Progesterone treatment preference in heavy menstrual bleeding: Per os or levonorgestrel releasing intrauterine device

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Original Article

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ABSTRACT

Objectives: To find out the most satisfactory progesterone treatment method in the women who have heavy menstrual bleeding.

Design: Open-label, randomized, parallel group, therapeutic study

Setting: The study was carried out at Istanbul Medeniyet University Göztepe Education and Research Hospital gynecology and obstetrics department. Random sequence methods were used; randomization was undertaken using computational random-number generators.

Subjects: This study covered 192 women aged between 32 and 50 years.

Intervention: Ninety-seven patients were applied LNG-IUD and 95 patients had been given oral norethisterone acetate (NETA) 10 mg (5 mg two times daily) during the cycle of 5-25 days. LNG-IUD has been applied in the first 10 days of the menstrual cycle.

Main Outcome Measures: The patients in both groups were called for the control on the first visit and on the following 6^{th} and 12^{th} months. In LNG-IUD group, on the level of hemoglobin in the sixth and twelfth months, the significant increase was seen and this increase was higher than oral progesterone group($p<0.01$). The ratio of decrease on the level of VBS in the sixth and twelfth month of the study in LNG-IUD group was found significantly high to the oral progesterone group. Due to the discontinuation of the treatment because of irregular drug usage, LNG-IUD is one step forward.

Results: By using LNG-IUD we can prevent needless hysterectomy and endometrial ablation in premenopausal women and so we can minimize postoperative mortality and morbidity. The cost-effectiveness of LNG-IUD is lower than surgery.

Conclusions: LNG-IUD is a more satisfying alternative treatment method than oral progestogens for overcoming the problem of heavy menstrual bleeding due to its ease of use.

KEYWORDS: Anemia, LNG-IUD, Heavy Menstrual Bleeding (HMB), Oral progesterone, menorrhagia.

INTRODUCTION

Heavy menstrual bleeding (HMB), or menorrhagia, is defined as excessive menstrual blood loss that occurs alone or in combination with other symptoms and has a negative impact on a woman's physical, social, emotional, and material quality of life[1]. HMB is menstrual blood loss of 80 ml or greater[2]. Approximately 30% of women are negatively affected by menorrhagia during their reproductive years[3,4]. Conventional medical treatment (mefenamic acid, tranexamic acid, norethindrone, medroxyprogesterone acetate injection, or combined oral contraceptive pills) in patients with menorrhagia were included. Although endometrial ablation is a less invasive surgical alternative to hysterectomy, it does not eliminate surgical risk and is followed by further surgery within 4 years in up to 38% of the women who undergo this treatment[5,6]. Hysterectomy is often used to treat women with this complaint, but medical therapy may be a successful alternative. The intrauterine coil device was originally developed as a contraceptive but the addition of uterine relaxing hormones, progestogens to these devices resulted in a large reduction in menstrual blood loss[7,8].

In the study, we have compared the use of levonorgestrel intrauterine device (LNG-IUD) and the most frequently used oral progesterone in respect to the effectiveness for minimizing the present symptoms, patient satisfaction and the side effects.

MATERIALS AND METHODS

The study was carried out at Istanbul Medeniyet University Göztepe Education and Research Hospital gynecology and obstetrics department between the November 30, 2011 and December 31, 2013. This study covered 192 women aged between 32 and 50. It was designed as an open-label, randomized, parallel group, therapeutic study. The two medical treatment methods were suggested to the women who refused any kind of surgery. Some of them didn't want to have an intrauterine device. Random sequence methods were used; randomization was undertaken using computational random-number generators. Consequently, not all patients who attended the hospital during the study period were included in the trial, even if they met the inclusion criteria. All women participated voluntarily and involved in the study based on their polyclinics application number. Each patient was examined by ultrasound. They gave their written informed consent before entry into the study. The study was granted ethical approval from Istanbul Medeniyet University Göztepe Education and Research Hospital Ethics Committee.

The criteria applied for the inclusion of the patients in the study are the following:

1) Heavy menstrual bleeding

2) The size of the uterus is less than 10 weeks

3) Not presence of the endometrial polyp, submucosal myomas, endometrial atypical hyperplasia and malignancy

4) Being decisive not to have children anymore

The unknown reason for vaginal bleeding, having gynecologic malignancy including ovarian and breast cancer, liver illness, diabetes mellitus, pelvic inflammatory disease and the septic abortus in the last three months are our criteria to exclude from the study.

All women were asked about their gynecological history, and general and pelvic examination was done for each of these patients. Transvaginal ultrasound was performed to assess the uterus, adnexa and endometrial line. To exclude cervical pathology, PAP smear has been done with pipelle and endometrial biopsy was done by pipelle not requiring general anesthesia.

To discriminate between menorrhagia and normal menstrual blood loss, a simple visual assessment technique was used as described by Jannsen *et al*[9]. Information on menstrual bleeding was obtained by interview prior to entering the study using a pictorial chart form to describe the degree to which the sanitary wear was soiled. A score was calculated by multiplying the number of slightly, moderately and heavily soiled pads and tampons by 1, 5 and 20 for pads, 1, 5 and 20 for tampons, according to their degree of staining (Figure 1). A score of 185 was used as a cutoff point as this score has a predictive value of 85% to be consistent with menorrhagia.

Another main outcome measure was health-related quality of life, measured by the SF-36 instruments. Women were followed-up at the first visit, and at 6 and 12 months following insertion of LNG-

IUD. During follow-up, women were interviewed about their bleeding patterns and any side effects or adverse reactions.

The patients were divided into two groups. Ninety-seven patients were applied LNG-IUD and 95 patients had been given oral norethisterone acetate (NETA) 10 mg (5 mg two times daily) during the cycle of 5-25 days. LNG-IUD was applied in the first 10 days of the menstrual cycle.

The patients in both groups were called for the control on the first visit and on the following 6th and 12th months. They were asked to bring their menstrual pictorial chart on their visits, performed by transvaginal ultrasound, required cell blood count, they filled up SF-36 questionnaire. In this way, we assessed the patients' view on the treatment, the complaints and the possible side effects.

The findings of the study were assessed by SPSS (Statistical Package for Social Sciences) for Windows 15.0 programmer. Besides descriptive statistical methods (mean, standard deviation); comparing quantitative data for normal distributed parameters into two groups were assessed by Student t test and not normal distributed parameters into two groups were assessed by Mann Whitney U test. Paired Samples T Test was applied within the group for the parameters which are normal distributed. Wilcoxon Signed Ranks test was applied within the group for the parameters which are not normal distributed. For the comparison of the qualitative data, we used Chi square and Fisher's Exact Chi square tests. The significance value is $p < 0.05$. The results are taken from all the patients who continued to participate in the study.

RESULTS

This study has been carried out between the dates November 30th, 2011 to December 31th, 2013 on 192 patients; 97 in LNG-IUD group, 95 in NETA group. The age of the patients ranged from 32 to 50, the average age was 40.47 ± 4.17 years in LNG-IUD group, parity 2.42 ± 1.03 and in NETA group the average age is 40.20 ± 4.28 years and the parity was 2.54 ± 0.93.

The level of VBS in the sixth and twelfth month of study in oral progestogens was significantly higher than LNG-IUD group ($p < 0.01$); the VBS in LNG-IUD at the beginning was significantly higher than oral progesterone group ($p < 0.01$) (Figure 2).

Table 1 summarizes the ratio of decrease on the level of VBS in the sixth and twelfth month of the study in LNG-IUD group was found significantly high to the oral progesterone group.

Table 2 shows in oral progesterone group, the hemoglobin levels at sixth and twelfth months were significantly increased ($p <0.01$). In LNG-IUD group, on the level of hemoglobin in the sixth and twelfth months, the significant increase was seen, and this increase was higher than oral progesterone group ($p <0.01$).

At the beginning, heavy menstrual bleeding was seen in patients in both groups. At the sixth month of the study, there was no statistical difference in their menstruation situation in both groups ($p >0.05$). However, there was a significant statistical difference in menstruation situations at the twelfth month of the study. The ratio of amenorrhea in LNG-IUD was 40.2% and in the oral progesterone group was 5.3% at the end of the twelfth month ($p <0.01$). The ratio of menorrhagia at the twelfth month was 12.2% in LNG-IUD

and 35.1% in oral progesterone group (p <0.01). Normal and oligomenorrhea situation had no statistical difference in both groups (p >0.05).

Table 3 summarizes the side effects. In looking for the side effects, there was a significant statistical difference at the end of six and twelve months. In oral progesterone group, edema ratio was 16.9% and in LNG-IUD it was 4.7% (p <0.05). In sixth month side effects, the other side effects had no significant difference in both groups. The depression ratio was 1.2% in LNG-IUD group, and 8.8% in oral progesterone group at the twelfth month of treatment (p <0.05). The ratio of edema was 10.5% in oral progesterone group and 1.2% in LNG-IUD at the end of twelve months (p <0.05). The other twelfth monthsside effects had no statistical difference in both groups (p >0.05).

Treatment discontinuations in oral progesterone group were 31.6% at the sixth month because of irregular drug usage (22 patients), edema (4 patients), depression (2 patients), mastalgia (1 patient) and hirsutisms (1 patient). At the end of the twelve months, there were 65 patients in oral progesterone group; 8 of them dropped out the study (irregular drug usage in 5, patient acne in 1, patient edema in 1, patient headache in 1). The number of patients who discontinued in LNG-IUD group was 11 patients (11.3%) at the sixth month and 4 patients (4.6%) from the remaining 86 patients at the twelfth month. The reasons for discontinuation were pelvic pain in 3, mastalgia in 3 and ovarian cyst in 3. At the end of twelve months discontinuation of 4 patients were due to mastalgia in 2 and pelvic pain and hirsutism in 1 one each.

DISCUSSION

HMB is one of the most common gynecological disorders affecting women of reproductive age, accounting for 20% of all gynecological visits to general practitioners [10]. HMB is associated with a lower quality of life, loss of productivity and increased healthcare expenses [11,12] and in usual practice, it is initially treated pharmacologically [13], with tranexamic acid and norethisterone believed to be the most effective[13]. Surgical treatment for HMB often follows unsuccessful or ineffective medical therapy; however, hysterectomy is a major surgical procedure with significant physical and emotional complications, in addition to the social and economic cost. Various minimally invasive surgical techniques, such as thermal balloon ablation (TBA), the LNG-IUD, transcervical resection of the endometrium, microwave ablation, diffused laser energy ablation, bipolar impedance-controlled ablation, cryoablation, hot saline instillation[14,15], and various methods of endometrial ablation have been developed, with the purpose of improving menstrual symptoms, and these have achieved great success.

The LNG-IUD was developed in Finland during the 1980s and is an intrauterine device that releases 20 µg levonorgestrel every 24 hours over 5 years. Although initially licensed as a contraceptive, in 1990 the LNG-IUD was tested and reported to be effective in the treatment of menorrhagia, as a non-contraceptive benefit [16].

In 2013, the Society of Gynecologic Surgeons Systematic Review Group published a review of 22 studies comparing non-surgical therapy for the treatment of AUB presumed due to endometrial dysfunction. The authors concluded that regarding reduction of menstrual bleeding, LNG-IUD (71–95% reduction), combined oral contraceptive pills (OCP) (35–69% reduction), extended cycle oral progestins (87%

reduction), tranexamic acid (26–54% reduction), and NSAIDs (10–52% reduction) were all effective treatments. The LNG-IUD, combined OCPs, and antifibrinolytics were all superior to luteal-phase progestins. The LNG-IUD was the best treatment, and it has been shown that it is superior to combined OCPs and nonsteroidal anti-inflammatory drugs (NSAID). Antifibrinolytics were superior to NSAIDs. The authors have also underlined the lack of data about the impact of such treatment on the quality of life. Once again, according to American and Canadian guidelines, surgical treatments (hysterectomy and endometrial ablation) should be restricted to the failure of medical therapy, inability to utilize medical therapies, significant anemia, impact on quality of life, and concomitant uterine pathology.

Intrauterine devices were initially introduced as contraceptives, but after the addition of progestogen (LNG-IUD) these devices also reduce menstrual bleeding effectively. The local release of levonorgestrel in the uterine cavity suppresses endometrial growth. A systematic review of the effectiveness of the LNG-IUD in heavy menstrual bleeding concluded that the reduction of menstrual blood loss was 79-96% in the LNG-IUD group [17,18]. In women with heavy menstrual bleeding who presented to primary care providers, the LNG-IUD was more effective than usual medical treatment in reducing the effect of heavy menstrual bleeding on quality of life [19]. However, up to 60% of women discontinue LNG-IUD within 5 years because of unscheduled bleeding, pain, and/or systemic progestogenic side-effects [20]. In the Royal College of Obstetricians and Gynecologists (RCOG) guideline on heavy menstrual bleeding, the use of the LNG-IUD is the first therapeutic option when drug treatment has failed. This is not based on proven cost-effectiveness [20].

The main problem for progesterone is poor attendance of the patients. In the study carried out by Andrew M *et al* in the sixth month for LNG-IUD group, the ratio of attendance to the medical treatment was 77%, for NETA group this ratio goes down to 22% [21]. In this study, the drop out ratio of the patients using oral progesterone group was 31.6% at the end of the sixth month. The drop out ratio for LNG-IUD was 11.3% at the end of the sixth month.

One hundred and sixty-five women were randomized (82 LNG-IUD/83 medroxyprogesterone acetate). Increases in median hemoglobin levels from baseline to Cycle 6 (7.5% vs. 1.9%; $p<0.001$) Baseline median hemoglobin levels were 12.4 g/ld. with the LNG-IUD and 12.2 g/dl with oral medroxyprogesterone acetate (MPA), respectively. At Cycle 6, the corresponding medians were 13.4 g/dl with the LNG-IUD and 12.6 g/dl with oral medroxyprogesterone acetate (MPA). At Cycle 6, the proportion of women who rated their bleeding as 'improved' was higher with the LNG-IUD than with oral MPA, both according to investigator assessment (93.6% vs. 61%) and self-assessment (93.6% vs. 67.1%), parallel to our findings [22]. In our study in oral progesterone group median hemoglobin levels at the beginning is 10.56± 0.81 and at the end of six months it is 10.97 ± 0.77; in LNG-IUD group the hematocrit levels at the beginning are 11.03 ± 0.99 and at the end of six months 11.74 ± 0.96. In oral progesterone group, the sixth and twelfth month hemoglobin levels were seen significantly increased ($p < 0.01$). In LNG-IUD group, on the level of hemoglobin in the sixth and twelfth months, the significant increase was seen, and this increase was higher than oral progesterone group ($p < 0.01$).

Spotting is the most common side effect in the usage of LNG-IUD in the literature [23]. The reason of spotting is levonorgestrel diffusion in the endometrium being was not homogeneous at the first months. This makes atrophy center patches and vessel variable changes in the endometrium and so irregular endometrial exfoliating occurs [23,24]. In this study in LNG-IUD group at the end of the six months, 22.1% of the patients and 13.4% at the end of the twelve months applied because of spotting. In oral progesterone group, the spotting ratio was %30.8 at the end of the six months and 29.8% at the end of the twelve months.

Two most important long-term effects of LNG-IUD were amenorrhea and oligomenorrhea. If patients were not informed clearly on this subject this could be the discontinue reason to the treatment. The contraceptive effect of LNG-IUD is reversible, and fertility returns soon after the LNG-IUD removing [25-27]. In our study after twelve months in LNG-IUD 40.2% amenorrhea and 18.3% oligomenorrhea were seen. In oral progesterone group, these ratios were 5.3% amenorrhea and 15.8% oligomenorrhea after twelve months. In both groups, nobody gives up their treatments.

While LNG-IUD usage the levonorgestrel excessing to the blood had some side effects. They are mastalgia, weight gain, edema, hirsutisms, acne, headache, ovarian cysts [28]. In this study after six months, 31.6% in oral progesterone group and 11.3% in LNG-IUD group gave up the treatment. In oral progesterone group discontinuation reasons; 22 of them irregular drug usage, 4 of them edema, 2 of them depression and 1 was because of mastalgia and 1 was hirsutisms. In LNG-IUD group among 11 discontinued patients 3 of them pelvic pain, 3 of them over cysts, 4 had mastalgia.

However, none of the patients had stopped the medical treatment; functional over cysts is mentioned to be one of the most frequently seen adverse effects in the literature (10%) [29,30]. In our study in LNG-IUD group at the end of the twelve months, five patients (6.1%) had functional over cysts. These cysts are smaller than 4 cm, simple and do not give pain. In oral progesterone group at the end of the twelve months, one patient (1.8%) had functional over cysts. All these cysts have naturally disappeared during the controls.

CONCLUSION

LNG-IUD is one of two hormonal IUDs with Food and Drug Administration approval. The other is Skyla, which prevents pregnancy for up to three years. LNG-IUD can prove to be an effective treatment for menorrhagia. This is because levonorgestrel is a very potent blocker of estrogen activity on the endometrium. The effect of LNG in the uterine cavity is that it gradually reduces the thickness and vascularity of the endometrium over an initial 3-6 months of use. Because of this suppression of the endometrium, most women experience a reduction of blood loss, but its therapeutic significance is greatest in women with menorrhagia.

Since LNG-IUD has reversible effects in the women of reproductive age especially who want to keep their fertilities, it is an effective, noninvasive method in heavy menstrual bleeding treatment which provides long-term efficacy. By using LNG-IUD we can prevent needless hysterectomy and endometrial

ablation in premenopausal women and so we can minimize postoperative mortality and morbidity. The cost-effectiveness of LNG-IUD is lower than surgery.

LNG-IUD is a more satisfying alternative treatment method than oral progestogens for overcoming the problem of heavy menstrual bleeding due to its ease of use.

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Ayse Kavasoglu conceived, designed and did statistical analysis, editing of the manuscript, did data collection and manuscript writing. Professor Dr. Ahmet Gocmen did the review and final approval of manuscript takes the responsibility and is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. No potential conflict of interest was reported by the authors.

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Table 1: VBS Evaluation

VBS	Treatment Oral Progesterone Average± SS (median)	Treatment LNG-IUD Average± SS (median)	^{+}p
Inception	400.21±105.58 (390)	491.86±126.02 (560)	*0.001***
6th month	169.92±163.13 (90)	73.95±103.36 (65)	*0.001***
12th month	129.91±104.06 (90)	64.21±86.91 (60)	*0.001***
Inception - 6th Month (%)Change	-55.03±44.55 (-75)	-83.37±25.12 (-87.17)	*0.001***
Inception - 12th Month (%)Change	-64.49±29.36 (-75.57)	-85.54±21.47 (-88.19)	*0.001***
6th Month - 12th Month (%)Change	23.89±166.02 (-11.1)	-13.21±6.33 (-12.5)	*0.950*
Inception - 6th Month $^{++}$p	*0.001***	*0.001***	
Inception - 12th Month $^{++}$p	*0.001***	*0.001***	
6th Month - 12th Month $^{++}$p	*0.041**	*0.001***	

$^{+}$Mann-Whitney U test $^{++}$Wilcoxon Sign test

*p<0.05 **p<0.01

Table 2: Hemoglobin Evaluation

Hemoglobin	Treatment		*P*
	Oral Progesterone Averages (median)	LNG-IUD Averages (median)	
•Inception	10.56±0.81	11.03±0.99	*0.001***
•6th Month	10.97±0.77	11.74±0.96	*0.001***
•12th Month	11.35±0.67	12.77±0.56	*0.001***
+Inception - 6th Month (%)Change	3.83±10.55 (3.77)	7.62±10.65 (6.94)	*0.031**
+Inception - 12th Month (%)Change	7.76±9.56 (7.31)	18.0±10.88 (17.99)	*0.001***
+6th Month - 12th Month (%)Change	3.57±8.86 (2.56)	9.66±8.39 (8.29)	*0.001***
Inception - 6th Month ++p	*0.013**	*0.001***	
Inception - 12th Month ++p	*0.001***	*0.001***	
6th Month - 12th Month ++p	*0.008***	*0.001***	

•*Student t test* +*Mann-Whitney U test* ++*Paired Samples t test*

**p<0.05* ***p<0.01*

Table 3: Side Effect Evaluation

	Side Effect	Treatment Oral Progesterone n (%)	Treatment LNG-IUD n (%)	*P*
6th Month	None	20 (30.8%)	39 (45.3%)	
	•Acne	3 (4.6%)	4 (4.7%)	*1.000*
	•Headache	4 (6.2%)	5 (5.8%)	*1.000*
	Depression	3 (4.6%)	2 (2.3%)	*0.652*
	•Hirsutism	5 (7.7%)	3 (3.5%)	*0.291*
	•Weight Gain	8 (12.3%)	6 (7.0%)	*0.263*
	•Mastalgia	7 (10.8%)	9 (10.5%)	*0.952*
	•Edema	11 (16.9%)	4 (4.7%)	*0.013**
	Ovarian Cyst	2 (3.1%)	8 (9.3%)	*0.189*
	Pelvic Pain	2 (3.1%)	6 (7.0%)	*0.467*
12th Month	None	26 (45.6%)	62 (75.6%)	
	Acne	2 (3.5%)	2 (2.4%)	*1.000*
	Headache	3 (5.3%)	2 (2.4%)	*0.401*
	Depression	5 (8.8%)	1 (1.2%)	*0.042**
	Hirsutism	3 (5.3%)	1 (1.2%)	*0.305*
	Weight Gain	5 (8.8%)	2 (2.4%)	*0.123*
	Mastalgia	5 (8.8%)	3 (3.7%)	*0.272*
	Edema	6 (10.5%)	1 (1.2%)	*0.019**
	Ovarian Cyst	1 (1.8%)	5 (6.1%)	*0.401*
	Pelvic Pain	1 (1.8%)	3 (3.7%)	*0.644*

*Fisher's Exact test is used •Pearson Chi-Square test *p<0. 05*

Pad	1	2	3	4	5	6	7	8
								
								
								

Figure1: Menstrual Bleeding Measurement with pads

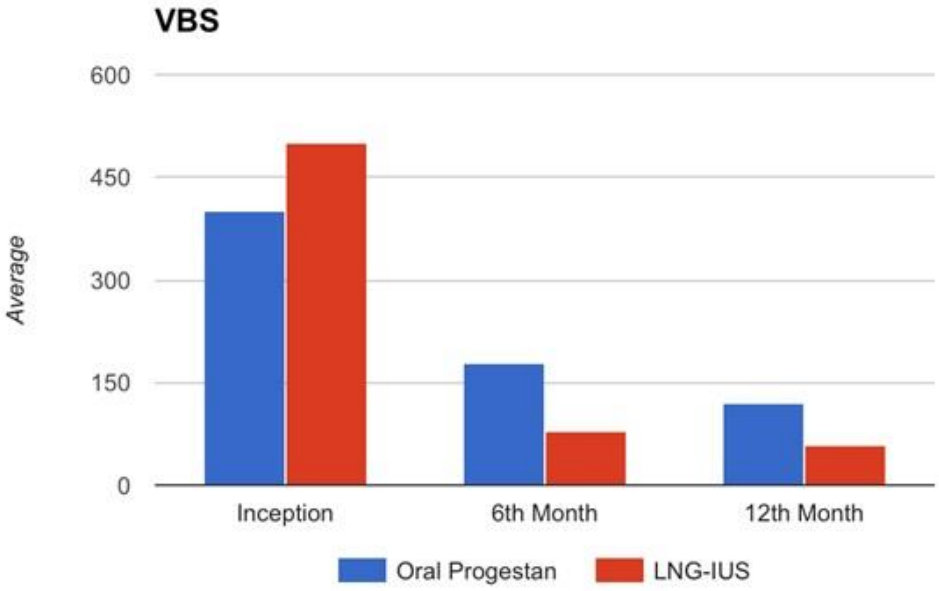

Figure 2: VBS Levels Distribution