

Original Article

The incidence and characteristics of uterine bleeding during postoperative GnRH agonist treatment combined with estrogen-progestogen add-back therapy in endometriosis patients of reproductive age

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Received June 12, 2013; Accepted June 27, 2013; Epub August 1, 2013; Published August 15, 2013

Abstract: To evaluate the incidence and characteristics of uterine bleeding during postoperative gonadotropin-releasing hormone agonist (GnRHa) treatment combined with the lowest effective dose of estrogen-progestogen add-back therapy in Chinese women of reproductive age with endometriosis. Seventy Chinese women aged 18 to 50 years with stage III or IV endometriosis and treated with postoperative GnRHa after conservative surgery for endometriosis were eligible for this study. Patients were randomly divided into two equal groups, G and A. Group G ($n = 35$) received three 28-day cycles of postoperative GnRHa treatment by subcutaneous injection (goserelin, 3.6 mg). Group A ($n = 35$) received the same GnRHa treatment in addition to daily estradiol valerate (0.5 mg) and dydrogesterone (5 mg) add-back therapy. Serum E_2 and FSH levels were assessed at the end of each treatment cycle, as well as incidence and patterns of uterine bleeding. After the last GnRHa treatment cycle, endometrial thickness was evaluated by ultrasonography and the recovery of menstruation was recorded. Uterine bleeding incidence was above 90% in both groups during the first treatment cycle (group G: 90.6%; group A: 93.8%), but decreased markedly in the second treatment cycle (group G: 15.6%; group A: 21.9%), and continued to decline until the end of the third treatment cycle (group G: 6.3%; group A: 12.5%). For each cycle, the incidence of uterine bleeding in group A was slightly but not statistically higher. Irregular spotting was the most common uterine bleeding pattern observed in each of the three treatment cycle. The addition of estrogen and progestogen therapy to a postoperative GnRHa regimen does not lead to an increase in the duration or amount of treatment-induced uterine bleeding.

Keywords: Endometriosis, GnRHa, estrogen, progestogen, add-back therapy, uterine bleeding

Introduction

Endometriosis affects approximately 10% of all women of reproductive age, making it the second most common gynecological condition, after uterine fibroids. Moreover, the incidence of the disease appears to have risen in recent years. The primary symptom associated with endometriosis is pelvic pain, but infertility, dysmenorrhea, abnormal bleeding, dyspareunia and backache may also be present [1]. Surgical treatment may be considered as first-line therapy to remove endometriotic lesions and restore normal reproductive anatomy [2], rates of recurrence after surgery are typically high and will vary based on the severity and duration of the disease (stages I and II: 37%; stages III and

IV: 70%; The stage is confirmed based on the revised American Fertility Society (rAFS) classification) [3, 4]. Gonadotropin-releasing hormone agonist (GnRHa) treatment has been effectively used to control endometriosis-related symptoms as well as preventing postoperative recurrence [5-8]. However, long-term GnRHa treatment is also associated with some significant negative side effects caused by prolonged hypoestrogenism, such as hot flashes, sweating, vaginal dryness and bone loss. In order to alleviate these side effects without reducing therapeutic efficacy, add-back therapy is widely employed in combination with GnRHa treatment.

Our group previously designed a clinical trial aimed at determining the lowest effective dose

Uterine bleeding, GnRH agonist treatment for endometriosis

Table 1. Baseline characteristics

Variable	Group A (n = 32)	Group G (n = 32)	p-Value
Age (yrs)	30.69 ± 6.72	32.19 ± 6.96	NS
Height (cm)	161.94 ± 4.77	161.64 ± 4.70	NS
Weight (kg)	54.34 ± 6.80	53.19 ± 9.84	NS
BMI (kg/m ²)	20.71 ± 2.35	20.32 ± 3.30	NS
r-AFS	35.88 ± 17.20	42.25 ± 23.92	NS
Menstrual cycle (days)	29.03 ± 2.24	29.25 ± 2.48	NS
Menstruation (days)	5.13 ± 0.98	5.38 ± 1.29	NS

Data are expressed as mean ± SD.

of continuous combined estrogen and progestogen add-back therapy for Chinese women with endometriosis being treated with GnRHa. The results of this trial demonstrated that oral continuous combined 0.5 mg/d estradiol valerate and 5 mg/d dydrogesterone as immediate add-back therapy during postoperative GnRHa treatment for severe endometriosis may be the most suitable regimen for Chinese women [9].

However, the uterine bleeding occasioned by the use of estrogen-progestogen add-back therapy leads to fear and discomfort, as well as reduced patient compliance. Therefore, we undertook the present study as a follow-up to those previously reported results [9], in order to evaluate the incidence of uterine bleeding and the inducing factors of uterine bleeding during postoperative GnRH agonist treatment combined with estrogen-progestogen add-back therapy in Chinese women with endometriosis.

Materials and methods

This study was approved by the local ethics committee. Seventy Chinese women of reproductive age (range: 18-50 years) diagnosed by pelviscopy or laparotomy with moderate to severe endometriosis (stages III-IV) according to the revised American Fertility Society (rAFS) classification were recruited from the Obstetrics and Gynecology Hospital of Fudan University, Shanghai, between June 2007 and October 2008. All patients signed an informed consent form prior to the study.

The 70 patients, who were being treated with postoperative GnRHa after conservative surgery (goserelin, Zoladex®, 3.6 mg, subcutaneous injection every 28 days; AstraZeneca, UK), were randomly divided into two equal groups, G

and A. Group G (n = 35) received three cycles of postoperative GnRHa treatment alone, while group A (n = 35) received the same GnRHa treatment in addition to combined daily estradiol valerate (Progynova®, 0.5 mg; Bayer Healthcare Co. Ltd. Guangzhou Branch, China) and dydrogesterone (Duphaston®, 5 mg; Abbott, USA) as add-back therapy.

Serum E₂ and FSH levels as well as uterine bleeding frequency were assessed at the end of each treatment cycle, and after the recovery of menstruation. Uterine bleeding patterns were divided into five types as follows: 0-none, 1-spotting, 2-less than regular menstruation-like bleeding, 3-regular menstruation-like bleeding and 4-more than regular menstruation-like bleeding. Ultrasonography was performed after treatment completion to evaluate endometrial thickness.

Statistical comparisons were made using *t*-tests for continuous variables with homogenous variance. When assumptions of normality were not met, the Mann-Whitney U test was used. Unless specified otherwise, all data are presented as mean and standard deviation (SD), with *p*-values of < 0.05 considered significant.

Results

Demographic profiles

Seventy women of reproductive age with endometriosis were enrolled in this study and split into two postoperative treatment groups. After conservative surgery, group A received GnRHa therapy (goserelin, 3.6 mg) combined with low dose estrogen (estradiol valerate 0.5 mg) and dydrogesterone (5 mg) as daily add-back therapy, and group G received GnRHa therapy alone. One patient in group G discontinued the study after being diagnosed with thyroid disease, and one patient in group A quit after refusing to receive continuous goserelin treatment. In addition, two patients in each group withdrew from the study due to poor drug compliance. No significant differences were observed between the two groups in terms of age, height, weight, body mass index (BMI), regularity of menstrual cycles or stage of endometriosis (Table 1).

Table 2. Frequency of uterine bleeding over three treatment cycles

Group	Frequency of uterine bleeding		
	4 weeks	8 weeks	12 weeks
G (n = 32)	90.6 (29)	15.6 (5)	6.3 (2)
A (n = 32)	93.8 (30)	21.9 (7)	12.5 (4)

Data are expressed as percentage (n).

Ultrasonographic evaluation after completion of treatment

Endometrial thickness was measured by ultrasonography after completion of the third treatment cycle. Median endometrial thickness was 3.5 ± 1.2 mm in group G and 3.5 ± 1.4 mm in group A. There was no statistically significant difference between the two groups.

Return of menses

Menses returned in all patients following the last goserelin injection, after 70.87 ± 14.29 days in group G and 69.41 ± 11.87 days in group A. No significant difference was observed between groups.

Incidence of uterine bleeding

During the first treatment cycle, the incidence of uterine bleeding was above 90% in both treatment groups (group G: 90.6%; group A: 93.8%). During the second treatment cycle, however, bleeding frequency decreased markedly in the two groups (group G: 15.6%; group A: 21.9%), and continued to decline right until the end of the third treatment cycle (group G: 6.3%; group A: 12.5%). In all three treatment cycles, uterine bleeding frequency was higher in group A, but not significantly (**Table 2**).

Bleeding patterns

We divided uterine bleeding patterns into five types and recorded the relative occurrence and duration of these different types during each treatment cycle (**Table 3**). Apart from no bleeding, spotting was the pattern of uterine bleeding most frequently seen in each of the treatment cycles, followed by less than menstruation-like bleeding. Spotting duration was longest in the first treatment cycle for both groups (group G: 18.5%; group A: 12.9%), and decreased significantly in the second treatment cycle (group G: 1.1%; group A: 3.6%).

During the third treatment cycle, spotting duration in group G remained the same as in cycle two (1.1%), while the duration of spotting in group A fell by 50% (1.8%). Overall, there were no statistically significant differences between the two groups in any of the treatment cycles.

Discussion

GnRHa therapy is widely used to treat endometriosis, due to its effectiveness in improving endometriosis-related symptoms and in preventing recurrence [6]. However, treatment with GnRHa is generally limited to 6 months, owing to concerns about the undesired effects of prolonged hypoestrogenism, such as bone loss. It is therefore recommended to combine GnRHa treatment with add-back therapy, in order to reduce hypoestrogenic side effects without compromising therapeutic efficacy [10, 11]. Various add-back therapies have been tested to date, including estrogen only, estrogen plus progestin, progestin only, and tibolone. Currently, however, no overall consensus exists among specialists as to the optimal add-back therapy [10].

Estradiol valerate is a synthetic esterified form of natural 17β -estradiol, the most potent endogenous human ovarian estrogen, and is rapidly hydrolyzed to estradiol after oral administration [12, 13]. Dydrogesterone is a retroprogesterone derivative that is similar in structure and pharmacology to endogenous progesterone. Dydrogesterone has demonstrated its efficacy in relieving the symptoms of endometriosis and preventing uterine bleeding in several studies, even leading to the regression of lesions and to improved rates of pregnancy in infertile patients [14, 15]. A large body of evidence has also shown that treatment with continuous oral estradiol in combination with sequential dydrogesterone is effective in relieving climacteric symptoms and preserving bone mineral density in postmenopausal women [16]. Barbieri [17] claimed that the serum estradiol levels over a range of 20-40 pg/ml would stimulate the endometriotic lesions to grow, and the estradiol levels below 20 pg/ml would cause the bone loss markedly. Therefore, the E_2 within a range of 30-45 pg/ml has been demonstrated to relieve menopausal symptoms and minimize the risk of bone loss without compromising the treatment of endometriosis [17]. Hornstein et al. [18] proposed that the E_2 levels should be

Uterine bleeding, GnRH agonist treatment for endometriosis

Table 3. Uterine bleeding patterns over three treatment cycles

Group	Bleeding pattern				
	4 weeks (Treatment cycle 1)				
	0	1	2	3	4
G	17.6 ± 5.8 (62.6)	5.2 ± 4.8 (18.5)	2.9 ± 2.5 (10.3)	2.2 ± 2.2 (7.8)	0.2 ± 0.8 (0.8)
A	18.3 ± 4.9 (65.4)	3.6 ± 2.5 (12.9)	2.5 ± 2.3 (8.9)	3.1 ± 2.6 (11.1)	0.5 ± 1.7 (1.7)

Group	Bleeding pattern				
	8 weeks (Treatment cycle 2)				
	0	1	2	3	4
G	27.4 ± 1.6* (98.2)	0.3 ± 0.8* (1.1)	0.2 ± 1.0* (0.7)	0.0 ± 0.0* (0)	0.0 ± 0.0* (0)
A	26.7 ± 2.5* (95.4)	1.0 ± 1.9* (3.6)	0.3 ± 1.3* (1)	0.0 ± 0.0* (0)	0.0 ± 0.0 (0)

Group	Bleeding pattern				
	12 weeks (Treatment cycle 3)				
	0	1	2	3	4
G	27.6 ± 1.6* (98.9)	0.3 ± 1.3* (1.1)	0.0 ± 0.2* (0)	0.0 ± 0.2* (0)	0.0 ± 0.0 (0)
A	26.9 ± 3.1* (96.1)	0.5 ± 1.3* (1.8)	0.5 ± 1.7* (1.8)	0.1 ± 0.5* (0.3)	0.0 ± 0.0 (0)

Data are expressed as mean days ± SD (percentage). 0: No bleeding; 1: Spotting; 2: Less than menstruation-like bleeding; 3: Menstruation-like bleeding; 4: More than menstruation-like bleeding. * $p < 0.01$ between treatment cycle 1 and treatment cycle 2 or 3 for a given bleeding pattern. * $p < 0.05$ between treatment cycle 1 and treatment cycle 2 or 3 for a given bleeding pattern.

controlled below 30 pg/ml in order to alleviate pain. In our study, add-back therapy consisting of estradiol valerate (0.5 mg/d) and dydrogesterone (5 mg/d), combined with postoperative GnRHa treatment, successfully maintained E_2 levels within the effective therapeutic range (25.61 ± 19.36 pg/ml), preventing boss loss while simultaneously alleviating endometriosis-related pain partially [9]. Our findings thus further confirm that this combination constitutes a safe and effective treatment for endometriosis.

The initial month of GnRHa treatment is often associated with irregular vaginal bleeding of variable duration and intensity, possibly due to an initial rise in estrogen levels followed by withdrawal. After this initial stimulatory phase, pituitary gonadotropins are inhibited, resulting in ovarian suppression and thus estrogen deficiency. Large fluctuations in serum estradiol levels within a short time frame can lead to an imbalance between estrogen and progestin levels, ultimately resulting in endometrial breakthrough bleeding.

It has been reported that uterine bleeding can occur in postmenopausal women undergoing hormone therapy and with endometrial thicknesses of less than 5 mm, even though pathological examination did not reveal any endometrial anomalies [19, 20]. In our study, uterine

bleeding characteristics after two treatment cycles were similar to those observed in postmenopausal women undergoing hormone replacement therapy, which may indicate that the factors underlying uterine bleeding in these two cases are also similar. Limited data currently suggest that hormone therapy can alter endometrial vascular, stromal and endothelial compartments in a manner which may increase vascular fragility, thus leading to abnormal bleeding [21, 22].

In 1992, Barbieri put forward the 'estrogen threshold hypothesis', which postulates that a certain concentration of estrogen can be achieved that will not stimulate endometriotic lesions while still preventing hypoestrogenic side effects [17]. This hypothesis was founded on the assumption that such a threshold would remain a range across different individuals. In view of individual variations in drug absorption, a fixed, standard dose of estrogen might be too much or too little for some women. Therefore, uterine bleeding associated with add-back therapy might also be explained by individual variations in the therapeutic window, as was previously found to be the case for tibolone add-back therapy [2].

In summary, the addition of estrogen and progestogen therapy to a postoperative GnRHa regimen does not lead to an increase in the

duration or amount of treatment-induced uterine bleeding.

Acknowledgements

This work was supported by a grant from the National Natural Science Foundation of China (No. 81200415) and a grant from the Ph.D. Programs Foundation of the Ministry of Education of China (No. 20090071120020).

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Uterine bleeding, GnRH agonist treatment for endometriosis

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