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Original Article

Efficacy of Vaginal Micronized Progesterone Versus Oral Micronized Progesterone in the Treatment of Abnormal Uterine Bleeding: A Prospective Randomized Controlled Trial

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Keywords: Abnormal uterine bleeding; lipid; oral micronized progesterone; vaginal micronized progesterone.

ABSTRACT

Objective: To compare the effect of oral and vaginal micronized progesterone in terms of regularity of menstrual cycle, blood hemoglobin and lipid levels, and endometrial thickness in patients with abnormal uterine bleeding (AUB).

Methods: A total of 80 patients with AUB were randomized into two groups: the oral micronized progesterone group (n=40) and the vaginal micronized progesterone group (n=40). After 3 months of treatment, patients were inquired about compliance to treatment, treatment satisfaction (satisfied-unsatisfied), whether a regular cycle was present, and side effects. Pre- and posttreatment parameters were compared in terms of ultrasonographic endometrial thickness measurement, and hematologic and biochemical parameters.

Results: Overall 66 patients, the first group (oral progesterone) and the second group (vaginal progesterone) were evaluated. There was no statistically significant difference between the two groups in terms of age, parity, and body mass index. In both groups, hemoglobin levels were found to be significantly increased after treatment (p=0.0001). No statistically significant intragroup or intergroup difference was found in either group in terms of lipid values before and after treatment. There was a significant decrease in endometrial thickness after treatment in both groups (p=0.0001). After treatment, in the oral progesterone group, the menstrual cycle became regular in 26 (81.25%) patients while in the vaginal progesterone group, it became regular in 30 (88.23%) patients, with no significant difference between groups. In the first group (n=25/32), 78.12% of patients were satisfied with the treatment, whereas in the second group (n=28/34) 82.35% were satisfied with the treatment, with no significant difference between groups.

Conclusion: Considering its efficacy and safety, easy toleration, and few side effects, vaginal micronized progesterone may be a good alternative to oral preparations in the treatment of AUB.

INTRODUCTION

Abnormal uterine bleeding (AUB) is a common gynecological condition affecting 20% of women of reproductive age.[1] A normal menstrual cycle is defined as bleeding every 24–38 days, with a duration of ≤8 days and at a volume of ≤80 mL, with a 7–9 days interval. Any bleeding apart from this definition is considered AUB.[2–4] The FIGO has developed a classification system for etiological factors underlying AUB ("PALM-COEIN: polyp, adenomy-

osis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified") system.[5] PALM represents structural abnormalities and COEIN nonstructural abnormalities. Dysfunctional uterine bleeding term is no longer used in this new classification. In the diagnosis of AUB, history, physical examination, laboratory and imaging methods, and histopathological sampling are important. Treatment of AUB may be surgical or medical depending upon the underlying etiology. In medical treatment, especially in intrauterine systems involving oral progestins and progestin, nonsteroid antiinflammatory drugs, tranexamic acid, combined oral contraceptives, danazol, and gonadotropin-releasing hormone analogs are employed.

Progesterone, in an estrogen-primed uterus, transforms proliferative endometrium to secretory endometrium via progesterone receptors A and B.[6] The bioavailability of progestin is determined by many factors, including the route of administration, metabolism, and its affinity to other steroid receptors.[7] The ability of progestogens to decidualize endometrium is variable, which determines their efficacy in decreasing or stopping endometrial bleeding.

This randomized controlled study aimed to compare the use of oral and vaginal micronized progesterone in the treatment of AUB in terms of their effect on the regulation of the menstrual cycle, blood hemoglobin, lipid values, and endometrial thickness and with respect to patient satisfaction.

MATERIALS AND METHODS

This prospective randomized controlled study was conducted on patients who presented to the gynecology and obstetrics outpatient clinic with the complaint of AUB between March 2009 and May 2010. Ethical approval was taken from the local ethics committee (Approval number: 2019/514/154/19). This study conforms to the ethical standards of the Helsinki Declaration. Before participation, all patients gave written informed consent.

Women who were 18–45 years of age, had no pregnancy, had no menopausal symptoms, did not receive hormonal treatment, did not use anticoagulant therapy, and had no organic pathology that can lead to AUB, such as leiomyoma, polyp, and adenomyosis, had no previous treatment for a similar complaint within the last 1 year, had no comorbidities, and contraindication to the use of progestins were included. Women over 45 years and menopausal for more than 1 year were excluded.

Sociodemographic information, past surgical and medical histories, and the menstrual history of the patients were noted. Physical and gynecological examinations were performed. On gynecological examination, cervicovaginal smear, and endometrial sampling, where necessary, were obtained. All patients underwent transvaginal ultrasonographic (TVUSG) examination. Complete blood count, beta-HCG, follicle-stimulating hormone, Luteinizing hormone, estradiol (E2), prolactin, thyroxine stimulating hormone, prothrombin time, partial thromboplastin time, alanine aminotransferase, aspartate aminotransferase (AST), creatinine, total cholesterol, triglyceride, low-density lipoproteins (LDL), and high-density lipoproteins were evaluated.

Of 87 patients, three patients were excluded due to leiomyoma, one endometrial polyp, one atypical endometrial hyperplasia, one hyperthyroidism, and one hyperprolactinemia. The remaining 80 were randomized into two groups. Simple randomization was conducted using a computer-generated sequence. Allocation concealment was not performed. The first group (n=40) was administered 400 mg oral micronized progesterone (progestin capsule, Koçak Farma, Turkey) between the 15th and 25th days of the cycle; and the second group (n=40) was administered 90 mg vaginal micronized progesterone (8% crinone gel, Serono İlaç, Turkey) between the 15th and 25th days of the cycle throughout three cycles. The flow diagram of the study is shown in Figure 1.

The patients were followed for three consecutive months from 1 month after the start of treatment. At follow-up visits, patients were questioned about their compliance with treatment, patient satisfaction (satisfied-unsatisfied), menstrual cycle regularity, and side effects. In addition, endometrial thickness was measured by TVUSG. Blood samples were repeated at follow-up visits. Patients were requested to record the day of the menstruation cycle onset, the length of the menstrual cycle, and whether there was spotting. Patients with a menstrual cycle frequency of 24–38 days, cycle duration of ≤8 days, maximum of 7–5 days between shortest and longest cycles, and who do not have spots were considered to have regular menstrual cycles.

The questionnaire also contained one more question "Please evaluate your general satisfaction with the treat-

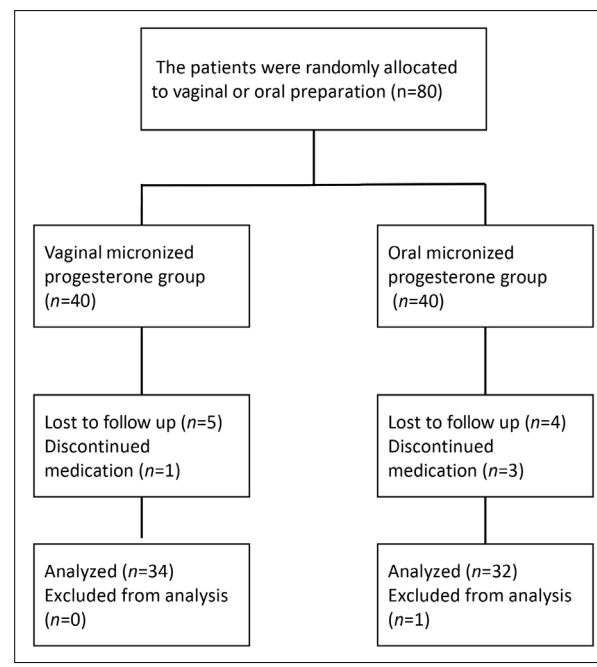

Figure 1. Flow diagram of the study.

ment you have received?" with responses on two answers – very dissatisfied to very satisfied.

Statistical analyses were carried out with NCSS 2007 program. Continuous variables were expressed as Mean±-Standard Deviation. In the comparisons, Chi-square and Fisher's exact, the Paired Samples t-test, Mann-Whitney U test were used. P<0.05 was considered statistically significant.

RESULTS

A total of 66 patients were eligible for final analysis. The first group (oral progesterone) consists of 32 patients, and the second group (vaginal progesterone) consists of 34 patients. Age, parity, and body mass index did not differ between the two treatment arms (Table 1).

Table 1. Demographic characteristics of patients

	Oral progesterone group	Vaginal progesterone group	p
Age	39.56±2.51	38.91±3.35	0.378
Parity	2.53±1.16	2.82±1.14	0.207
BMI	26.92±3.58	27.76±3.81	0.358

BMI: Body mass index.

Table 2. Mean hemoglobin and blood lipid values in groups before and after treatment

	Oral progesterone group	Vaginal progesterone group	p
Hemoglobin			
Before treatment	10.93±1.22	10.56±1.91	0.092
After treatment	11.26±0.94	10.94±1.61	0.439
p	0.042	0.033	
Cholesterol			
Before treatment	187.75±21.59	192.12±23.13	0.431
After treatment	182.59±23.25	193.82±23.46	0.097
p	0.404	0.601	
Trygliceride			
Before treatment	111.63±23.89	116.09±31.77	0.523
After treatment	119.13±33.68	122.47±28.13	0.662
p	0.229	0.359	
LDL			
Before treatment	118.69±21.53	121.35±20.82	0.611
After treatment	115.88±17.68	122.88±14.63	0.083
p	0.538	0.476	
HDL			
Before treatment	57.19±13.84	57.62±16.38	0.909
After treatment	57.88±20.69	58.59±20.04	0.887
p	0.803	0.836	

LDL: Low-density lipoproteins; HDL: High-density lipoproteins.

There was no significant difference between the two treatment groups for mean hemoglobin values before and after treatment. In oral and vaginal progesterone groups, a significant increase was found in hemoglobin values after the completion of treatment (p=0.042, p=0.033, respectively). No statistically significant intra or intergroup differences were found in serum lipid levels before and after treatment (Table 2).

There was no significant difference between the two groups regarding endometrial thickness before and after treatment. In both groups, a significant decrease was found in endometrial thickness after treatment (p=0.0001) (Table 3).

A regular cycle was observed in 81.25% (26⁄32) and 83.22% (30⁄34) of patients after 3 months in the vaginal and oral treatment arms. The rate of regular cycles did not differ between the two groups (Table 4).

There were no statistically significant differences in patient satisfaction between the groups. In total, 82.35% (28⁄34) and 78.12% (25⁄32) of the patients were satisfied with their treatment in the vaginal and oral medication groups, respectively.

During the study period, nausea occurred in one patient, and breast tenderness and swelling occurred in one pa-

Table 3. Mean endometrial thickness values in groups before and after treatment

Endometrial thickness	Oral progesterone group	Vaginal progesterone group n	p
Before treatment	10.28±2.9	11.18±3.49	0.260
After treatment	7.21±1.97	7.17±3.09	0.952
p	0.0001	0.0001	

Table 4. The effect of oral and vaginal progesterone use on the menstrual cycle

Endometrial thickness	Oral progesterone group n (%)	Vaginal progesterone group n (%)	
First cycle			
Regular	23 (71.88)	27 (79.41)	χ^2:0.18 p=0.669
Irregular	9 (28.12)	7 (20.59)	
Second cycle			
Regular	26 (81.25)	29 (85.29)	χ^2:0.012 p=0.912
Irregular	6 (18.75)	5 (14.71)	
Third cycle			
Regular	26 (81.25)	30 (88.23)	χ^2:0.2 p=0.654
Irregular	6 (18.75)	4 (11.77)	

tient in the oral treatment group. Genital pruritus was observed in two patients in the vaginal treatment arm. None of the patients discontinued treatment due to of aforementioned side effects.

DISCUSSION

The abnormal amount, duration, or frequency of bleeding in the menstrual cycle is defined as AUB. AUB accounts for about 20% of outpatient presentations for gynecological diseases.[4] Progestins are the main components in the medical treatment of AUB. Although many studies investigating the effect of micronized vaginal progesterone on threatened abortion,[8,9] luteal phase support,[10,11] prevention of premature birth,[12,13] and menopausal symptoms,[14,15] there are few studies on the efficacy of these drugs with vaginal administration in the treatment of AUB. Therefore, we aimed to compare oral and vaginal micronized progesterone with respect to treatment efficacy and patient satisfaction.

Progesterone refers to the natural hormone or micronized form, while progestogen refers to synthetic progestogens.[16] The limitations of the use of progesterones are poor absorption after oral intake and rapid-first-pass metabolism in the liver. Synthetic progestagens such as norethisterone, dydrogesterone, and medroxyprogesterone acetate have been produced to overcome low oral bioavailability. Although these synthetic progestagens exert a more potent effect on endometrium than natural progesterones, they also have a higher rate of undesirable androgenic side effects, fluid retention, headache, and mood disturbance.[17] Side effects of synthetic progesterones, the low oral bioavailability of natural progesterones led to the production of micronized progesterones, which enhanced the bioavailability and efficacy of natural progesterone. Due to micronization, administration via the vaginal route has gained interest. After vaginal administration, the drug passes to the uterus through direct diffusion, and uterine tissue concentration becomes unexpectedly higher than the plasma concentration.[17]

The study by Cicinelli et al.[18] on postmenopausal patients undergoing abdominal hysterectomy were randomized to receive either vaginal progesterone or intramuscular progesterone showed that endometrial tissue progesterone levels were markedly higher than serum progesterone levels in women who received vaginal progesterone.

The study by Karakus et al.[19] on 69 patients with AUB, in which oral dydrogesterone treatment was compared with vaginal micronized progesterone gel treatment with regard to their effect on the menstrual cycle and endometrial histology reported that after 3 months of treatment, the rate of regular cycles was 92.6% in vaginal micronized progesterone group, whereas it was 85.2% in oral dydrogesterone group. Both treatments were found to be effective in cycle regulation and the formation of secretory endometrium. The researchers found no significant difference between treatment arms. The study by Kostova and Zlatkov[20] concluded that vaginal micronized progesterone reduced the amount and duration of menstrual bleeding, and endometrial thickness, while there was no significant increase in hemoglobin values measured after treatment. The study by Di Carlo et al.[21] on 100 premenopausal women using transdermal 17-beta E2 divided into oral and vaginal micronized progesterone groups, who were administered between 14 and 25th days of the cycle reported that the rate of regular cycles was higher and the rate of spotting was lower in vaginal progesterone group, whereas no difference was found between groups with respect to endometrial thickness. In the study by Affinito et al.[22] on 78 premenopausal women with endometrial hyperplasia, 1000 mg micronized progesterone vaginal gel was administered between the 10th and 25th days of the menstrual cycle for 3–6 months. The researchers observed complete remission in 67 (90.5%) patients, 58 (78.3%) within the first 3 months, and 9 (11.5%) after 6 months of treatment. In addition, a significant decrease was observed in the amount, duration, and frequency of bleeding.

The literature investigating the effect of micronized progesterone on blood lipid levels has focused mostly on postmenopausal hormone replacement treatment. Various studies demonstrated that short-term use of vaginal micronized progesterone combined with intranasal or transdermal estrogen did not change the favorable effect of estrogen on lipid levels in postmenopausal women.[23,24] Similarly, our study found no significant alteration in blood lipid levels after oral or vaginal use of micronized progesterone.

A single-center, small sample size, a lack of long-term data, and the absence of anthropometric measures related to the lipid profile could be considered limitations of our study. However, this study is one of the most comprehensive studies in the literature comparing oral and vaginal micronized progesterone in AUB and patient satisfaction.

CONCLUSION

Considering its easy administration, fewer side effects, and well tolerability, vaginal micronized progesterone gel may be an alternative to oral preparations in the treatment of AUB.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 27.04.2022, Decision No: 2022/514/224/22).

Informed Consent

Prospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: P.Y., R.B.B., A.K., E.A.; Design: P.Y., G.Y., E.A., R.B.B.; Supervision: G.Y., E.K., A.K.; Materials: G.Y., E.M., A.K., R.B.B.; Data: P.Y., K.K., A.K., R.B.B.; Analysis: G.Y.,

E.K., K.K., R.B.B., E.M.; Literature search: E.A, P.Y., E.K, G.Y.; Writing: E.K., Ö.K., A.E., R.B.B., K.K.; Critical revision: P.Y., E.K., E.A., G.Y., E.M., K.K., R.B.B., Ö.K., A.E., P.B., A.K.

Conflict of Interest

None declared.

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Anormal Uterin Kanamanın Tedavisinde Oral ve Vajinal Mikronize Progesteronların Etkinliklerinin Karşılaştırılması: Prospektif Randomize Kontrollü Çalışma

Amaç: Anormal uterin kanaması olan hastalarda menstrüel siklusun düzenliliği, kan hemoglobin ve lipid seviyeleri, endometrial kalınlık açısından oral ve vajinal mikronize progesteronun etkisini karşılaştırmak.

Gereç ve Yöntem: Anormal uterin kanaması olan toplam 80 hasta iki gruba ayrıldı: oral mikronize progesteron grubu (n=40) ve vajinal mikronize progesteron grubu (n=40). Üç aylık tedaviden sonra hastaların tedaviye uyumu, tedaviden memnuniyeti (memnun-memnun değil), düzenli bir siklusu olup olmadığı ve tedavinin yan etkileri sorgulandı. Tedavi öncesi ve sonrası hastalar endometrial kalınlık, hematolojik ve biyokimyasal parametreler açısından karşılaştırıldı.

Bulgular: Toplam 66 hasta, birinci grup (oral progesteron) ve ikinci grup (vajinal progesteron) olarak ayrıldı. İki grup arasında yaş, parite ve vücut kitle indeksi (VKİ) açısından istatistiksel olarak belirgin fark yoktu. Her iki grupta da tedaviden sonra hemoglobin düzeylerinin önemli ölçüde arttığı bulundu (p=0.0001). Tedavi öncesi ve sonrası lipid değerleri açısından her iki grupta da istatistiksel olarak belirgin grup içi veya gruplar arası fark bulunmadı. Her iki grupta da tedaviden sonra endometriyal kalınlıkta anlamlı bir azalma oldu (p=0.0001). Tedavi sonrası oral progesteron grubunda 26 (%81.25) hastada, vajinal progesteron grubunda 30 (%88.23) hastada menstrüel siklus düzenli hale gelmesine rağmen gruplar arasında anlamlı fark bulunmadı. Birinci grupta (n=25/32) hastaların %78.12'si tedaviden memnun kalırken, ikinci grupta (n=28/34) %82.35'i tedaviden memnun kaldı ve gruplar arasında anlamlı fark bulunmadı.

Sonuç: Etkinliği ve güvenliği, kolay tolere edilmesi ve az yan etkisi göz önüne alındığında, vajinal mikronize progesteron, anormal uterin kanamanın tedavisinde oral preparatlara iyi bir alternatif olabilir.

Anahtar Sözcükler: Anormal uterin kanama; lipid; oral mikronize progesteron; vajinal mikronize progesteron.