Continuous oral or intramuscular medroxyprogesterone acetate versus the levonorgestrel releasing intrauterine system in the treatment of perimenopausal menorrhagia: a randomized, prospective, controlled clinical trial in female smokers

T. Küçük[1], K. Ertan[2]

[1]*Department of Obstetrics and Gynecology, GATA School of Medicine, Ankara (Turkey)*
[2]*Department of Obstetrics and Gynecology, University Clinic Homburg, Saar (Germany)*

Summary

Objective: To compare the efficacy of three progestin regimens in perimenopausal menorrhagia. *Design:* One hundred thirty-two women with menorrhagia were included in this prospective, randomized, comparative trial. Women were randomized to three groups of 44 in each, either to get a single shot of depot medroxyprogesterone acetate, intramuscularly (Group 1), or medroxyprogesterone acetate in a daily dose of 5 mg orally (Group 2), or the levonorgestrel releasing intrauterine system (LNG-IUS) (Group 3). The Mann-Whitney U-test was applied to compare independent groups. *Results:* Pictorial blood loss assessment chart (PBAC) score, the duration of bleeding and mean hemoglobin level were improved in all groups. Comparing the groups we noted that for the PBAC, there was no statistically significant difference between groups 1 and 2, while group 3 was superior to both groups 1 and 2 ($p < 0.05$ and $p < 0.05$, respectively). Mean duration of menstruation showed no differences among the groups. Hemoglobin levels were no statistically significant differences between groups 1 and 2, while group 3 was superior to both groups 1 and 2 ($p < 0.05$ and $p < 0.05$, respectively). *Conclusion:* The efficacies of oral and intramuscular medroxyprogesterone acetate in the treatment of menorrhagia were comparable each other, however, the efficacy of LNG-IUS was superior to both.

Key words: Menorrhagia; Perimenopause; Progestin; Medroxyprogesterone acetate; LNG-IUS.

Introduction

Dysfunctional uterine bleeding is one of the most common complaints during the perimenopausal transition [1]. It is defined as abnormal bleeding in the absence of pelvic organ disease or systemic disease and therefore is a diagnosis of exclusion. It is estimated that a woman has a life-time chance of 1: 20 to consult her gynecologist for complaints due to dysfunctional uterine bleeding [2]. Twenty-five percent of all gynecologic operations center around the clinical problem of abnormal uterine bleeding during this period [3]. Perimenopausal bleeding disorders can be challenging for the clinician. The differential diagnosis in recent years is vast, as anatomic, hormonal, and metaplastic processes have a higher incidence.

Dysfunctional uterine bleeding can be anovulatory, characterized by irregular unpredictable bleeding, or ovulatory, characterized by heavy but regular periods (i.e., menorrhagia) [4]. On the other hand, anovulation can manifest in different ways, ranging from amenorrhea to intermittent spotting to erratic, prolonged, heavy menses. This further adds to the difficulty of the diagnosis and the management. Ten to thirty percent of menstruating women experience menorrhagia during their reproductive lives, especially at the both ends of the reproductive period [5].

Since only 40-50% of the women who complain of heavy menstrual bleeding suffer from objective menorrhagia, it is important to quantify the amount of menstrual blood loss. To obtain a semi-quantitative measurement of menstrual blood loss, Higham *et al*. developed a pictorial blood loss assessment chart [6]. Jansen *et al*. investigated the usefulness of a modified pictorial chart in a large study, and recommended a cut-off score of 185 for the diagnosis of menorrhagia [7]. Although the use of a pictorial chart might implicate misclassification of menorrhagia, the method is clearly more accurate than history alone. Menstrual blood loss can be measured objectively by the alkaline hematin method, which defines a cut-off score for menorrhagia of 80 ml per cycle. However, patient selection in dysfunctional uterine bleeding trials is often not defined, such as blood loss in excess of 80 ml or as increase in pictorial chart score.

Progestins are the cornerstone of most hormonal treatments of menorrhagia. Progestins mediate downregulation of endometrial estrogen receptors to blunt proliferation. They facilitate the conversion of estradiol to less potent estrone through activation of 17-β hydroxysteroid dehydrogenase [8]. Progestin treatment in dysfunctional uterine bleeding can be given in various forms and dosages and protocols [9-11]. For the last decade, progestin-delivering intrauterine devices have introduced a novel modality for progestin treatment. The levonorgestrel releasing intrauterine system (LNG-IUS) was developed for contraceptive purposes, but also provides

Revised manuscript accepted for publication December 6, 2007

several noncontraceptive health benefits. Experience in women using Mirena (releasing 20 mcg levonorgestrel a day) for contraception demonstrated a significant decrease in menstrual flow [12].

The objecitive of the present trial was to compare the efficacy of continuous oral or intramuscular medroxyprogesterone acetate to levonorgestrel-releasing intrauterine system in perimenopausal women with menorrhagia.

Material and Method

Patient selection

Four hundred and five perimenopausal patients were admitted to our center because of irregular and/or heavy vaginal bleeding between August 2005 and May 2006. The term "perimenopause" refers to women over age 40 in this study. The diagnosis of menorrhagia was established after the following diagnostic work-up: Hemogram, modified pictorial blood loss assessment chart, prothrombin time, activated prothrombin time, ALT, AST, hormonal profile including FSH, LH, estradiol, prolactin, β-HCG, sTSH, T_3, T_4, Pap smear, endometrial biopsy, transvaginal sonography and saline infusion sonography, and diagnostic office hysteroscopy when needed. Patients were not included in the study when an organic pathology was found.

Using this evaluation protocol, 32 women were excluded because they were having only irregular bleeding but were non-menorrhagic; they were given cyclic progestin treatment. Of the rest, 229 patients were nonsmokers and were given combined oral contraceptive pills; they were not included in the study. One hundred and forty-four women were diagnosed as menorrhagia, but 12 of them refused to participate in the study. One hundred and thirty-two were included in the study. Institutional Review Board approval and signed informed consents were obtained.

Baseline demographic characteristics were as follows: mean age was 43.8 ± 2.9 years, mean parity was 1.9 ± 0.6, mean BMI was 27.9 ± 4.7 kg/m^2, and the percentage of smokers was 100% because the non-smokers were given combined oral contraceptive pills. Occasional smokers were also excluded. Forty-four patients were scheduled for each arm of the study. Randomization was performed by a predefined application order. The first applicant to the first group, the second applicant to the second group and the third applicant to the third group, and so on.

Treatment groups

Group 1 consisted of 44 women who were given a single shot of depot medroxyprogesterone acetate (DMPA) (Depo Provera ampoule, Eczacibasi, Istanbul, Turkey) intramuscularly on the first day of the cycle.

Group 2 consisted of 44 women who were given daily medroxyprogesterone acetate (MPA) (Farlutal tablets, Deva, Istanbul, Turkey) in a dose of 5 mg orally every day, starting on the first day of the cycle.

Group 3 consisted of 44 women who received the LNG-IUS (Mirena, Schering, Berlin, Germany) on the second or third day of the cycle. Patients were not prescribed iron supplements and were advised to stay on their usual diet.

Demographic characteristics of the patients randomized to groups are given in Table 1.

Patients continued to give blood samples for hemograms every month and continued to record a modified pictorial blood loss assessment chart (PBAC) score for each treatment cycle.

Table 1. — *Patient characteristics after randomization to the groups*.

	Group 1 (DMPA)	Group 2 (daily MPA)	Group 3
Mean age (years)	43.1 ± 1.6	42.6 ± 1.9	42.8 ± 1.1
Mean parity (number)	1.8 ± 0.4	1.9 ± 0.6	1.9 ± 0.3
Mean BMI (kg/m^2)	27.1 ± 4.4	26.4 ± 3.9	29.1 ± 3.3
Smoker (%)	100	100	100

MPA: medroxyprogesterone; DMPA: depot medroxyprogesterone; LNG-IUS: levonorgestrel releasing intrauterine system.

When the menstrual blood loss score was > 185 on the PBAC in the second treatment cycle it was considered as unresponsiveness to the treatment. Response was pre-defined as a score < 185 in the modified PBAC and stabilization and/or any increase of hemoglobin level.

Patients were followed-up for six months. No drop-outs occurred in any arm of the study.

Statistical analysis

Statistical analyses were performed using SPSS 10.0 (Chicago, USA). Pretreatment values were compared to treatment cycle 2 values. The Mann-Whitney U-test was applied to compare two independent groups. A p value of < 0.05 was accepted as statistically significant.

Results

In group 1 the treatment was successful in 33 of 44 women (75%). The modified pictorial blood loss assessment chart score decreased significantly in the second treatment cycle, from 284 ± 50 units to 146 ± 21 units ($p < 0.001$). The duration of bleeding was 9 ± 2 days pretreatment, which decreased to 7 ± 1 days in the second cycle of the treatment ($p < 0.001$). Mean hemoglobin level was 9.7 g/dl pretreatment and it increased to 10.2 g/dl in the second cycle of the treatment ($p < 0.01$) (Table 2).

Table 2. — *Results in the depot medroxyprogesterone acetate (DMPA) group*.

DMPA	Pretreatment	Cycle 2	p
Pictorial blood loss score (units)	284 ± 50	146 ± 21	$p < 0.001$
Mean duration of menstruation (days)	9 ± 2 7-11	7 ± 1 5-8	$p < 0.001$
Hemoglobin (g/dl)	9.7 ± 0.4	10.2 ± 0.4	$p < 0.01$

In group 2 the treatment was successful in 30 of 44 women (68%). The modified PBAC score decreased significantly at the second treatment cycle, from 230 ± 36 units to 154 ± 30 units ($p < 0.001$). The duration of bleeding was 9 ± 1 days pretreatment, which decreased to 5 ± 1 days in the second cycle of the treatment ($p < 0.001$). Mean hemoglobin level was 10.2 g/dl pretreatment and it increased to 10.8 g/dl in the second cycle of the treatment ($p < 0.01$) (Table 3).

In group 3 the treatment was successful in 38 of 44 women (86%). The modified PBAC score decreased significantly in the second treatment cycle, from 287 ± 57 units to 77 ± 41 units ($p < 0.001$). The duration of bleed-

Table 3. — *Results in the daily medroxyprogesterone acetate (MPA) group.*

MPA	Pretreatment	Cycle 2	p
Pictorial blood loss score (units)	230 ± 36	154 ± 30	p < 0.001
Mean duration of menstruation (days)	9±1 8-11	5±1 4-7	p < 0.001
Hemoglobin (g/dl)	10.2 ± 0.7	10.8 ± 0.7	p < 0.01

ing was 9 ± 2 days, which decreased to 5 ± 2 days in the second cycle of the treatment ($p < 0.001$). Mean hemoglobin level was 10.1 g/dl pretreatment and it increased to 10.9 g/dl in the second cycle of the treatment ($p < 0.01$) (Table 4).

Table 4. — *Results in the LNG-IUS group.*

LNG-IUS	Pretreatment	Cycle 2	p
Pictorial blood loss score (units)	287 ± 57 146-412	77 ± 41 44-112	p < 0.001
Mean duration of menstruation (days)	9 ± 2 8-10	5 ± 2 4-7	p < 0.001
Hemoglobin (g/dl)	10.1 ± 0.4	10.9 ± 0.4	p < 0.01

Comparing the groups, we noted that there was no statistically significant difference between groups 1 and 2 in PBAC score while group 3 was superior to both groups 1 and 2 ($p < 0.05$ and $p < 0.05$, respectively). For mean duration of menstruation there was no difference among the groups. For hemoglobin levels there was no statistically significant difference between groups 1 and 2, while group 3 was higher to both groups 1 and 2 ($p < 0.05$ and $p < 0.05$, respectively). Comparisons are given in Table 5.

Table 5. — *Comparisons between groups.*

	DMPA vs daily MPA	DMPA vs LNG-IUS	Daily MPA vs LNG-IUS
Pictorial blood loss score (units)	NS	p < 0.01	p < 0.01
Mean duration of menstruation (days)	NS	NS	NS
Hemoglobin (g/dl)	NS	p < 0.05	p < 0.05

Common side-effects of progestin treatment are irregular bleeding and mineralocorticoid effects as manifested by breast tenderness. Side-effects are shown in Table 6. There were no significant differences between DMPA and daily MPA groups (20.4% vs 27.2%), while there were fewer side-effects in the LNG-IUS group (13.6%). Patients were asked whether they were willing to continue the treatment. Twenty-one in group 1 (56.8%), 19 in group 2 (43.1%), and 38 in group 3 (86.3%) agreed to continue the treatment as it was. It should be noted that continuing or stopping treatments required different actions by patients.

Table 6. — *Side-effects.*

	DMPA (%)	Daily MPA (%)	LNG-IUS (%)
Irregular bleeding	9/44 (20.4)	12/44 (27.2)	6/44 (13.6)
Breast tenderness	9/44 (20.4)	12/44 (27.2)	6/44 (13.6)
Willing to continue	25/44 (56.8%)	19/44 (43.1%)	38/44 (86.3%)

Discussion

Several theories have been proffered to elucidate the hormonal mechanisms responsible for perimenopausal bleeding. In one theory, ovulation occurs but with a longer follicular phase, during which there is a slow rise in the estrogen level. This slow rise in proliferative stimulus from estrogen causes the endometrium to proliferate excessively. This lengthened follicular/proliferative phase thus leads to a heavier/longer menstruation after progesterone is withdrawn [13]. A prospective analysis using age matched controls for perimenopausal women over the age of 40 with menometrorrhagia determined that higher levels of serum estradiol (0.55 vs 0.24 nmol/l) were noted in the abnormal group, but with no significantly different FSH levels [14].

Progestins are able to induce a secretory transformation in otherwise estrogen-stimulated proliferative endometrium. Progestins halt endometrial growth and allow for an organized sloughing of the endometrium. They also increase the PGF2a/PGE ratio by stimulating arachidonic acid formation in the endometrium, which may also contribute to decreasing abnormal uterine bleeding [11]. Continuous progestin is administered with the rationale of inducing endometrial atrophy and preventing estrogen stimulated endometrial proliferation, resulting in diminished blood loss during menstruation.

It is almost routine practice to give a hormonal treatment regimen for perimenopausal dysfunctional uterine bleeding. For hormonal treatment of menorrhagia, women can be offered either oral contraceptives or progestins. The decision between oral contraceptives and progestins is often based on contraindications to estrogen, most commonly smoking. In our group the percentage of smokers was 100% because the non-smokers were allocated to another mode of treatment.

To our knowledge, there is no study evaluating the continuous use of progestins for meno-metrorrhagia. Most studies in the literature compare regimens such as antifibrinolytics, nonsteroidals, combined contraceptives, and the LNG-IUS to norethindrone, administered in the luteal phase of women having menometrorrhagia. Because menometrorrhagia is not due to a deficiency of progestin, studies comparing norethisterone to mefenamic acid [15], danazol [16], and tranexamic acid [17] all suggest that there is no benefit to administering oral progestin in the luteal phase.

Given as a 21-day course from cycle days 5-26, norethisterone and medroxyprogesterone acetate reduced blood loss substantially [18]. When 5 mg of norethindrone was given three times a day, menstrual blood loss was reduced by 87%. However, this therapy was poorly tolerated; 78% of women refused to continue the therapy beyond three months [19]. Daily low-dose (2.5-5 mg/day) medroxyprogesterone has been used to treat women with ovulatory menorrhagia with anecdotal success; but there has been no clinical trial yet. In our study 5 mg of daily medroxyprogesterone acetate showed a comparable effect on menorrhagia with depot medroxyprogesterone acetate and LNG-IUS.

Continuous systemic therapy with depot medroxyprogesterone acetate is generally more effective, better tolerated, and longer acting than high-dose oral progestins. DMPA effectively suppresses ovarian steroidogenesis and thus reduces estrogen stimulation of the endometrium. DMPA exerts powerful atrophic effects on the endometrial cells. There are no published studies testing the impact of DMPA in women with menorrhagia, although it is often used in clinical practice for this indication. Our results show for the first time that DMPA can be successfully used in the treatment of menorrhagia.

The efficacy of the LNG-IUS in the treatment of menorrhagia has been studied in numerous clinical trials. In a study in which it was the sole treatment for menorrhagia, the LNG-IUS caused an 86% decrease in menstrual blood loss in the third month after insertion and a 97% decrease in the 12th month [12]. Five other studies that investigated the effects of the LNG-IUS on menorrhagia confirmed the effectiveness of the LNG-IUS in markedly reducing menstrual blood loss from 85% to 97% for up to three years after insertion [20]. In addition, the LNG-IUS increased hemoglobin and serum ferritin levels [21].

The LNG-IUS has demonstrated superiority over other medical therapies in comparative clinical trials. In their 2005 Cochrane review, Lethaby *et al*. concluded that the LNG-IUS is more effective than cyclical norethisterone (for 21 days) as a treatment for heavy menstrual bleeding [22]. Milsom *et al*. [23] compared the LNG-IUS directly with oral medications. Flurbiprofen and tranexamic acid reduced menstrual blood loss by 21% and 44%, respectively, while the LNG-IUS reduced menstrual blood loss by 82% after three months, 88% after six months, and by 96% after 12 months. Irvine found that the LNG-IUS and oral norethisterone given days 5-26 in the cycle reduced blood loss significantly, but more women in the LNG-IUS group were amenorrheic and willing to continue the therapy at the end of the trial [18]. When Reid compared the LNG-IUS with mefenamic acid in a 6-month trial, he found that LNG-IUS users had a greater decrease in blood loss, but no higher rates of discontinuation [24]. In our study, menstrual blood loss was significantly lower in the LNG-IUS group.

Although the power of the study does not allow us to draw strong conclusions, the results of the current study are considerable, because to the best of our knowledge this is the only study comparing all the different modes of delivery of progestins in menorrhagia.

In conclusion, the efficacies of oral and intramuscular medroxyprogesterone acetate in the treatment of menorrhagia were comparable each other. However, the efficacy of the LNG-IUS was superior to both. Moreover, patient compliance was much better in the LNG-IUS group.

References

[1] Bayer S.R., DeCherney A.H.: "Clinical manifestations and treatment of dysfunctional uterine bleeding". *J. Am. Med. Assoc.,* 1993, *269,* 1823.

[2] Luoto R., Keskimaki I., Reunanen A.: "Socioeconomic variations in hysterectomy: evidence from a linkage study of the Finish hospital discharge register and population census". *J. Epidemiol. Community Health*., 1997, *51,* 67.

[3] Nesse R.E.: "Abnormal vaginal bleeding in perimenopausal women". *Am. Fam. Physician.,* 1989, *40,* 185.

[4] ACOG practice bulletin: "Management of anovulatory bleeding". *Int. J. Gynaecol. Obstet.,* 2001, *72,* 263.

[5] Livingstone M., Fraser I.S.: "Mechanisms of abnormal uterine bleeding". *Hum. Reprod. Update,* 2002, *8,* 60.

[6] Higham J.M., O'Brian P.M.S., Shaw R.W.: "Assesment of menstrual blood loss using a pictorial chart". *Br. J. Obstet. Gynecol.,* 1990, *97,* 734.

[7] Jansen C.A., Scholten P.C., Heintz A.P.: "A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss". *Obstet. Gynecol.,* 1995, 85, 977.

[8] Awwad J.T., Toth T.L., Schiff I.: "Abnormal uterine bleeding in the perimenopause". *Int. J. Fertil. Menopausal Stud*., 1993, *38,* 261.

[9] Irvine G.A., Cameron I.T.: "Medical management of dysfunctional uterine bleeding". *Baillieres Best Pract. Res. Clin. Obstet. Gynaecol.,* 1999, *13,* 189.

[10] Hickey M., Higham J., Fraser I.S.: "Progestogens versus oestrogens and progestogens for irregular uterine bleeding associated with anovulation". *Cochrane Database Syst Rev.,* 2000, CD001895.

[11] Progestins. In: Hardman J.G., Limbird L.E. (eds.). Goodman & Gilman's the Pharmalogical Basis of Therapeutics. New York, McGraw-Hill, 1996, 1426.

[12] Andersson J.K., Rybo G.: "Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia". *Br. J. Obstet. Gynecol.,* 1990, *97,* 690.

[13] Sowers M.R., La Pietra M.T.: "Menopause: its epidemiology and potential association with chronic diseases". *Epidemiol. Rev*., 1995, *17,* 287.

[14] Moen M.H., Kahn H., Bjerve K.S.: "Menometrorrhagia in the perimenopause is associated with increased serum estradiol". *Maturitas,* 2004, *47*, 151.

[15] Cameron I.T., Haining R., Lumsden M.A.: "The effects of mefenamic acid and norethisterone on measured menstrual blood loss". *Obstet. Gynecol*., 1990, *76,* 85.

[16] Hingham J.M., Shaw R.W.: "A comparative study of danazol, a regimen of decreasing doses of danazol, and norethindrone in the treatment of objectively proven unexplained menorrhagia". *Am. J. Obstet. Gynecol.,* 1993, *169*, 1134.

[17] Preston J.T., Cameron I.T., Adams E.J.: "Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia". *Br. J. Obstet. Gynecol.,* 1995, *102,* 401.

[18] Lethaby A., Irvine G., Cameron I.: "Cyclical progestogens for heavy menstrual bleeding". *Cochrane Database Syst. Rev*., 1998, CD001016.

[19] Irvine G.A., Campbell-Brown M.B., Lumsden M.A.: "Randomised comparative trial of the LNG-IUS and norethisterone for treatment of idiopathic menorrhagia". *Br. J. Obstet. Gynecol.,* 1998, *105*, 592.

[20] Xiao B., Wu S.C., Chong J.: "Therapeutic effects of the levonorgestrel-releasing intrauterine system in the treatment of idiopathic menorrhagia". *Fertil. Steril.,* 2003, *79*, 963.

[21] Monteiro I., Bahamondes L., Diaz J.: "Therapeutic use of levonorgestrel-releasing intrauterine system in women with menorrhagia". *Contraception,* 2002, *65,* 325.

[22] Lethaby A.E., Cooke I., Rees M.: "Progesterone or progestogen releasing intraauterine systems for heavy menstrual bleeding". *Cochrane Database of Syst. Rev*., 2005, CD002126.

[23] Milsom I., Andersson K., Andersch B.: "A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia". *Am. J. Obstet. Gynecol*., 1991, *164,* 879.

[24] Reid P.C., Virtanen-Kari S.: "Randomised comparative trial of the levonorgestrel intrauterine system and mefenamic acid for the treatment of idiopathic menorrhagia: a multiple analysis using total menstrual fluid loss, menstrual blood loss and pictorial blood loss assesment charts". *Br. J. Obstet. Gynecol.,* 2005, *112,* 1121.

Address reprint requests to:
T. KÜÇÜK, M.D.
Department of Obstetrics and Gynecology
GATA School of Medicine
06018 Etlik, Ankara (Turkey)
e-mail: tansukucuk@gmail.com