Gynecologic Oncology 140 (2016) 234–238

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Effect of oral versus intrauterine progestins on weight in women undergoing fertility preserving therapy for complex atypical hyperplasia or endometrial cancer☆

Diana Cholakian [a], Kari Hacker [b], Amanda N. Fader [a], Paola A. Gehrig [b], Edward J. Tanner III [a,*]

[a] The Kelly Gynecologic Oncology Service, Department of Gynecology and Obstetrics, Johns Hopkins Medicine, Baltimore, MD, United States
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, NC, United States

HIGHLIGHTS

- LNG-IUD was associated with less weight gain than megestrol acetate during therapy.
- Obese women gained less weight with progestin therapy for endometrial cancer.
- Obese women gained less weight with LNG-IUD than megestrol acetate during therapy.

ARTICLE INFO

Article history:
Received 17 September 2015
Received in revised form 2 December 2015
Accepted 13 December 2015
Available online 17 December 2015

Keywords:
Endometrial cancer
Fertility preservation
Progestin therapy

ABSTRACT

Objective. The objective of this analysis was to evaluate weight changes associated with oral progestin therapies versus the levonorgestrel-containing intrauterine device (LNG-IUD) in women undergoing fertility-preserving therapy for complex atypical hyperplasia (CAH) and endometrial cancer (EMC).

Methods. All patients diagnosed with CAH or EMC managed with fertility-preserving progestin therapy at two institutions from 1998 to 2012 were identified. Those with serial weight measurements before, during and after therapy were included. Patients were categorized according to the type of progestin therapy administered. The rate of weight change over time of patients treated with oral versus intrauterine progestins was compared using the Mann Whitney U test.

Results. Sixty patients with EMC (35) or CAH (25) were treated during the study period, with 12 patients receiving multiple regimens. These included megestrol acetate (MA, n = 42), LNG-IUD (n = 22), and other oral progestins (n = 11). The median age at diagnosis was 32 and median pre-progestin body mass index (BMI) was 40.4 kg/m^2. The median therapy duration was 11.7 months [range: 2.3–118.5]. Median weight change during therapy was greater with MA versus LNG-IUD (+2.95 vs. +0.05 kg, P = 0.03). Patients with a BMI < 35 gained more weight during therapy versus patients with BMI ≥ 35 (+2.30 vs. −0.70 kg/month, P = 0.04); however, in patients with BMI ≥ 35, MA was still associated with more weight gain than LNG-IUD (+2.2 vs.-5.40 kg, P = 0.05).

Conclusion. Oral progestin therapy for conservative treatment of young EMC/CAH survivors is associated with increased weight gain, especially when megestrol acetate is utilized. Utilization of LNG-IUD may result in less weight gain.

1. Introduction

With rising obesity rates in the United States, it is postulated that the incidence of complex atypical endometrial hyperplasia (CAH) and endometrial adenocarcinoma (EMC) in premenopausal women will also increase [1]. Even now, up to 14% of women with endometrial cancer are diagnosed at 40 years of age or younger [2,3]. While the standard of care for the management of CAH or EMC includes hysterectomy, this recommendation may conflict with the fertility plans of younger women, especially in a society where the age of first delivery is delayed to later in life [4].

In recent years, progestin therapy has been successfully used to treat select women with endometrial cancer and hyperplasia who desire to preserve fertility. The efficacy of progestin therapy on treatment of

☆ Disclosure statement: The authors report no conflicts of interest. No industry or pharmaceutical support was obtained to conduct this research or produce this manuscript.

* Corresponding author at: 600 N Wolfe Street, Phipps 281, Baltimore, MD 21287, United States.
E-mail address: etanner4@jhmi.edu (E.J. Tanner).

http://dx.doi.org/10.1016/j.ygyno.2015.12.010
0090-8258/

CAH or grade 1 EMC has been studied widely; however, most reports are retrospective [5–11]. The most common progestin regimens include megestrol acetate (MA) and the levonorgestrel intrauterine system (LNG-IUD). These modalities may be equally effective [12], with a recent meta-analysis showing a pooled regression rate of 66–76.2% and relapse rate of 40.6% for both regimens [13,14]. In fact, women with endometrial hyperplasia were more likely to show regression with an LNG-IUD compared to oral progestins [36], prospective head-to-head comparisons of these treatment modalities are lacking.

It is well established that use of progestins in women for contraception or treatment of benign gynecologic conditions leads to weight gain, especially in women who are obese at baseline [15–17]. Progestins can even be used to help patients gain weight in some circumstances. A recent Cochrane Review of MA used for anorexia-cachexia syndrome showed an 8% weight gain in MA-treated patients versus control patients [7]. Given that obesity is one of the strongest risk factors for CAH and EMC, use of progestin therapy in this setting is problematic — and potentially counterproductive. Additionally, numerous reports demonstrate decreased disease-specific and overall survival with increasing BMI in patients with EMC [13,18–20]. Importantly, obesity appears to be a modifiable risk factor for mortality from disease [21].

In theory, the LNG-IUD system should offer the same advantages for the treatment of CAH and EMC without the degree of weight gain associated with systemic absorption of oral progestins. Although response rates and pregnancy outcomes are frequently evaluated in studies of patients treated conservatively for CAH and EMC, the role of potential weight gain with progestin therapies during gynecologic cancer treatment has not yet been well evaluated [12]. It is, therefore, important to define whether any of the progestin therapies used in the conservative management of women with CAH or EMC are more likely to result in weight gain.

2. Methods

After obtaining Institutional Review Board approval at both institutions, we identified all women 45 years of age or younger treated with progestin therapy for at least two months for complex atypical endometrial hyperplasia (CAH) or grade 1–2 endometrioid adenocarcinoma of the endometrium (EMC) at one of two institutions (Johns Hopkins Hospital, Baltimore, MD and University of North Carolina School of Medicine, Chapel Hill, NC) from 1998 to 2012. Women were excluded from the analysis if they were treated with progestin therapy for reasons other than fertility preservation or did not have serial weight measurements available pre, during and post-progestin therapy. Demographic data was collected including age at diagnosis, ethnicity, BMI and other comorbidities.

Patients were categorized according to the type and number of progestin therapies received. For purposes of comparison, patients that received both oral progestins and LNG-IUD were categorized in the LNG-IUD group. The date that progestin therapy started and ended was collected as well as the starting and ending patient weights. Using this data, we were able to calculate the total weight change and the rate of weight change over time (kg/month) for each progestin therapy. Using patient heights collected at time of diagnosis, we calculated the body mass index (BMI) at diagnosis and change in BMI over time (kg/m^2/month) during therapy. If dates or weights were missing for a regimen, we excluded data for that regimen from analysis.

SPSS version 22 was used to calculate differences in weight change for oral progestin regimens versus LNG-IUD. Testing for normality of the data was performed using the Shapiro–Wilk test. To compare demographic data between treatment groups, categorical data were assessed using the Chi Square test while continuous variables were assessed using the Student T test for variables with normal distribution. Comparisons of weight changes during therapy and weight change over time during therapy were performed using the Mann Whitney U test due to non-normal distribution of the data.

3. Results

We identified 60 eligible patients treated at two institutions, Johns Hopkins Hospital (n = 34) and the University of North Carolina Medical Center (n = 26) from 1998 to 2012. Twenty-five patients were initially treated for CAH and 35 were initially treated for EMC. Demographic data is found in Table 1. The median age at diagnosis was 32.0 years (range: 22–45) with 13 patients (19%) having concurrent diabetes mellitus. Seven of these 13 diabetic patients were taking metformin during progestin therapy.

The median starting weight for the entire cohort was 110.4 kg (range: 45.4–198.6) and the median starting BMI was 40.4 kg/m^2 (range: 18.3–70.7).

Most patients were treated with just one progestin-containing regimen (n = 48, 80.0%), although 11 (18.3%) were treated with two and one (1.7%) was treated with three consecutive regimens (Table 2). Three patients were treated with both LNG-IUD and oral progestins and were categorized in the LNG-IUD group for comparison purposes. Results were not significantly altered by including the three patients treated with both regimens in the oral progestin group or by including them in a separate third group.

Megestrol acetate (MA) was the most commonly prescribed regimen (n = 40, 55.6%), followed by LNG-IUD (n = 22, 30.6%), medroxyprogesterone acetate (MPA, n = 5, 6.9%), and other oral progestin-containing regimens (n = 5, 6.9%). The dosing regimen for patients receiving oral therapy varied. For patients receiving MA, doses ranged between MA 40 mg twice daily to 160 mg twice daily. For MPA, the average dose varied between 10 mg daily and 40 mg daily. In many patients, the progestin doses were changed throughout the course of their treatment, making assessment of any dose-related impact on weight change infeasible to assess.

LNG-IUD was used as first line therapy in 28.3% of patients. LNG-IUD was more likely to be used as first line therapy in patients with diabetes (53.8% versus 25.4%, P = 0.04) and increased BMI (48.4 kg/m^2 versus 39.0 kg/m^2, P = 0.03) but was not influenced by patient age or ethnicity. Patients were treated with an individual progestin regimen for a median of 11.7 months (range: 2.3–118.6). The median overall weight change during therapy was +0.9 kg (range: −53.0–+24.5) with a median weight change over time of +0.08 kg/month (range: −4.5–+2.0). The median duration of progestin therapy for first, second, and third line regimens were 11.7, 10.8, and 47 months, respectively. Twenty-six patients (43.3%) eventually underwent hysterectomy due to persistent disease (13), patient preference (3), inability to tolerate progesterone (3), or disease progression (1). There was no correlation between weight gain during progestin therapy and risk of persistent/progressive disease (P = 0.989).

The median weight change during therapy in patients treated with any oral progestin regimen was not statistically different versus patients treated with LNG-IUD (+1.40 versus +0.05 kg, P = 0.09). The median weight change during therapy with MPA was not different from LNG-IUD (−1.60 versus +0.05 kg, P = 0.60); however, the median weight

Table 1
Demographics of patients with endometrial hyperplasia or carcinoma treated with fertility preserving progestin therapy.

Characteristic	All cases (%)
Median age at diagnosis, years (range)	32 (22–45)
Ethnicity	
Caucasian	33 (56.9)
African-American	16 (27.6)
Asian	4 (6.9)
Hispanic	3 (5.2)
Other/unknown	2 (3.4)
Diabetes mellitus	11 (19.0)
Median starting weight per regimen, kg (range)	110.4 (45.4–198.6)
Median starting BMI per regimen, kg/m^2 (range)	40.4 (18.3–70.7)
BMI ≥ 35 at diagnosis	35 (60.3)