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ARAŞTIRMA / RESEARCH

Micronised vaginal progesterone versus oral dydrogestrone in the treatment of dysfunctional uterine bleeding: efficacy and effects on lipid profile

Disfonksiyonel uterin kanamanın tedavisinde mikronize vajinal progesteron ile oral didrogestronun karşılaştırılması: etkinlikleri ve lipid profili üzerindeki etkileri

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Abstract

Purpose: The aim of this study was to compare the efficacy of short-course oral dydrogesterone versus vaginal micronized progesterone and to determine their effects on the lipid profile of the premenopausal women with dysfunctional uterine bleeding.

Materials and Methods: A total of 70 premenopausal women with dysfunctional uterine bleeding were randomly assigned to receive 90 mg of vaginal micronized progesterone (8% gel) (Group 1, n = 35) or 20 mg of oral dydrogesterone (Group 2, n = 35). The group 1 treatment consisted of self-application of vaginal progesterone, every other evening from the 17th to the 27th day of the menstrual cycle, for three cycles. The patients in Group 2 were treated with dydrogesterone 10 mg orally twice daily for 10 days, starting from the 15th day of the menstrual cycle, for three cycles.

Results: Body mass index increased significantly after three cycles of vaginal progesterone treatment whereas body mass index and serum LDL concentration increased significantly after three cycles of oral dydrogesterone treatment. The number of patients with secretory endometrium increased significantly after the completion of treatment in both groups.

Conclusion: Vaginal administration of micronized progesterone may be an alternative to oral progestins in the treatment of dysfunctional uterine bleeding. Vaginal micronized progesterone treatment seems to be as effective as oral progestin treatment and it also appears to have the advantage of easy application and no adverse effects on the lipid profile.

Keywords: dysfunctional uterine bleeding; oral dydrogesterone; vaginal progesterone

Öz

Amaç: Bu çalışmanın amacı, kısa süreli oral didrogesteron ile vajinal mikronize progesteronun etkinliğini karşılaştırmayı ve disfonksiyonel uterin kanamalı premenopozal kadınlarda lipid profili üzerindeki etkilerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Disfonksiyonel uterin kanaması olan toplam 70 premenopozal kadın, çalışmaya dahil edildi. 35 hastaya (Grup 1) 90 mg vajinal mikronize progesteron (% 8 jel), diğer 35 hastaya20 mg oral didrogesteron (Grup 2) almak üzere rastgele atandı. Grup 1 tedavisi, adet döngüsünün 17. ila 27. günü arasında her akşam üç döngü boyunca kendi kendine vajinal progesteron uygulamasından oluşuyordu. Grup 2'deki hastalar menstrüel siklusun 15. gününden başlayarak 10 gün süreyle günde iki kez 10 mg oral didrogesteron ile üç döngü boyunca tedavi edildi.

Bulgular: Üç kür vajinal progesteron tedavisinden sonra vücut kitle indeksi anlamlı olarak artarken, oral didrogesteron tedavisi sonrası vücut kitle indeksi ve serum LDL konsantrasyonu anlamlı olarak arttı. Her iki grupta da tedavinin tamamlanmasından sonra sekretuar endometriumlu hasta sayısı anlamlı olarak arttı.

Sonuç: Mikronize progesteronun vajinal uygulaması, disfonksiyonel uterin kanamasının tedavisinde oral progestinlere bir alternatif olabilir. Vajinal mikronize progesteron tedavisi oral progestin tedavisi kadar etkili görünmektedir ve aynı zamanda kolay uygulama avantajına sahip olduğu ve lipid profili üzerinde hiçbir yan etkisi olmadığı görülmektedir.

Anahtar kelimeler: Disfonksiyonel uterin kanama, oral dydrogesterone, vaginal progesterone

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INTRODUCTION

Dysfunctional uterine bleeding is an abnormal bleeding of uterine origin which does not occur because of pregnancy or any recognizable pelvic or systemic disease. In general, progestogens or estrogens and progestogens in combination are already widely used in the management of dysfunctional uterine bleeding, but the regime, dose and type of progestogen vary widely. There is no consensus on the optimum treatment approach for this clinical situation[1,2]. Progestogens encompass both progesterone and its synthetic derivatives, which are named progestins. Progestins in clinical use today belong to three main chemical families: progesterone derivatives (progesterone, retro-progesterone, 19-norprogesterone and 17alpha-hydroxyprogesterone); gonane and 19-nortestosterone derivatives (norethisterone, levonorgestrel, desogestrel, gestodene, norgestimate) and spironolactone derivatives[3,4].

Dydrogesterone is a retro-progesterone with a molecular structure similar to that of natural progesterone. As a C-21 steroid, it has a high affinity for progesterone receptors, a low anti-gonadotropic activity and anti-estrogenic activity, but no estrogenic or androgenic activity. The effect of 10 mg of dydrogesterone is comparable with that of 10 mg of medroxyprogesterone acetate[5,6].

Micronized progesterone preparation (8% gel, Crinone; Merck Serono, Bedfordshire, UK) has been designed for vaginal use. It has bio-adhesive characteristics, as a polycarbophil-based gel that conveys controlled and sustained-release properties. The vaginal route of administration has some advantages because it avoids the hepatic first-pass effect and direct vagina-to-uterus transport causes endometrial changes similar to those seen in the luteal phase despite the subphysiological plasma progesterone levels[7,8].

The aim of this study was to compare the efficacy of short-course oral dydrogesterone treatment versus vaginal micronized progesterone treatment and to determine their effects on the lipid profile of premenopausal women with dysfunctional uterine bleeding.

MATERIALS AND METHODS

Approval for the study was granted by the ethics Committee of Kahramanmaras Sütcü Imam University Medical Faculty (decision no: 88, dated: 09.06.2008). The study was conducted in Outpatients Clinic of the the Gynecology and Obstetrics Department of the Medical Faculty of Kahramanmaras Sütcü Imam University. Between July 2008 and January 2009. Written and verbal consent was obtained from all the study participants. All procedures were in compliance with The principles of the Declaration of Helsinki.

Sample

A total of 70 premenopausal women with dysfunctional uterine bleeding were randomly assigned to receive 90 mg of vaginal micronized progesterone (8% gel) (Group 1, n = 35) or 20 mg of oral dydrogesterone (Duphaston; Solvay Pharmaceuticals B.V., Weesp, Netherlands) (Group 2, n = 35). Simple randomization was conducted using computer-generated sequence. Allocation concealment was not performed.

Treatment in Group 1 consisted of self-application of vaginal progesterone cream, every other evening from the 17th to the 27th day of the menstrual cycle, for three cycles. Coitus was discouraged for 2 hours after drug administration. No women discontinued treatment and no women were lost during the follow-up in Group 1.

The patients in Group 2 were treated with dydrogesterone 10 mg orally twice daily for 10 days, starting from the 15th day of the menstrual cycle, for three cycles. No women discontinued treatment and no women were lost during the follow-up in Group 2.

Procedure

The diagnosis of dysfunctional uterine bleeding was made after the exclusion of other vaginal bleeding causes, including genital tract pathologies, iatrogenic causes and systemic conditions. For this purpose, a detailed history was obtained and physical examination was carried out. A menstrual cycle questionnaire for previous 3–6 months was used to obtain information about bleeding characteristics. An initial transvaginal ultrasound and saline infusion sonohysterography followed by endometrial sampling were performed in all patients.

The patients included in the study were those with no menopausal symptoms, did not take hormone therapy, were between 30 and 40 years of age,

diagnosed with dysfunctional uterine bleeding, had no contraindication for progesterone treatment and had endometrial thickness >5 mm on transvaginal ultrasound.

Patients taking anti-coagulants or anti-prostaglandins, preferring hormonal contraceptive methods, with known intolerance to progesterone or progestins, or with an endometrial pathology (endometritis, endometrial hyperplasia or carcinoma) were excluded from the study.

Blood samples

Venous blood was collected for routine hemogram, coagulation tests (PT, PTT), biochemistry and hormone analysis between 08.00 and 11.00 in the morning, following a 10-12 hour fasting. Hemogram in blood sample for EDTA tubes and PT and PTT tests in citrated tube samples were studied within half an hour after the tests. If sample samples were given to the yellow capped gel biochemistry tubes, they were centrifuged for 5 minutes at 4000 g after 30 minutes. Serum was separated immediately. Serums were stored in a freezer at -80^0C until the day of analysis. Among the samples included in the study, serum total cholesterol level (mg / dl), triglyceride level (mg / dl), LDL level (mg / dl), HDL level (mg / dl) were used in Siemens Advia 2400 brand autoanalyzer device with Siemens AdviaChemistry (USA) ready-made commercial kits.), ALT (U / L), AST (U / L) and prolactin (ug / L) measurements were made.

Blood samples were tested for complete blood count, liver transaminases, prothrombin time, activated partial thromboplastin time, thyroid-stimulating hormone (TSH), free thyroxine and prolactin at the admission of the patients.

Data related to body mass index and serum concentrations of cholesterol, triglyceride, high density lipoprotein (HDL) and low density lipoprotein (LDL) were recorded before the initiation of medical treatment and after the completion of three treatment cycles. Endometrial sampling from all participants was repeated at the 22nd day during the third treatment cycle.

Patient satisfaction

Patient satisfaction was evaluated by an interview in the outpatient clinic after the completion of treatment. It was measured with the question of, "Please assess your overall satisfaction during treatment". Patients were asked to choose one of the six answers: not satisfied (0), very little satisfied (1), less satisfied (2), moderately satisfied (3), satisfied (4) or very satisfied (5) (Table 1).

A questionnaire about menstrual irregularities and grading satisfaction after treatment was done face-to-face by the researcher. Menstrual cycle patterns at the beginning and at the 3rd month were questioned. Patients were asked to rate their medication satisfaction between 0 and 5. Average satisfaction score was 4.28 points in the group using oral preparations, while it was 4.77 points in the vaginal preparation group. However, in the statistical analysis performed, it was observed that there was no significant difference in satisfaction between the two drugs. It was observed that the effectiveness of both drugs in regulating patients' menstruation was similar.

Table 1. Satisfaction scores achieved in patients using Duphaston and Crinone

Satisfaction scores *	Duphaston (n= 35)	Crinone (n= 35)
0	2	1
1	0	0
2	1	0
3	4	0
4	4	3
5	24	31
Mean	4.28	4.77

not satisfied (0), very little satisfied (1), less satisfied (2), moderately satisfied (3), satisfied (4) or very satisfied (5).

Statistical analysis

Data obtained in the study were analyzed statistically using Statistical Package for Social Sciences version 13.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (range: minimum-maximum) and categorical variables as number or percentage. Fisher's Exact test, The Paired Samples t-test and Pearson Chi-square test were used in the comparisons. A two-tailed p values of $< 0.05$was accepted statistically significant.

RESULTS

The women in the vaginal progesterone and oral dydrogesterone groups had statistically similar age, body mass index, hemoglobin, prothrombin time, activated partial thromboplastin time and hepatic transaminases. Serum concentrations of total cholesterol, triglyceride, HDL, LDL, TSH, free thyroxine and prolactin were statistically similar in

both groups (Table 2). Body mass index increased significantly after three cycles of vaginal progesterone treatment (p=0.04). The women in the vaginal progesterone group had statistically similar serum levels of total cholesterol, triglyceride, HDL and LDL levels before the initiation of treatment and after the completion of three treatment cycles (Table 3). Body mass index and serum LDL concentration increased significantly after three cycles of oral dydrogesterone treatment (p=0.04 and p=0.03 respectively). The women in the oral dydrogesterone group had statistically similar serum levels of total cholesterol, triglyceride and HDL levels before the initiation and after the completion of treatment (Table 3).

Table 2. Baseline characteristics of the patients

	Vaginal progesterone (n=35)	**Oral dydrogesterone (n=35)**	**P**
Age (years)	34.7±6.8	32.5±8.0	0.23
Body mass index (kg/m²)	27.6±3.8	26.7±4.2	0.16
Hemoglobin (g/dl)	12.5±1.7	12.8±1.5	0.46
Prothrombin time (seconds)	13.1±0.6	13.0±0.9	0.55
Activated partial thromboplastin time (seconds)	29.1±2.0	28.38±3.21	0.26
Alanine transaminase (U/L)	42.3±12.1	42.9±12.1	0.81
Aspartate transaminase (U/L)	25.4±10.9	24.1±8.8	0.59
Total cholesterol (mg/dl)	167.0±38.2	167.7±44.1	0.66
Triglyceride (mg/dl)	128.5±73.3	117.8±62.1	0.49
High density lipoprotein (mg/dl)	41.2±9.6	38.9±8.9	0.44
Low density lipoprotein (mg/dl)	100.9±34.1	104.3±36.5	0.27
Thyroid-stimulating hormone (U/ml)	2.1±1.7	2.4±1.9	0.88
Free thyroxine (ng/dl)	1.3±0.9	1.6±0.7	0.92
Prolactin (ng/ml)	6.9±4.5	6.7±5.8	0.86

Table 3. Characteristics of the patients before and after treatment

Vaginal Progesterone Group			
	Before treatment	After three cycles of treatment	P
Body mass index (kg/m²)	27.6±3.82	28.8±3.9	0.04*
Total cholesterol (mg/dl)	167.0±38.2	173.4±51.1	0.49
Triglyceride (mg/dl)	128.5±73.3	120.6±67.5	0.60
High density lipoprotein (mg/dl)	41.2±9.6	40.9±7.2	0.87
Low density lipoprotein (mg/dl)	100.9±34.1	114.4±35.6	0.06
Oral Dydrogesterone Group			
	Before treatment	After three cycles of treatment	P
Body mass index (kg/m²)	26.7±4.2	27.9±4.3	0.04*
Total cholesterol (mg/dl)	167.7±44.1	169.0±45.9	0.77
Triglyceride (mg/dl)	117.8±62.1	117.1±64.9	0.95
High density lipoprotein (mg/dl)	38.9±8.9	39.4±8.3	0.75
Low density lipoprotein (mg/dl)	104.3±36.5	116.1±53.0	0.03*

*p<0.05 was accepted to be statistically significant.

Table 4. The assessment of patient satisfaction

	Vaginal progesterone (n=35)	**Oral dydrogesterone (n=35)**
Not satisfied (0)	2 (5.7%)	1 (2.9%)
Very little satisfied (1)	0 (0.0%)	0 (0.0%)
Less satisfied (2)	1 (2.9%)	0 (0.0%)
Moderately satisfied (3)	4 (11.4%)	0 (0.0%)
Satisfied (4)	4 (11.4%)	3 (8.5%)
Very satisfied (5)	24 (68.6%)	31 (88.6%)

$\chi 2 = 59,124$, p=0.66

The mean satisfaction scores of the two groups were statistically similar (4.8±3.2 vs 4.3±2.9, p=0.57). (Table 3). At the initiation of treatment, secretory endometrium was detected in 27 women in the vaginal progesterone group and 26 women of the oral dydrogesterone group (77.1% vs 74.3%, p=0.88). At the end of the three-month period, secretory endometrium was determinated in 32 women in the vaginal progesterone group and 29 women in the oral dydrogesterone group (91.4% vs 82.9%, p = 0.74). Secretory endometrium was present in 27 women at the beginning of vaginal progesterone treatment and in 32 women at the end of the treatment (77.1% vs 91.4%, p=0.004). Secretory endometrium was diagnosed in 26 women at the beginning of oral dydrogesterone treatment and in 29 women at the completion of oral dydrogesterone treatment (74.3% vs 82.9%, p=0.004).

DISCUSSION

Dysfunctional uterine bleeding is a common problem in women of childbearing age. It is diagnosed after all other causes of abnormal uterine bleeding, such as pregnancy, iatrogenic causes, systemic conditions and obvious genital tract pathologies, have been ruled out[9]. Several medical treatment options have been used successfully for the management of dysfunctional uterine bleeding. These medications include danazol, combined oral contraceptives, progestogens (both micronized progesterone and progestins) and gonadotropin releasing hormone analogues[10].

The biological potency of progestins varies depending on the clinical outcomes which are usually ovulation inhibition and endometrial transformation. When these outcomes are considered, gonane derivatives appear to be the most active compounds, with potency 100 fold greater than that of the natural hormone. A progestin inhibits ovulation if it is administered systemically in adequate doses. This action is mainly exerted at the hypothalamic level where, physiologically, progesterone decreases the number of luteinizing hormone pulses[7,11].

The routes most commonly preferred in drug delivery are oral for systemic effects and topical for local effects. Progestins in current use differ largely in their pharmacokinetics. In general, after oral intake, these compounds are rapidly absorbed and distributed so that serum concentrations reach their peak between 1 hour and 4 hours. It has been proven that--even when administered in doses that do not constantly inhibit ovulation--a progestin can still remain effective by acting on the cervical mucus and endometrium[7,11,12].

Modern technology has allowed the development of vaginal drug delivery systems that optimize pharmacokinetic profiles. Progesterone can be delivered directly to the endometrium by means of hormonal intrauterine devices or hormonal preparations which have been approved for vaginal administration. Local progesterone therapy is one of the methods used in the treatment of dysfunctional uterine bleeding[11-13].

Many studies have investigated the effects of vaginal micronized progesterone in luteal phase support, in the treatment of endometrial hyperplasia, secondary amenorrhea, cyclical mastodynia, threatened abortion and menopausal symptoms. It has been reported that the action of micronized progestin seems to be purely local when it is directly delivered to the uterine cavity. However, vaginal administration of micronized progesterone results in serum progesterone levels that are sufficient to sustain serum progesterone levels and, therefore, exert systemic effects[14,15].

Another issue to be considered is that long term progestin treatment may lead to bleeding irregularities. It has been demonstrated that vaginal delivery of micronized progesterone could achieve an acceptable incidence of irregular bleeding when combined with transdermal administration of low dose estrogen in early postmenopausal women[16,17].

Data are limited on the efficacy and safety of local micronized progesterone in the treatment of dysfunctional uterine bleeding[6,8]. Karakus et al. found that both vaginal and oral progesterone preparations had similar effects clinically and histopathologically, with acceptable side effects in premenopausal women with dysfunctional uterine bleeding[6]. Kostova et al. also stated that vaginal delivery of micronized progesterone significantly attenuated bleeding intensity and shortened the bleeding duration in premenopausal women with dysfunctional uterine bleeding[8]. Accordingly, the results of the current study show that vaginal delivery micronized progesterone is as effective as oral dydrogesterone treatment. This finding has been verified by the statistical similarity in the patient satisfaction scores, adverse effect incidence and endometrial biopsy results of the vaginal

progesterone and oral dydrogesterone groups.

In general, progestins can induce adverse alterations in lipid metabolism. These synthetic compounds have varying pharmacological properties depending on the molecules from which they are derived, either testosterone or progesterone. Very small structural changes in these molecules may induce considerable differences in their effects on various targets and especially on the surrogate markers of cardiovascular disease risk. These differences may be significant to the point of reversing the beneficial effects of estrogen. Natural progesterone and some of its derivatives such as the 19-norprogesterone molecules or the new molecules drospirenone and dienogest have no negative effect on the lipids[18,20].

A few studies have indicated that micronized progesterone may have a better risk profile in respect of variables related to cardiovascular risk[21,22]. Casanova et al. declared that short term exposure to cyclic vaginal micronized progesterone did not alter the metabolic and cardiovascular effects of percutaneous or intranasal estradiol in apparently healthy, early postmenopausal women. They showed that serum concentrations of total cholesterol and LDL decreased significantly (even below the baseline values) in postmenopausal women who used estradiol in combination with micronized progesterone[23]. In the present study, only body mass index increased significantly after three cycles of vaginal progesterone treatment whereas body mass index and serum LDL concentration increased significantly after three cycles of oral dydrogesterone treatment.

These findings suggest that vaginal administration of micronized progesterone may represent an alternative for oral progestins in the treatment of dysfunctional uterine bleeding. Vaginal micronized progesterone treatment seems to be as effective as oral progestin treatment. Moreover, such treatment appears to have the advantages of ease of application, a large potential area for absorption and no the adverse effects on the lipid profile.

The power of the present study is limited by the relatively small cohort size, lack of long term data, and the absence of anthropometric measures related to the lipid profile.

Further research is warranted to evaluate the efficacy of oral dydrogesterone and vaginal micronized progesterone and to determine their effects on the lipid profile of premenopausal women with dysfunctional uterine bleeding.

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REFERENCES

1. Davidson BR, Dipiero CM, Govoni KD, Littleton SS, Neal JL. Abnormal uterine bleeding during the reproductive years. J Midwifery Womens Health 2012;57:248-54.
2. Tsai MC, Goldstein SR. Office diagnosis and management of abnormal uterine bleeding. Clin Obstet Gynecol. 2012;55:635-50.
3. Bitzer J, Heikinheimo O, Nelson AL, Calaf-Alsina J, Fraser IS. Medical management of heavy menstrual bleeding: a comprehensive review of the literature. Obstet Gynecol Surv. 2015;70:115-30.
4. Hillard PA. Menstrual suppression: current perspectives. Int J Womens Health. 2014;6:631-7.
5. Schindler AE. Progestational effects of dydrogesterone in vitro, in vivo and on the human endometrium. Maturitas. 2009;65:3-11.
6. Karakus S, Kiran G, Ciralik H. Efficacy of micronised vaginal progesterone versus oral dydrogestrone in the treatment of irregulardysfunctional uterine bleeding: a pilot randomised controlled trial. Aust N Z J Obstet Gynaecol. 2009;49:685-8.
7. Royer PA, Jones KP. Progestins for contraception: modern delivery systems and novel formulations. Clin Obstet Gynecol. 2014;57:644-58.
8. Kostova P, Zlatkov V. Clinical study on the effect of vaginal administration of micronized progesterone at dysfunctional uterinebleeding in premenopause. Akush Ginekol (Sofia). 2009;48:3-7.
9. Deligeoroglou E, Creatsas G. Menstrual disorders. Endocr Dev. 2012;22:160-70.

10. Hickey M, Higham JM, Fraser I. Progestogens with or without estrogen for irregular uterine bleeding associated with anovulation. Cochrane Database Syst Rev. 2012;9:CD001895.
11. Paulson RJ, Collins MG, Yankov VI. Progesterone pharmacokinetics and pharmacodynamics with 3 dosages and 2 regimens of an effervescent micronized progesterone vaginal insert. J Clin Endocrinol Metab. 2014;99:4241-9.
12. Africander D, Verhoog N, Hapgood JP. Molecular mechanisms of steroid receptor-mediated actions by synthetic progestins used in HRT and contraception. Steroids. 2011; 6:636-52.
13. Sitruk-Ware R. Pharmacology of different progestogens: the special case of drospirenone. Climacteric. 2005;8:4-12.
14. Fujiwara T. A multi-center, randomized, open-label, parallel group study of a natural micronized progesteronevaginal tablet as a luteal support agent in Japanese women undergoing assisted reproductive technology. Reprod Med Biol. 2015;14:185-193.
15. CoomarasamyA, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S et al. A Randomized Trial of Progesterone in Women with Recurrent Miscarriages. N Engl J Med. 2015;373:2141-8.
16. Fernández-Murga L, Hermenegildo C, Tarín JJ, García-Pérez MÁ Endometrial response to concurrent treatment with vaginal progesterone and transdermal estradiol. Climacteric. 2012;15:455-9.
17. Di Carlo C, Tommaselli GA, Gargano V, Savoia F, Bifulco G, Nappi C. Transdermal estradiol and oral or vaginal natural progesterone: bleeding patterns. Climacteric. 2010;13:442-6.
18. Nath A, Sitruk-Ware R. Different cardiovascular effects of progestins according to structure and activity. Climacteric. 2009;12:96–101.
19. Sitruk-Ware R, Nath A. Metabolic effects of contraceptive steroids. Rev Endocr Metab Disord. 2011;12:63-75.
20. Rafie S, Borgelt L, Koepf ER, Temple-Cooper ME, Lehman KJ. Novel oral contraceptive for heavy menstrual bleeding: estradiol valerate and dienogest. Int J Womens Health. 2013;5:313-21.
21. Spritzer PM, Vitola D, Vilodre LC, Wender MC, Reis FM, Ruschel S et al. One year follow-up of hormone replacement therapy with percutaneous estradiol and low-dose vaginal natural progesterone in women with mild to moderate hypertension. Exp Clin Endocrinol Diabetes. 2003;111:267–73.
22. Bukowska H, Stanosz S, Zochowska E, Millo B, Sieja K, Chelstowski K et al. Does the type of hormone replacement therapy affect lipoprotein (a), homocysteine, and C-reactive protein levels in postmenopausal women? Metabolism. 2005;54:72–8.
23. Casanova G, Spritzer PM. Effects of micronized progesterone added to non-oral estradiol on lipids and cardiovascular risk factors in early postmenopause: a clinical trial. Lipids Health Dis. 2012;11:133.