RESEARCH ARTICLE

Endometrial Curettage in Abnormal Uterine Bleeding and Efficacy of Progestins for Control in Cases of Hyperplasia

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Abstract

Background: Abnormal uterine bleeding (AUB) is the most important symptom of endometrial hyperplasia and endometrial curettage (EC) is the gold standard diagnostic procedure. We present the results of patients who underwent EC for AUB and the efficacy of progestin administration in those with endometrial hyperplasia. Materials and Methods: A total of 415 female patients who presented to Duzce Public Hospital in 2011-2012 for AUB and who underwent EC were included. We determined the reasons for AUB, and females with hyperplasia were treated with 10 mg/day medroxyprogesterone acetate for 14 days/month or 160 mg/day megestrol acetate continuously for 3 months. We evaluated the efficacy of progestins for periods of three and/or six cycles by repeating EC. A statistical analysis of specific endometrial causes according to age of presentation was conducted using the chi-square test. Results: Among the 415 females (average age, 53.5 years) followed for 6 months, 186 had physiological changes (44.8%), 89 had simple hyperplasia (21.44%), 1 had atypical hyperplasia (0.2%), 6 had (1.44%) complex hyperplasia, 3 had (0.72%) atypical complex hyperplasia, and 5 had adenocarcinoma (1.2%). Regression rates were 72.7-100%, and the optimum results were observed after 6 months of hormonal therapy. Conclusions: The main cause of AUB was physiological change. Progestin therapy resulted in significant regression even in females with atypical hyperplasia.

Keywords: Abnormal uterine bleeding - endometrial curettage - endometrial hyperplasia - MPA - megestrol acetate

Asian Pac J Cancer Prev, **15 (8)**, 3737-3740

Introduction

The prevalence of abnormal uterine bleeding (AUB) is 11-13% in the general population, and increases with age, reaching 24% in females aged 36-40 years (Marret et al., 2010). AUB may be acute or chronic and is defined as bleeding from the uterine corpus that is abnormal in regularity, volume, frequency, or duration and occurs in the absence of pregnancy (Munro et al., 2011; ACOG, Practice Bulletin, 2012). The recent classification for AUB has been described as PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia-coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not yet classified), and was approved by the International Federation of Obstetrics (Munro et al., 2011).

Endometrial hyperplasia is a common diagnosis (5-10%) in females presenting with AUB and can progress to cancer if left untreated (Gallos et al., 2010). Adenocarcinoma of the endometrium is the most common gynecological cancer; and endometrial hyperplasia is a precursor lesion of adenocarcinoma (Turan et al., 2012; Acmaz et al., 2014). Therefore, the first aim in a patient diagnosed with AUB should be to exclude an oncological lesion. Endometrial hyperplasia is classified as simple and complex with or without cytologic atypia. Simple hyperplasia (SH) often regresses spontaneously and rarely progresses to endometrial cancer. Complex hyperplasia (CH) and hyperplasia with atypia(CAH) are more likely to progress to cancer; thus, they are commonly treated with progestins or hysterectomy. Treatment protocols generally suggest treating CH with progestins, and atypical hyperplasia (AH) with hysterectomy. In contrast, the necessity for a hysterectomy and progestins to treat patients with CH and AH continues to be controversial (Epplein et al., 2008; Marret et al., 2010). However, the efficacy of hormonal therapy for patients with endometrial hyperplasia remains unclear, and most relevant studies are based on large case series.

Progestins are effective for treating endometrial hyperplasia because they activate progesterone receptors, which results in stromal decidualization and subsequent thinning of the endometrium. Progestin exposure decreases the number of estrogen and progesterone receptors and activates hydroxylase enzymes to convert estradiol to its less-active metabolite estrone. The main progestational agents used to treat endometrial hyperplasia are oral progestogens (norethisterone acetate, megestrol acetate, and medroxyprogesterone 17-acetate [MPA]) and the levonorgestrel-releasing intrauterine system. However, there is no consensus on dose, treatment

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duration, administration route, or the most effective type of progestin (Ferenczy et al., 1989; Tasci et al., 2014). No evidence from randomized controlled trials is available, and no randomized controlled trials on the efficacy of progestin treatment in terms of achieving a pathologically complete response are currently underway (Baker et al., 2012).

Although hysteroscopic evaluation is the gold standard for AUB, endometrial curettage (EC) continues to be performed in public hospitals. Endometrial sampling is a preferred procedure for diagnosis of the endometrial pathology (Balik et al., 2013); and EC (with conventional dilatation and curettage) is a valuable and cost-effective technique for evaluation of intrauterine pathologies that clearly demonstrates the hormonal response of the endometrium and provides beneficial information regarding atrophy, infections, or other lesions (Sarwar et al., 2005). In this study, the histopathological results of EC in females aged 21-86 years who had AUB were collected from our outpatient clinic without regard to menopausal status. We also investigated the efficacy of progestins (MPA and megestrol acetate) for 3 and/or 6 months in patients with endometrial hyperplasia.

Materials and Methods

Subjects

Our study included 415 females (mean age, 53.5±8.53 years; range 21-86 years) who underwent EC for AUB during from October 2011 to December 2012 at Duzce Public Hospital, Duzce, Turkey. This study protocol was approved by the Ethics Committee of Duzce University, and written informed consent was obtained from all subjects.

Subjects with isolated endometrial causes of AUB were included, and those with fibroids, cervical, and vaginal and hemostatic disorders were excluded. EC was performed in the late luteal phase under general anesthesia by conventional dilatation and curettage. All specimens were transported to the pathology laboratory in 10% formalin and stained with hematoxylin and eosin. Histopathological results were evaluated, and patients with hyperplasia were identified. Patients with simple hyperplasia were given 10 mg/d MPA orally (Tarlusal™ , Deva, Turkey), 14 days per month for 3 months. Patients with atypia who declined surgery or who were medically unfit to undergo surgery were given 160 mg/d megestrol acetate (MA) orally (Megace™ , Bristol-Meyers Squibb, New York, NY, USA) continuously for 3 months. EC was repeated after hormone therapy. Females diagnosed with regression and persistence at the second curettage while using progestins were offered the same progestin for another 3 months, and were then re-evaluated with a third EC at 6 months following treatment. The results of histopathological evaluations were classified as physiological changes (benign findings and proliferative changes), simple hyperplasia (SH), CH, AH, and CH with atypia (CAH), polyps, or cancer. A progestin was given only to the hyperplasia group. The results were associated with the menopausal status and age differences of the patients.

Statistical analysis

Data are presented as means±standard deviations or as frequencies (percentages). One-way analysis of variance was used to compare the pathology results according to age. Categorical variables were assessed using Pearson's chi-square test. A $p \leq 0.05$ was considered to indicate significance. The PASW ver. 18 (SPSS, Inc., Chicago, IL, USA) software was used for the statistical analysis.

Results

The most common finding in the 415 patients with AUB was benign physiological changes (44.8%). Other results were polyps (30%), SH (21.44%), CH (1.44%), adenocarcinoma (1.2%), CAH (0.72%) and AH (0.2%). The pathology results differed significantly according to age and menopausal status (p=0.008 and 0.002, respectively; Table 1).

Sixty-nine patients with SH of the eighty-nine administered MPA gave feedback regarding control of EC. After the first 3 months of treatment, hyperplasia persisted in 19.7%. The regression rate to benign findings was 77.1%; atypia and progression to CH occurred in 3.2% of the patients. Five patients with CH of the six administered MPA gave feedback regarding control of EC. There was no persistence but one progression. Regression rate was 80%. The patient with hyperplasia and atypia was operated on and removed from the group. Two of the three females with CAH provided feedback. Benign findings were seen in both of the patients at the first control after MA treatment. The feedback rate for the first control EC after progestin in all hyperplasia groups was 67% (Table 2).

Table 1. Pathology Results of First Endometrial Curettage, Menopausal Status, and Mean Age

Result of endometrial curettage,	No* (%)	Menopausal status**	Mean age
Benign,	186 (44.8)	M+ (50) M- (136)	47.3 (±11.4)
Simple hyperplasia,	89 (21.4)	M+ (7) M- (82)	44.4 (±7.6)
Complex hyperplasia,	6 (1.4)	M+ (2) M- (4)	50 (±5.2)
Atypical hyperplasia,	1 (0.2)	M+ (1) M- (0)	52
Complex-atypical hyperplasia,	3 (0.7)	M+ (1) M- (2)	38 (±14.9)
Cancer,	5 (1.2)	M+ (3) M- (2)	55.6 (±8.5)
Polyps,	125 (30.1)	M+ (23) M- (102)	44.4 (±8.9)
Total	415 (100)		

*Number of patients; **M+, postmenopausal period

Table 2. Efficacy of 3 Months of Progestin Therapy

Diagnosis	No. of patient	Follow up* no (%)	Regression (%)	Persistence (%)	Progression (%)
Simple hyperplasia	89	61 (68.5)	77	19.70	3.20
Complex hyperplasia	6	5 (83.3)	80	0	20
Atypical hyperplasia	1	0 (0)**			
Atypical complex hyperplasia	3	2 (66.6)	100	0	0
Total	98	68			

*All patients with endometrial hyperplasia were called for control EC after 3 months of progestin therapy, but not all patients attended the control; **This patient was operated on and excluded from the control group

Table 3. Efficacy of 6 Months of Progestin Therapy

Diagnosis	No. of patient	Follow up* no (%)	Regression (%)	Persistence (%)	Progression (%)
Simple hyperplasia	12	11 (91.6)	8 (72.7)	3 (27.3)	0 (0)
Complex hyperplasia	1	1 (100)	1(100)	0 (100)	0 (0)
Atypical hyperplasia	1	0 (0)**			
Atypical complex hyperplasia	2	1 (50)	1(100)	0 (0)	0 (0)

*Patients who returned for the third endometrial curettage; **Excluded from the control group

The proportion of patients who attended the third EC after 6 months of therapy was 85%. Regression rates were 72.7%, 100%, and 100% for SH, CH, and CAH. No persistence or progression was observed in patients with CH and CAH, but 27.3% of patients with SH exhibited persistence (Table 3).

Discussion

Few studies of AUB have included all ages, because age-related causes are important from an oncological perspective. The majority of our patients had benign findings (44.8%), followed by polyps (30%), endometrial hyperplasia (24%) and adenocarcinoma (1.2%). The proportions of polyps and hyperplasia in EC specimens were greater than those reported previously (Montgomery et al., 2004; Espindola et al., 2007). In a similar study including patients of all ages, benign findings included disordered proliferation (93.4%), polyps (3.9%), hyperplasia (2.5%), and malignancy (0.7%) (Soleymani et al., 2013). When we evaluated the responses to progestin, our regression rates were 77.1% for SH; 80% for CH, and 100% for CAH after 3 months of hormone therapy. We had a limited number of hyperplasia cases (89 cases). Our regression rates after 6 months of hormone therapy were 72.7%, 100%, and 100% for SH, CH, and CAH, respectively. Our persistence and progression rates were 22.9% for SH, 20% for CH, and 0% for CAH after 3 months of therapy, and we identified no persistence or progression in patients after 6 months of therapy.

The SH regression rate has been reported to be 74-80%, with a 1% progression rate (Tabata et al., 2001; Montgomery et al., 2004). In a recent study, complete resolution was found in 72% of 60 cases after 3 months of progestin therapy, with no progression (Tasci et al., 2014). Most studies have focused on only SH or CAH. In a similar study of 31 females aged 30-70 years with endometrial hyperplasia, persistence was evident in 45% following MPA therapy; this was the highest rate reported in the literature. However, all endometrial hyperplasia types were evaluated, as in our study, which might explain the high rate of persistence (Vereide et al., 2003).

Orbo et al. reported that 54% of patients receiving oral MPA (10 mg/day, 10 days) showed responses, whereas spontaneous regression was seen in 50% of the cases after 6 months (Orbo et al., 2008). In contrast, Tabata et al. observed spontaneous regression of endometrial hyperplasia in all risk groups, and the overall regression rates were 79% for SH, 100% for AH, 94% for CH, and 55% for CAH; regression occurred mostly within the first year (Tabata et al., 2001). Clearly, results were improved with a follow-up of longer duration. In a similar study, the regression rates were 96.66% and 3.3% for SH and AH, respectively (Ismail et al., 2013).

In a recent cohort study, the likelihood of histological persistence/progression of CH and AH among females treated with a progestin compared with those not treated was investigated. Females with CAH who received MA had a 69% decreased risk of persistence/progression compared with those who did not receive progestin, and those who received MPA had a 49% decreased risk of persistence/progression (Reed et al., 2009). Those authors concluded that there were no differences in endometrial hyperplasia regression rates in females administered various oral progestogens. Ozdegirmenci et al. reported that the rate of resolution of endometrial hyperplasia without atypia was 96.7% and that of persistence was 3.3% (Ozdegirmenci et al., 2011). Ferenczy and Gelfand used the same MPA protocol as our study and reported a persistence rate of 14% in females without cytological atypia (Ferenczy et al., 1989). We also concluded that most studies of MPA efficacy are based on the results of a 10 days/month protocol.

Another study examined the likelihood of regression of endometrial hyperplasia in relation to progestin therapy. In that study, females with CH without atypia were treated with norethisterone acetate and MPA (10-20 mg/day) for 3-5 months, and a second biopsy was performed. Regression was evident in 61.5% of the patients (Horn et al., 2004). Approximately 60-70% of cases of CH have been reported to respond to progestin treatment (Wang et al., 2003). According to a meta-analysis of nine studies (n=213) of females with SH treated with oral progestins, the regression rate was 89% in 389 females with CH; and in 14 studies with 189 females with AH the regression rate was 69% (Gallos et al., 2010). In a study that had the longest follow-up duration to date, 81 females with CH exhibited regression and persistence rates of 90% and 0.09% respectively. The median duration of follow up was 95.1 months. According to previous studies, the risk of progression or persistence is 0-60% for CH and 10-100% for AH following progestin therapy (Ferenczy et al., 1989; Randall et al., 1997; Horn et al., 2004).

The levonorgestrel-releasing intrauterine system, which has been advocated in many studies, has been found to be superior to oral progestins. However, no randomized studies of the efficacy of all types of oral progestins with an at least 5-year follow-up have been conducted (Gallos et al., 2010; 2012; 2013a; 2013b). The duration and type of progestin therapy, and the optimal biopsy time, remain controversial in females with endometrial hyperplasia. A follow-up biopsy at 3 months following the initial treatment has been suggested as it corresponds to the average response time. A lack of response at the first biopsy (8-12 weeks after initiating treatment) suggests treatment failure (Simpson et al., 2014).

Ca. 60% of females with CAH had concurrent endometrial carcinoma, which is similar to recent reports (Robbe et al., 2012). Therefore, each patient should be evaluated individually and be informed of the risks of medical therapy.

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