International Journal of Gynecology and Obstetrics 104 (2009) 236–239

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

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

CLINICAL ARTICLE

Gonadotropin-releasing hormone analog combined with a low-dose oral contraceptive to treat heavy menstrual bleeding

Nadire N. Cetin [a], Onur Karabacak [a,b,*], Umit Korucuoglu [a], Nese Karabacak [c]

[a] Department of Obstetrics and Gynecology, Gazi University Faculty of Medicine, Ankara, Turkey
[b] Department of Population and Family Health Sciences, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA
[c] Department of Nuclear Medicine, Gazi University Faculty of Medicine Ankara, Turkey

ARTICLE INFO

Article history:
Received 10 July 2008
Received in revised form 29 September 2008
Accepted 8 October 2008

Keywords:
GnRH analog
Combined therapy
Heavy menstrual bleeding
Oral contraceptives
Treatment

ABSTRACT

Objective: To compare the effects of low-dose oral contraceptives used alone and in combination with a gonadotropin-releasing hormone (GnRH) analog to treat heavy menstrual bleeding. *Methods:* Fifty-eight patients with heavy menstrual bleeding were prospectively randomized into two treatment groups to receive either a low-dose oral contraceptive alone (group 1), or combined with a GnRH analog (group 2) for 6 months. The patients' hormonal profiles, and hemoglobin and hematocrit levels were measured at the beginning and at the end of the treatment period. *Results:* Hemoglobin and hematocrit levels significantly improved in both groups after 6 months of treatment ($P<0.05$ and $P<0.01$, respectively). Even in the first month of the study, the number of pads used and the duration of menstruation were significantly decreased in both groups and markedly lower in group 2 ($P<0.01$). *Conclusion:* The addition of a GnRH analog to low-dose oral contraceptive treatment for heavy menstrual bleeding resulted in better control of vaginal bleeding, even in the first month of therapy.

1. Introduction

The menstrual cycle is typically 28 days, and menstruation generally lasts around 4 days, where the mean volume of bleeding has been reported as 40±20 mL [1,2]. "Heavy menstrual bleeding," suggested by Fraser et al. [3,4] as the international term to describe abnormal uterine bleeding, may result from organic diseases such as uterine fibroids, endometrial polyps, or endometrial cancer; from systemic problems, such as thyroid function disorders or coagulation disorders; or simply from use of anticoagulant drugs. In 30% of cases, no organic disease is determined and the cause is irregular and mostly anovulatory bleeding, a condition formerly termed dysfunctional uterine bleeding [5,6].

Heavy, irregular, menstrual bleeding is generally managed by oral contraceptives or cyclic progesterone administration [7]. Danazol and gonadotropin-releasing hormone (GnRH) analogs are not used as first-line therapeutic agents because of adverse side effects [8]. However, studies have shown that combined use of GnRH analogs with hormone-replacement therapies dramatically reduced the unwanted side effects, enabling the use of these agents for longer periods of time [9,10]. Based on these findings, the aim of the present study was to compare the effects of a low-dose, third-generation, oral contraceptive alone and in combination with a GnRH analog to treat heavy, irregular, menstrual bleeding.

2. Material and methods

Sixty-one patients who were referred to the Department of Obstetrics and Gynecology, Gazi University Faculty of Medicine, with heavy menstrual bleeding were included in the study, which was conducted between January 2002 and December 2003. All patients underwent transvaginal pelvic ultrasound, endometrial curettage, and diagnostic tests for systemic and endocrine abnormalities. Patients with uterine fibroids, endometrial polyps, endometrial hyperplasia, endometrial cancer, systemic disorders (chronic liver or renal disease), and endocrine abnormalities (ie, hyperprolactinemia, hypothyroidism) were excluded from the study. Patients with a contraindication for oral contraceptives were also excluded. These contraindications consisted of heavy smoking, severe systemic disorders, such as hypertension, or an elevated body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters).

During the study, all patients paid for their medicine. Institutional Review Board (IRB) approval was obtained from the Local Ethics Committee of Gazi University Faculty of Medicine. Each patient's informed consent was obtained before inclusion in the study.

A prospective, randomized treatment protocol was developed for the patients diagnosed with "heavy menstrual bleeding" and two treatment groups were formed using a random numbers table (Fig. 1). Group 1, consisting of 29 patients, received cyclic therapy with an oral

* Corresponding author. PO Box 61-06500 Besevler, Ankara, Turkey. Tel.: +90 543 468 8866; fax: +90 312 428 6677.
E-mail address: okarabacak@gmail.com (O. Karabacak).

0020-7292/$ – see front matter
doi:10.1016/j.ijgo.2008.10.032

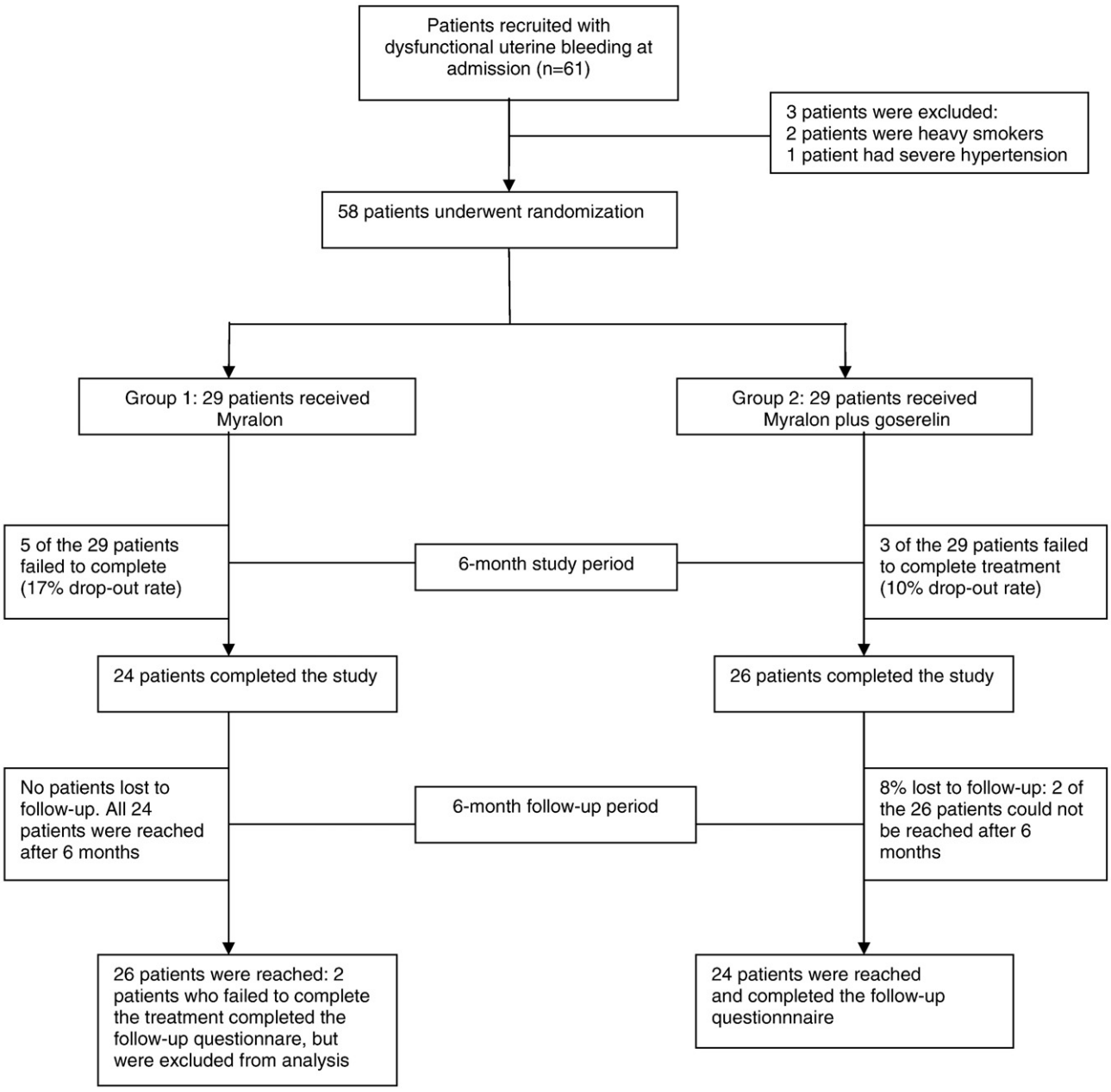

Fig. 1. Flow-chart of the study: 6-month study period and additional 6-month follow-up period.

contraceptive containing 20 μg of ethinyl estradiol and 150 μg of desogestrel (Myralon; Organon, Oss, Netherlands). Group 2, consisting of 29 patients, received 10.8 μg of the GnRH analog goserelin (Zoladex; AstraZeneca, London, UK) for 3 months (each patient received 2 GnRH analog injections within the 6-month treatment period) combined with the same oral contraceptive given to group 1. Both treatment protocols were applied for 6 months.

Blood samples were taken from all patients both at presentation and after completion of therapy. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone, testosterone, thyroid-stimulating hormone (TSH), free thyroxine (FT4), and prolactin were determined using immunoassay kits (Diagnostic Products Corporation, Los Angeles, CA, USA). The overall sensitivity was 0.6%–0.9%, and inter and intra-assay variability was 2%–8% and 3%–7% of the coefficient of variation, respectively. Hemoglobin and hematocrit values were evaluated for all patients before treatment and after completion of therapy using STKS and Gen-S hematology analyzers (Beckman Coulter, Fullerton, CA, USA).

All patients were instructed to record their bleeding pattern each month on a chart. They were asked to change their sanitary pads when a 5-cm diameter area stained with blood was observed, and to note the number of pads they used.

After completion of treatment, all patients were followed-up for the next 6 months. Their bleeding patterns, major and minor surgeries performed during the follow-up period, and patient satisfaction were evaluated via a telephone interview, and data were collected using a predefined questionnaire. The questionnaire included information about the patients' daily activities, bleeding patterns, and quality of life. The final question was whether or not the patient was satisfied with the treatment (Fig. 1).

Data analysis was carried out using SPSS version 11.0 (SPSS, Chicago, IL, USA). Data were expressed as mean ± SD. Baseline

characteristics and values in the 2 groups were compared using an independent sample *t* test. The change in hormonal parameters and hemoglobin and hematocrit values for both groups during the 6-month treatment period were evaluated using the Wilcoxon test. The range of change was defined as (B–A/B)×100, where A is the pretreatment value and B the post-treatment value. The difference between the percentage change in group 1 and group 2 was tested using the Mann–Whitney U test. $P<0.05$ was considered significant.

3. Results

Of the 61 women recruited to the study, 3 were excluded (2 women were heavy smokers and 1 woman had severe hypertension), leaving 58 women randomized to the two treatment groups (29 in each). A total of 5 patients in group 1 and 3 patients in group 2 failed to complete the study and were excluded from the analysis.

There were no significant differences between the 2 groups in terms of age, weight, body mass index, number of previous pregnancies, or endometrial thickness ($P>0.05$; Table 1). Pretreatment FSH, LH, E2, progesterone, testosterone, TSH, FT4, prolactin, hemoglobin, and hematocrit levels were also similar in both groups ($P>0.05$).

In group 1, the mean percentage change in FSH levels after 6 months of treatment was −10%, whereas this change was −50% in group 2 ($P<0.05$). In group 1 the mean percentage change in E2 after 6 months of therapy was −51%, whereas this change was −73% in group 2 ($P<0.01$).

Hemoglobin and hematocrit values improved significantly after 6 months of treatment in both groups, without any supplementation or dietary modifications ($P<0.05$ and $P<0.01$, respectively). After 6 months, mean hemoglobin level had increased from 11.5±1.7 to 13.3±1 in group 1 and from 11.4±1.0 to 13.8±0.6 in group 2. When evaluated as a percentage change, the 16% change in group 1 was similar to the 19% change in group 2 ($P>0.05$). Mean hematocrit level had increased from 34.6±4.4 to 40.3±3.3 in group 1 and from 34.4±1.8 to 42.1±2.2 in group 2. When evaluated as a percentage change, the 18% change in group 1 was similar to the 21% change in group 2 ($P>0.05$).

Endometrial sampling performed before the initiation of treatment revealed a proliferative endometrium in all patients. Both groups of patients underwent endometrial sampling at the end of the 6-month treatment program (Table 2). Of the 29 patients in group 1, 17 (58.6%) had a secretory endometrium and 5 (17.2%) had a proliferative endometrium. An atrophic endometrium was detected in only 5 (17.2%) women in this treatment group. Of the 29 patients in group 2, 24 (82.8%) were diagnosed with an atrophic endometrium. A proliferative endometrium was detected in only 1 (3.4%) patient and a secretory endometrium was seen in only 2 (6.9%) patients in group 2.

Table 1
Distribution of baseline characteristics, pretreatment endometrial thicknesses, hormonal profiles, and hematologic parameters[a]

	Group 1: low-dose oral contraceptive only (n=29)	Group 2: low-dose oral contraceptive plus GnRH analog (n=29)	*P* value
Age, y	43.3±6.4 (33–49)	43.0±6.3 (35–48)	>0.05
Weight, kg	68.2±5.2 (51.5–86.7)	69.6±5.6 (49.5–88.8)	>0.05
Body mass index[b]	24.6±1.6 (19.2–28.7)	25.2±1.8 (20.4–27.9)	>0.05
Number of pregnancies	4.0±2.3	4.4±2.5	>0.05
Endometrial thickness, mm	7.7±2.8 (4–13)	9.1±3.2 (5–17)	>0.05
Hemoglobin, g/dL	11.5±1.7	11.4±1	>0.05
Hematocrit, %	34.6±4.5	34.2±1.8	>0.05

[a] Values are given as mean±SD (range).
[b] Body mass index calculated as weight in kilograms divided by square of height in meters.

Table 2
Results of endometrial biopsies at the end of the treatment period[a]

	Group 1: low-dose oral contraceptive only (n=29)	Group 2: low-dose oral contraceptive plus GnRH analog (n=29)	*P* value
Atrophic endometrium	5 (17.2)	24 (82.8)	<0.001
Proliferative endometrium	5 (17.2)	1 (3.4)	>0.05
Secretory endometrium	17 (58.6)	2 (6.9)	<0.001
Endometritis	2 (6.9)	2 (6.9)	>0.05

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

The incidence of endometritis was similar in both treatment groups ($P>0.05$).

In both treatment groups bleeding was also evaluated by the number of sanitary pads used as reported by the women. At the first menstruation after initiation of treatment there was a significant difference in the mean number of pads used, with fewer used in group 2 than in group 1 (10.4±1.5 vs 13.5±3.1 pads, $P<0.01$). The mean duration of the first menstruation after the initiation of treatment was 6.4±1.7 days in group 1 and 4.7±0.6 days in group 2 ($P<0.01$). When the mean total number of pads used at the end of the 6-month treatment period was evaluated, significantly fewer pads had been used by patients in group 2 compared with group 1 (47.3±6.6 vs 52.3±7.1 pads, $P<0.05$). The mean number of pads used at the end of the 6-month treatment period was significantly lower for patients in group 2 compared with group 1 (7.9±1 vs 8.7±1.2 pads, $P<0.05$). The mean duration of menstruation at the end of the 6-month period was again significantly lower in group 2 than in group 1 (3.9±0.5 vs 4.5±0.8 days, $P<0.01$).

Because GnRH analogs were introduced a second time to the patients in group 2 at the end of 3 months, the mean number of pads used in both groups was evaluated separately, both after 3 months and after 6 months. The mean total number of pads used was 10.6±1.9 after 3 months and 7.5±1 after 6 months for group 1, and 8.7±2.8 after 3 months and 7.4±2.6 after 6 months for group 2. The difference between 3 and 6 months was significant in both groups ($P<0.05$). However, the difference between the groups was significant after 3 months, but was insignificant after 6 months ($P>0.05$).

No major or minor adverse effects occurred within the treatment period. There were no hypoestrogenic adverse effects, such as vaginal dryness or hot flushes, caused by the combination of the GnRH analog and low-dose oral contraceptive. The degree of satisfaction of the women in the 2 groups was also evaluated 6 months after the 6-month treatment period. All patients were telephoned to participate in an interview. Twenty-six patients in group 1 and 24 patients in group 2 completed the interview; the remaining patients could not be contacted or did not want to participate. Fifty-four percent of patients treated with the low-dose oral contraceptive only declared their satisfaction with the treatment, whereas 92% of patients treated with the low-dose oral contraceptive combined with a GnRH analog stated they were satisfied with the treatment ($P<0.05$).

No patients underwent a hysterectomy within the 6-month follow-up period. However, 7 (27%) patients in group 1 and 3 (12.5%) patients in group 2 underwent curettage at other health centers for diagnostic or therapeutic purposes. When these patients were excluded, because they had received follow-up surgical therapy, 58% of all patients appeared to be successfully treated medically at the end of 1 year or after 6 months of follow-up. There were no differences between the 2 groups regarding the requirement of additional therapy after the 6-month treatment period ($P>0.005$).

Among patients in group 2, more than 60% had amenorrhea and received cyclic progesterone as treatment, however in group 1, only 20% had amenorrhea. The transition to menopause was similar in both groups (17% in group 1 vs 19% in group 2). In our study, 80% of patients in group 1 who needed additional therapy after the 6-month treatment period were treated with oral contraceptives.

4. Discussion

Anovulatory, irregular, heavy menstrual bleeding is classically managed by either combined oral contraceptives or cyclic progesterone [11]. GnRH analogs result in medical castration by inhibition of ovarian steroid synthesis via the suppression of gonadotropin release from the pituitary gland [12]. By the same mechanism they can cause hypoestrogenic adverse effects, such as vasomotor symptoms, vaginal dryness, and osteopenia [9,12]. Although they have been found to be effective in the treatment of heavy menstrual bleeding [13], their use is limited due to these complications. However, recent reports on the successful use of GnRH analogs combined with hormone-replacement treatments in the treatment of estrogen-dependent diseases, such as endometriosis and uterine fibroids [14], have encouraged clinicians to use GnRH analogs in the management of heavy menstrual bleeding. Thomas et al. [10] used GnRH analogs in combination with cyclic hormone-replacement therapy (estradiol valerate 1 mg/day for 11 days and estradiol valerate 1 mg/day plus norgestrel 0.5 mg/day for 10 days) for 3 cycles. They reported a significant decrease in the quantity and duration of bleeding with tolerable side effects.

We designed the present prospective, randomized, clinical study to investigate the use of GnRH analogs to treat heavy menstrual bleeding. The addition of a GnRH analog to a low-dose oral contraceptive treatment created a significant difference in the control of FSH, LH, and E2 levels compared with low-dose oral contraceptive therapy alone. Combined therapy was associated with a significantly higher incidence of atrophic endometrium at 6-month endometrial sampling, whereas the prominent biopsy result was secretory endometrium in the low-dose oral contraceptive only treatment group. This difference in functioning mechanisms is undoubtedly related to the suppressive effect of the GnRH analog on pituitary gonadotropins. Although the combined therapy appeared to be more effective in controlling acute bleeding and preventing recurrent abnormal uterine bleeding than low-dose oral contraceptives alone, the changes in hemoglobin and hematocrit values were similar in both groups and both treatment protocols were successful in treating anemia. We conclude that because GnRH analog treatment is relatively more expensive, it should not be used as a first-line treatment for anemia.

In a similar study, Franke et al. [15] concluded that the addition of combined estradiol/norethisterone acetate therapy to goserelin acetate treatment for heavy menstrual bleeding in perimenopausal women initially prevented bone loss and improved climacteric complaints, while having no negative impact on vaginal bleeding or abdominal pain [15]. Although in support of our findings that the addition of a GnRH analog resulted in beneficial effects, the study design by Franke et al. was different and the patients were randomized to receive either a GnRH analog alone or combined with an oral contraceptive. Thus, the study by Franke et al. focused on the beneficial effects of the addition of an oral contraceptive to a GnRH analog treatment, whereas the present study mainly focused on the beneficial effects of the addition of a GnRH analog to oral contraceptive treatment.

The levonorgestrel intrauterine system is recommended in the NICE guideline as the first-line therapy for heavy menstrual bleeding [16]. We did use a levonorgestrel intrauterine system in the present study owing to the degree of bleeding in the patients.

In conclusion, in patients with heavy menstrual bleeding, the addition of a GnRH analog to low-dose oral contraceptive treatment resulted in prompt and improved control of vaginal bleeding, even in the first month of treatment. Because of the significant hormonal decreases, remarkable endometrial atrophy was achieved by the sixth month. At the additional 6-month follow-up interview, patients who underwent the combined treatment experienced 40% more amenorrhea and reported better patient satisfaction.

The present study suggests that the combination of 1 month of treatment with an effective GnRH analog may be enough for prompt control of vaginal bleeding. In order to correct low hemoglobin and hematocrit levels, both treatments are effective, but low-dose oral contraceptives are cheaper. If long-term amenorrhea is the objective, a 6-month course with addition of a GnRH analog is beneficial.

References

[1] Long CA, Gast MJ. Menorrhagia. Obstet Gynecol Clin N Am 1990;17(2):343–59.
[2] Long CA. Evaluation of patients with abnormal uterine bleeding. Am J Obstet Gynecol 1996;175(3 p 2):784–7.
[3] Fraser IS, Critchley HO, Munro MG, Broder M. Can we achieve international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding? Hum Reprod 2007;22(3):635–43.
[4] Fraser IS, Critchley HO, Munro MG, Broder M. A process designed to lead to international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding. Fertil Steril 2007;87(3):466–76.
[5] Brenner PF. Differential diagnosis of dysfunctional uterine bleeding. Am J Obstet Gynecol 1996;175(3 pt 2):766–9.
[6] Field CF. Dysfunctional uterine bleeding. Prim Care 1988;15(3):561–75.
[7] Shwayder JM. Pathophysiology of abnormal uterine bleeding. Obstet Gynecol Clin N Am 2000;27(2):219–34.
[8] Agarwal N, Kriplani A. Medical management of dysfunctional uterine bleeding. Int J Gynecol Obstet 2001;75(2):199–201.
[9] Laufer MR, Rein MS. Treatment of abnormal uterine bleeding with gonadotrophine-releasing hormone analogues. Clin Obstet Gynecol 1993;36(3):668–78.
[10] Thomas EJ, Okuda KJ, Thomas NM. The combination of a depot gonadotropin-releasing hormone agonist and cyclical hormone replacement therapy for dysfunctional uterine bleeding. Br J Obstet Gynecol 1991;98(11):1155–9.
[11] Munro MG. Medical management of abnormal uterine bleeding. Obstet Gynecol Clin N Am 2000;27(2):287–305.
[12] Henzl MR. Gonadotropin-releasing hormone and its analogues: from laboratory to bedside. Clin Obstet Gynecol 1993;36(3):617–35.
[13] Petrucco OM, Fraser IS. The potential for the use of GnRH agonists for treatment of dysfunctional uterine bleeding. Br J Obstet Gynaecol 1992;99(Suppl 7):34–6.
[14] Barbieri RL. Gonadotropin-releasing hormone agonists and estrogen–progesterone replacement therapy. Am J Obstet Gynecol 1990;162(2):593–5.
[15] Franke HR, Snaaijer FF, Houben PW, van der Mooren MJ. Treatment of dysfunctional uterine bleeding in the perimenopause: the effects of adding combined estradiol/norethisterone acetate therapy to goserelin acetate treatment—a randomized, placebo-controlled, double-blind trial. Gynecol Endocrinol 2006;22(12):692–7.
[16] National Collaborating Centre for Women's and Children's Health. Heavy menstrual bleeding. Clinical Guideline. London: NICE; 2007.