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Significance of body weight change during fertility-sparing progestin therapy in young women with early endometrial cancer

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HIGHLIGHTS

- We evaluated the influence of body weight change on progestin therapy outcomes.
- A pretreatment BMI of ≥25 kg/m^2 was predictive of poor response and high recurrence.
- A posttreatment BMI of ≥25 kg/m^2 was predictive of high recurrence.
- Weight change during progestin therapy was not associated with response or recurrence.
- Pre, posttreatment BMI and weight change were not associated with fertility outcomes.

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ABSTRACT

Objective. To evaluate the influence of body weight change during fertility-sparing progestin therapy on oncologic and reproductive outcomes in young women with early-stage endometrial cancer who did not complete child bearing.

Methods. This multicenter, retrospective study included 154 young patients with well-differentiated, endometrium-confined endometrioid endometrial adenocarcinoma on magnetic resonance imaging who received fertility-sparing progestin therapy.

Results. The mean body weight and body mass index (BMI) at baseline and progestin therapy completion was 65.3 ± 16.2 and 66.5 ± 15.9 kg ($P = 0.044$), respectively, and 25.51 ± 5.99 and 25.99 ± 5.94 kg/m^2 ($P = 0.034$), respectively. During progestin therapy, 51 (33.1%), 29 (18.8%), and 74 patients (48.1%) had weight loss, no weight change, and weight gain, respectively, of which 11 (7.1%) had 10% weight loss and 30 (19.5%) had 10% weight gain. A pretreatment BMI of ≥25 kg/m^2 was significantly associated with a lower complete response rate to progestin therapy ($P = 0.003$) and a high recurrence rate ($P = 0.033$). A posttreatment BMI of ≥25 kg/m^2 was also a significant factor for high recurrence rate ($P = 0.049$). However, weight change during therapy was not significantly associated with complete response or recurrence rate. Pre and posttreatment BMIs and weight change were not associated with pregnancy and live birth rates.

Conclusion. Weight change during progestin therapy has little influence on complete response, recurrence, pregnancy, and live birth rates. However, pre and posttreatment BMIs of ≥25 kg/m^2 were significant predictors for poor treatment response and high recurrence. Therefore, it is important to maintain patients' normal BMIs during progestin therapy.

1. Introduction

Endometrial cancer is the most common gynecologic cancer in North America and Europe [1,2]. Although most endometrial cancers are diagnosed in postmenopausal women, 3%–14% of cases are diagnosed in young women [3,4]. However, the incidence of endometrial cancer in young women has recently increased [5]. As endometrial

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cancers diagnosed in young women are mostly well-differentiated, endometrium-confined endometrioid adenocarcinoma, the cure rate is high [6,7].

Fertility-sparing management using oral progestin is a widely accepted alternative treatment for selected young women with early-stage endometrial cancer who wish to preserve their fertility [5]. Well-known indications for fertility-sparing progestin therapy are well-differentiated, endometrium-confined endometrioid adenocarcinoma of the uterus [5]. Approximately 75% of patients achieve complete remission with progestin therapy [8,9], and the pregnancy rate is approximately 73% after treatment in complete responders [10]. Overweight and obesity, measured with body mass index (BMI), are important risk factors for developing endometrial cancer [11]. Each 5-unit increase in BMI corresponds to a 0.5-fold increase in the risk for developing endometrial cancer [12]. Of all cancer types, the association of overweight and obesity with the development of endometrial cancer is the strongest [12]. Progestin therapy has a high efficacy in the treatment of early-stage endometrial cancer in young women, but is associated with a significant increase in body weight [13]. However, the influence of body weight change during fertility-sparing progestin therapy on oncologic and reproductive outcomes has not yet been evaluated. Therefore, this study aimed to evaluate the influence of body weight change during fertility-sparing progestin therapy on complete response, recurrence, pregnancy, and live birth rates in young women with early-stage endometrial cancer.

2. Materials and methods

This study had a multicenter, retrospective design and was approved by the institutional review boards of the participating centers. Demographic and clinicopathologic data were gathered from five tertiary centers in Korea. The inclusion criteria for this study were 1) previously untreated, histologically diagnosed endometrial cancer, 2) endometrioid histology, 3) well-differentiated tumor (International Federation of Obstetrics and Gynecology classification), 4) endometrial cancer confined to the endometrium on pretreatment magnetic resonance imaging (MRI), 5) no evidence of lymph node metastasis or complex ovarian tumor on pretreatment MRI, 6) age below 45 years, 7) patients who received fertility-sparing management using oral progestin, and 8) patients with available data for body weight and height at baseline and progestin therapy completion.

Clinicopathologic and follow-up data were obtained from patient medical records. Body weights at baseline and progestin therapy completion were also collected, and mean body weight was calculated. The mean body weight change was correlated with demographic and clinicopathologic factors to investigate factors associated with body weight change during progestin therapy. Patient responses to progestin therapy and recurrence rate in complete responders were correlated with demographic and clinicopathologic factors to evaluate factors associated with response to progestin. Recurrent disease included endometrial hyperplasia and adenocarcinoma both. Frequency distribution was compared using chi-square and Fisher's exact tests. Mean values were compared using student's *t*-tests and Mann–Whitney *U* tests. The change in mean values over time was compared using paired *t*-tests. The correlation between two continuous variables was accessed using Pearson's correlation coefficient. *P*-values of <0.05 in two-sided tests were considered statistically significant. All statistical analyses were performed with SPSS Version 21.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Study population

In total, 154 patients met our inclusion criteria. Table 1 presents patient characteristics. The mean age (±standard deviation) was 32 ± 4.7 years, and 145 patients (94.2%) were nulliparous. All patients received daily oral progestin therapy, of which 51 (33.1%) received megestrol acetate and 103 (66.9%) received medroxyprogesterone acetate. The median daily dose of oral megestrol acetate was 160 mg/day (range 40–500 mg/day) and that of oral medroxyprogesterone acetate was 500 mg/day (range 80–1000 mg/day). All patients completed the recommended progestin therapy. No one stopped progestin therapy due to side effects including weight gain and thromboembolism, etc. Response to progestin was pathologically evaluated by dilatation, curettage, and biopsy or hysteroscopic biopsy at 3-month intervals until complete response was documented. Complete response was defined as the complete disappearance of endometrial hyperplasia and adenocarcinoma on pathologic evaluation. The median treatment duration was 18 months (range 3–49 months). In total, 111 patients (72.1%) showed complete response to oral progestin therapy. The median time interval between baseline and complete response was 18 weeks (range 3–224 weeks). Among 111 complete responders, 64 patients (57.7%) immediately spotted high dose progestin therapy and 47 patients (42.3%) continued high dose progestin therapy for several months after achieving complete response. Twenty three patients (20.7%) received low dose cyclic progestin or progestin-releasing intrauterine device as a maintenance therapy after completion of treatment. Complete responders were followed up every 3–6 months with history taking, physical examination, and imaging study (transvaginal ultrasonography or abdominal and pelvic MRI). If symptoms or signs of recurrence were present, endometrial biopsy was performed using dilatation, curettage, and biopsy or hysteroscopic biopsy. Routine follow-up endometrial biopsy in complete responders was not recommended due to possible adverse effect on reproductive outcomes.

Table 1
Patient characteristics ($n = 154$).

Characteristics		Values
Age (years), mean ± SD		32 ± 4.7
Parity, n (%)	0	145 (94.2)
	1	8 (5.2)
	2	1 (0.6)
History of infertility, n (%)	No	102 (66.2)
	Yes	52 (33.8)
History of PCOS, n (%)	No	123 (79.9)
	Yes	31 (20.1)
History of anovulation, n (%)	No	77 (50)
	Yes	77 (50)
History of irregular menstruation, n (%)	No	70 (45.5)
	Yes	84 (54.5)
History of medical disease, n (%)	No	131 (85.1)
	Yes	23 (14.9)
Body weight (kg), mean ± SD	Pretreatment	65.3 ± 16.2
	Posttreatment	66.5 ± 15.9
Body mass index, n (%)	Pretreatment	25.51 ± 5.99
	Posttreatment	25.99 ± 5.94

PCOS, polycystic ovary syndrome; SD, standard deviation.

3.2. Body weight change during progestin therapy

The mean body weight at baseline was 65.3 ± 16.2 kg and at progestin therapy completion was 66.5 ± 15.9 kg ($P = 0.044$). The mean BMI at baseline was 25.51 ± 5.99 kg/m^2 and at progestin therapy completion was 25.99 ± 5.94 kg/m^2 ($P = 0.034$). The median time interval between the two measurements was 18 months (range 3–49 months). During progestin therapy, 51 patients (33.1%) had weight loss, 29 (18.8%) had no weight change, and 74 (48.1%) had weight gain, of whom 11 (7.1%) had 10% weight loss and 30 (19.5%) had 10% weight gain. Twenty one patients (13.6%) had weight gain rate of ≥1 kg/month during progestin therapy and 7 patients (4.5%) had weight gain rate of ≥2 kg/month during progestin therapy. Pretreatment BMI (<25 kg/m^2 vs. ≥25 kg/m^2), progestin type (megestrol acetate vs. medroxyprogesterone acetate), daily progestin dose (≤500 mg/day vs.

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