 (14)	
Spontaneous abortion	9 (17)[c]	3 (19)	6 (16)	
Ectopic pregnancy	1 (2)	1 (6)	0	
No	36 (68)	7 (44)	29 (78)	

Abbreviations: CEH, complex endometrial hyperplasia; EC, endometrial carcinoma; GnRH-a, gonadotropin-releasing hormone agonist; LNG-IUS, levonorgestrel-releasing intrauterine system.

[a] Values are given as number (percentage) unless indicated otherwise.

[b] Calculated as weight in kilograms divided by the square of height in meters.

[c] There were five patients (2 with CEH, 3 with EC) in whom spontaneous abortion occurred once without a subsequent live birth. One patient with CEH and one patient with EC had a spontaneous abortion before a subsequent live birth. One patient with EC had two spontaneous abortions before a subsequent live birth.

3. Results

A total of 53 patients met the inclusion criteria and were included in the study (Table 1). Of these patients, 37 had been diagnosed with EC and 16 with CEH. The median age of the overall group was 32 years (range 21–41). All 37 patients with EC underwent a pelvic MRI to confirm that there was no myometrial invasion or extrauterine disease before the initiation of progestin therapy. Of the 53 patients, 32 (60%) received MPA and 21 (40%) received MA. Nine (17%) patients were given GnRH-a because of an unsatisfactory treatment response and LNG-IUS were placed in 2 (4%) patients as maintenance therapy. The mean duration of progestin treatment for all patients was 8 months (range 2–18).

In terms of adverse effects, three (6%) patients had increased levels of alanine aminotransferase and four (8%) had breast pain. Three (6%) patients had transient liver dysfunction (grade 1 according to the National Cancer Institute Common Terminology Criteria (NCI-CTC v.4.0)) [13]. All three patients recovered within 3 months after the application of polyene phosphatidylcholine.

Overall, 39 (74%) patients showed a CR to progestin treatment after a median period of 6 (3–24) months. No significant differences were observed with regard to the response rate and the time to CR between patients with CEH and those with EC (Table 1). A CR was achieved within 6 months in 24 (62%) patients. Only 5 (13%) of these 39 patients achieved CR after a treatment period of over 12 months.

The 14 patients who failed to achieve a CR (4 with CEH, 10 with EC) underwent a hysterectomy. The final pathological examinations for the four patients with CEH indicated that only two had been correctly diagnosed with CEH; one had superficial grade 1 endometrioid adenocarcinoma and one had grade 1 endometrioid adenocarcinoma and type II carcinoma. Endometrial biopsy samples for this patient had originally indicated CEH at the 1- and 3-month follow-ups; however, samples obtained at the 6-month follow-up and at the final pathologic analysis showed that the disease had developed into a mixture of grade 1 endometrioid carcinoma and type II EC. Nevertheless, inadequate sampling at the initial biopsy, rather than disease progression, is the likely cause for this discrepancy. With respect to the 10 cases of EC, pathologic findings were all of grade 1 endometrioid adenocarcinoma confined to the endometrium, with two exceptions. Ultrasonography indicated that one patient had an ovarian and pelvic mass after 6 months of progestin therapy; the final pathologic analysis showed that this tumor was grade 1 endometrioid adenocarcinoma that had invaded less than half of the myometrium, with ovarian and pelvic metastases. The second patient had developed myometrial invasion detected by MRI at the 9-month follow-up; the final pathological