

Prognostication, prevention and treatment of disorders in the menopause in women with hyperproliferative processes of reproductive system

T.F. Tatarchuk, L.I. Butina

Donetsk National Medical University

The objective: to evaluate the efficiency of prognostication, prevention and treatment, of disorders in the menopause in women with hyperproliferative processes of reproductive system (HPPRS)

Materials and methods. To identify factors associated with severity of the course of disorders in the menopause, namely, the climacteric syndrome (CS) and evaluation of the degree of their influence on the passage of the menopause, the method of construction and analysis of multivariable mathematical models was used. While constructing the model of our method the results of research of 19 indexes in 124 women aged 45 to 79 with signs of disorders in menopause such as climacteric syndrome and the signs of HPPRS taking into consideration the results of ultrasound research uterine and appendages, and on the basis of pathohistological mucosal scraping of uterine cavity. The substitutive hormone prevention (SHP) of neurovegetative and psycho-emotional disorders in menopause (NVPDM) was conducted among 60 women aged 40 to 53 and treatment was performed in 36 women (1 T-P) after substitutive hormone prevention (SHP) of neurovegetative and psycho-emotional disorders in menopause (NVPDM) and in 31 women (1-T) after naturally menopause aged 48 to 60 with the signs of HPPRS according to the data of ultrasound uterine and the results of histological investigations of mucosal scrapings of the uterus. To evaluate the effectiveness of prevention and treatment of NVPDM in women with HPPRS the hormone level was measured: follicle-stimulating (FSH), luteinizing (LH), estradiol (E), progesterone (PH), prolactin (PRL), testosterone (TS), cortisol (CR), insulin, indices of the level of immunoglobulin A, G, M, (IgA, IgG, IgM) of interleukin 1,2 (IL-1, IL-2), of tumor necrosis factor (TNF) before and after prophylaxis and treatment. The control group for prevention included 50 women and for treatment 35 women of the same age category without NVPDM and HPPRS. The control group for the prevention included 50 women and for the treatment 35 women of the same age category without NVPDM and HPPRS.

Results. After treatment the intensity of NVPDM declines and MIK in women after the usage of our medical prognostication complex (n=36) is $9,2 \pm 1,2$, which is 2,5 times less than before treatment, in women with natural menopause MIK is $11,6 \pm 1,4$, which is 2,1 times less than before treatment. Consistent application of substitution hormone prognostication and treatment by our worked out method allow to decrease the intensity of NVPDM in women with HPPRS (n=36) according to the MIK data in 1,26 times, as compared in women with natural menopause (n=31), after treatment according our method, without previous SHP.

Conclusions. The using of the method of prognostication, prevention and treatment allows to reduce the intensity of NVPDM on the account of the decline of the gonadotropins level as compared with healthy women, to recover the index of

humoral link of immune system and to prevent the exhaustion of the antitumor protection factors.

Key words: mathematical model, disorders in the menopause, prognostication, treatment, hyperproliferative processes of reproductive system, adaptation system, hormonal homeostasis, immune system.

The relevance of problem of disorders in menopause is connected with the fact in that both in the world and in Europe the number of women with menopause is quickly increasing. By present moment 10% of women population are women of postmenopause age. Different levels of severity of the course of neurovegetative and psychoemotional disorders in menopause climacteric syndrome are met in 40–60% of women aged after 40. The first signs appear on the border between 45–49 in post menopause [5].

Usually we appoint the treatment of these disorders after their appearance and use the substitutive hormone therapy by estrogenous preparations. But for women with hyperproliferative processes of the reproductive system, including myoma and endometrial hyperplasia, the appointment of estrogenous preparations is forbidden, because it may lead to the activation of proliferative processes [9].

That's why, to our mind, it's very important to forecast of the possibilities of the development of disorders in menopause in women, then correct the proliferative process, and, if necessary, treat climacteric disorders.

We decided to work out a scientifically based method of prognostication, prevention and treatment of menopause disorders in women with hyperproliferative processes of reproductive system and evaluate its efficiency.

The objective: to evaluate the efficiency of prognostication, prevention and treatment, of disorders in the menopause in women with hyperproliferative processes of reproductive system (HPPRS)

MATERIALS AND METHODS

To identify factors associated with severity of the course of disorders in the menopause, namely, the climacteric syndrome (CS) and evaluation of the degree of their influence on the passage of the menopause, the method of construction and analysis of multivariable mathematical models was used [7]. While constructing the model of our method the results of research of 19 indexes in 124 women aged 45 to 79 with signs of disorders in menopause such as climacteric syndrome and the signs of HPPRS taking into consideration the results of ultrasound research uterine and appendages, and on the basis of pathohistological mucosal scraping of uterine cavity [2].

The substitutive hormone prevention (SHP) of neurovegetative and psycho-emotional disorders in menopause (NVPDM) was conducted among 60 women aged 40 to 53 with the signs of HPPRS according to the data of ultrasound uterine and the results of histological investigations of mucosal scrapings of the uterus [1].

The treatment was performed in 36 women (1 T-P) after substitutive hormone prevention (SHP) of neurovegetative and psycho-emotional disorders in menopause (NVPDM) and in 31 women (1-T) after naturally menopause aged 48 to 60 with the signs of HPPRS according to the data of ultrasound uterine and the results of histology investigations of mucosal scrapings from the uterus, and the appointment of the complex of preparations [3].

To evaluate the effectiveness of prevention and treatment of NVPDM in women with HPPRS the hormone level was measured: follicle-stimulating (FSH), luteinizing (LH), estradiol (E), progesterone (PH), prolactin (PRL), testosterone (TS), cortisol (CR), insulin, indices of the level of immunoglobulin A, G, M, (IgA, IgG, IgM) of interleukin 1,2 (IL-1, IL-2), of tumor necrosis factor (TNF) before and after prophylaxis and treatment. The control group for prevention included 50 women and for treatment 35 women of the same age category without NVPDM and HPPRS.

RESULTS AND DISCUSSION

First there were established the most significant risk factors, of the development of disorders in the menopause in women with hyperproliferative processes of the reproductive system. There was first installed that the presence in women with hyperproliferative processes of the reproductive system of chronic foci of inflammation in the appendages of the uterus, hypermenstrual syndrome, hystero-myoma, hypertensive illness, chronic extragenital hearths of infection increase ($p < 0,05$) the severity of the course of disorders in the menopause [2].

For the first time on the basis of prognosis some groups of women with hyperproliferative processes of the reproductive system, in the period of before and after menopause with the risk of development of disorders in menopause were chosen, and the hormonal homeostasis, the state of the immune and adaptative system, the morphological peculiarities of reproductive system were studied.

By the results of forecasting of the severity of the course of disorders in menopause in 60 women with HPPRS in premenopause, a slight degree of the course of disorders in menopause was prognosticated in 20 women (24,7%) one of fourth women. The middle degree of the course of disorders in menopause was prognosticated in 37 women (45,7%), half of women. The heavy degree of the course of disorders in menopause was prognosticated in 24 women (29,6%), each of third women.

For maintaining cyclic changes in the endometrium women with HPPRS need a greater level of sex hormones than healthy ones, which is provided by the increased production of gonadotropic hormone and is accompanied by the development of NVPDM. The increase of the level of prolactin, cortisol, insulin forms the state of «hormonal stress» the consequence of which may be the process of disorders of microcirculation and the following activation of proliferative processes in reproductive system. Than the index of the immunity in organism increases that testifies about the activation of adaptation system of the antinoplastic defense [1, 4].

The hyperproduction of cytokiniv (IL-1, IL-2, TNF) may increase the severity of the course of neurovegetative and psycho-emotional disorders in menopause. The presence of hyperproliferative processes in endometrium with morphological sings of chronic inflammation supports tense activity of humoral link of the immunity. It can be seen from the increased level of all immunoglobulins, and this may lead to the denutrition of their compensatory possibilities and to the development of immunodeficiency. This will complicate the passage of the hyperproliferative disease and cause the development of disorders in menopause [10]. So the premises for the development of disorders in menopause are formed in women with HPPRS in premenopause, which results in changes of hormonal homeostasis, immunoreactivity and processes of immunoregulation of organism. No doubt, they need of correction [4].

For the first time the scientifically based method of prevention of disorders in menopause using the substitutive hormone prevention and immunocorrection therapy, has been developed and applied in premenopause of women with HPPRS on the basis of the results obtained. The effectiveness of this prevention was evaluated [1, 4].

After prevention use in 24 women the menstrual function was recovered and the symptoms of NVPDM disappeared. So the prevention of NVPDM was performed among 40% of women. In 36 women the frequency of heavy degree of the course of disorders in menopause decreased to 6 times compared with the results, of prognostication. The middle index of modified index of Kupermana [6] is $22,8 \pm 1,5$. This intensity of the symptoms of NVPDM corresponds to the middle degree of the course of disorders in menopause [1].

The use of SHP of NVPDM among women with HPPRS reduces the level of gonadotropic hormone, reduces the exertion of immunologic reaction and reduces the risk of denutrition of their compensatory possibilities and allows to liquidate NVPDM for 40% of women in the period of premenopause [1, 4].

For the benefit of the application of the proposed prevention of disorders in menopause is the positive influence on the activity of hyperproliferative processes of reproductive system. After prevention the tendency to decrease the dimension of uterus was observed, and this testifies about the profit of its implementation [1].

Among women with HPPRS 1 L-P group (n=36) disorders of hormonal homeostasis appeared in premenopause. When they applied for help to the gynecology department, the heavy degree of the course of disorders in menopause is prognosticated for each of third women (27,8%). The middle degree of the course of disorders in menopause is prognosticated for half of women (44,4%). It is a bare necessity the introduce the prevention method of disorders in menopause for decreasing the symptoms of NVPDM in women in premenopause.

The slight degree of the course of disorders in menopause is prognosticated in 20 women (24,7%) each of fourth women. The middle degree of the course of disorders in menopause is prognosticated in 37 women (45,7%), half of women. The heavy degree of the course of disorders in menopause is prognosticated in 24 women (29,6%), each of third women. In women with menopausal HPPRS after naturally menopause (n=31) the heavy degree of the course of disorders in menopause is prognosticated in 19,4% of women which is less as compared with women of 1 L-P group (n=36), but the middle degree of the course of NVPDM is prognosticated in 61,3% of women. That is more than with women of 1 L-P group ($p < 0,05$). So in women with HPPRS in which NVPDM was developed in premenopause to 1,4 times the risk of the development of heavy degree of the course of disorders in menopause increased as compared with women after naturally menopause.

Before treatment the difference of index investigated of the hormone level of adaptation system (insulin, cortisol, prolactin) was not observed in women with HPPRS (myoma uterus and hyperplasia of endometrium) in menopause compared with healthy women of the same age category without HPPRS ($p > 0,05$). But compared with healthy women in premenopause this index was increased ($p < 0,05$) [3].

This testifies about equal tense work of these systems in women in menopause independently either of presence or absence of HPPRS. It is necessary for prevention of denutrition of compensatory possibilities of adaptation system to appoint the preparations for recovery of functional possibilities of adaptation system, to adapt to the existence of the deficit of sex hormones.

In women with HPPRS after substitutive hormone prevention in premenopausal was proposed (n=36), the level of estrogens increased and for mechanism of negative reverse signals the

Table 1

Index of humoral link of immunity in women with hyperproliferative processes of reproductive system(HPPRS) in the menopause after prophylaxis of neurovegetative and psychoemotional disorders in the menopause(NVPDM) and without it (M±m)

Index	Groups		
	Women after prophylactic NVPDM without menstrual function (n=36) ^Δ	Women with naturally menopause without prophylactic NVPDM (n=31) [°]	Control group (n=35)
IgA, g/l	2,37±0,08 ^Δ	2,14±0,03 [°]	3,6±0,05
IgG, g/l	10,4±0,6	9,29±0,6 [°]	10,9±0,4
IgM, g/l	0,91±0,03 ^Δ	0,9±0,04 [°]	1,3±0,02

Note: ^Δ – statistical difference between index in women after prophylactic NVPDM without menstrual function compared with healthy women in the menopause p<0,05; [°] – statistical difference between index in women with naturally menopause compared with healthy women in the menopause p<0,05.

Table 2

Index of cytokinin in women with hyperproliferative processes of reproductive system (HPPRS) in the menopause after prophylaxis of neurovegetative and psychoemotional disorders in the menopause (NVPDM) and without it (M±m)

Index	Groups		
	Women after prophylactic NVPDM without menstrual function (n=36) ^Δ	Women with naturally menopause without prophylactic NVPDM (n=31) [°]	Control group (n=35)
IL-1, pg/ml	19,2±0,9 ^Δ	11,5±0,9 [°]	6,5±0,5
IL-2, pg/ml	9,2±0,2 ^Δ	8,6±0,2	11,3±0,3
Tumor necrosis factor, pg/ml	41,1±1,6 ^Δ	26,8±1,9	28,7±1,2

Note: ^Δ – statistical difference between index in women after prophylactic NVPDM without menstrual function compared with healthy women in the menopause p<0,05; [°] – statistical difference between index in women with naturally menopause compared with healthy women in the menopause p<0,05.

level of FSH decreased, and the intensity of the symptoms of NVPDM reduced, according to the modified index of Kupermana (MIK) [6] at the beginning of menopause. Gonadotropins do not stimulate the follicular apparatus of the ovaries, and that is why the production of estrogens and the activity of HPPRS do not increase. The usage of SHP lessen the pressure on the hypothalamic pituitary system during adaptation of women with HPPRS to hormone disbalance in the period of menopause which stimulates the development of NVPDM. So the usage of SHP in women with NVPDM makes the beginning of the menopause better and promotes efficiency in treatment of disorders in menopause period [1, 3].

In women with HPPRS in menopause a greater level of sex hormones was observed than in healthy ones, which is provided by the increased production of gonadotropic hormone and is accompanied by the development of NVPDM [3].

Compared with the healthy women in menopause in women 1 L-P group (n=36) the level of IgA decreases for 35%, IgM – for 25%, (p<0,05), in women of 1-L group (n=31), IgA decreased for 41%, IgM – for 31%, IgG- for 15% (p<0,05) (table 1).

Among tested women the level of the apoptosis inhibitor IL-2 becomes less for 19% (n=36), and for 24% (n=31) compared with healthy women in the period of menopause (p<0,05) and the level of the apoptosis inductor IL-1 [8] becomes 2,95 times higher (n=36), and 1,8 times higher (n=31). The level of TNF remains high 1,4 times, compared with healthy women in menopause. All these factors testify for activation of antitumor protection (table 2).

So we can trace the decline of humoral link of immunity and activation of antitumor protection in women with HPPRS, compared with healthy women. This may lead to the denutrition of antitumor protection factors. That's why we added preparations for recovery of immunity and antitumor protection to the invented complex method of treatment of NVPDM in women with HPPRS.

After treatment in women with naturally menopause the levels of FSH increased for 36%, estradiol – for 29% (p<0,05). In women after SHP and treatment (n=36) the level of estrogens decreased in 3,2 times, the level of FSH increased in 1,4 times but it was less for 35%, compared with healthy women (p<0,05).

Among women of both groups after the treatment we can trace statistically bigger increase of IgA and IgM level as compared with the index before treatment (p<0,05). Their concentration the same as IgG level doesn't differ from the index of healthy women in the menopause period (p>0,05). IL-1 level decreased as compared with the data before treatment, but it remains higher as compared with the data of healthy women (p<0,05). This is due to the fact, that there are places of hyperproliferation among tested women, and the activity of antitumor protection factors remains in tense condition, compared with the healthy women, which may lead to denutrition. Evidently the TNF level decreased 1.8 times, compared to the data before treatment (p<0,05), so it was 21% less than with healthy women in menopause (p<0,05). IL-2 level increased (p<0,05) as compared with the level before treatment, as a result the denutrition activity of apoptosis inhibitor was restored, which testifies the decrease of the hyperproliferation activity in reproductive system and the decline of tension on the antitumor protection system. After treatment the intensity of NVPDM declines and MIK in women after the usage of our medical prognostication complex (n=36) is 9,2±1,2, which is 2,5 times less than before treatment, in women with natural menopause MIK is 11,6±1,4, which is 2,1 times less than before treatment. Consistent application of substitution hormone prognostication and treatment by our worked out method allow to decrease the intensity of NVPDM in women with HPPRS (n=36) according to the MIK data in 1,26 times as compared in women with natural menopause (n=31), after treatment according our method, without previous SHP.

CONCLUSIONS

The using of the method of prognostication, prevention and treatment allows to reduce the intensity of NVPDM on the account of the decline of the gonadotropins level as compared with healthy women, to recover the index of humoral link of immune system and to prevent the exhaustion of the antitumor protection factors.

Прогнозування, профілактика та лікування порушень у менопаузі у жінок з гіперпроліферативними процесами репродуктивної системи
Т.Ф. Татарчук, Л.І. Бутіна

Мета дослідження: оцінювання ефективності прогнозування, профілактики та лікування порушень у менопаузі у жінок з гіперпроліферативними процесами репродуктивної системи (ГППРС).

Матеріали та методи. Для виявлення чинників, пов'язаних з тяжкістю перебігу клімактеричного синдрому (КС), і оцінювання їхнього впливу на розвиток важкого ступеня перебігу порушень у менопаузі був використаний метод побудови і аналізу багатфакторних математичних моделей. Під час побудови моделі використовували результати дослідження 19 показників у 124 пацієнток віком від 45 до 79 років з наявністю порушень у менопаузі у формі КС та ознак міоми матки та гіперплазії ендометрія за даними ультразвукового дослідження матки і придатків чи на підставі патогістологічного дослідження зскрібка з порожнини матки.

Замісну гормональну профілактику (ЗГП) нейровегетативних та психо-емоційних порушень у менопаузі (НВПМ) проводили у 60 жінок віком від 40 до 53 років, а лікування НВПМ проводили у 67 жінок віком від 48 до 60 років після ЗГП – 1 Л-П група (n=36) та з природною менопаузою – 1-Л група (n=31) з наявністю ознак ГППРС за даними УЗД матки та результатами гістологічного дослідження зскрібка з порожнини матки. Для оцінки ефективності профілактики та лікування НВПМ досліджували рівень гормонів: фолікулостимулювального (ФСГ), лютеїнізуючого (ЛГ), естродіолу (Е), прогестерону (ПГ), тестостерону (ТС), пролактину (ПРЛ), кортизолу (КР), інсуліну, рівні імуноглобулінів А, М, G (IgA, IgM, IgG), інтерлейкінів-1, -2, (ІЛ-1, ІЛ-2), фактор некрозу пухлини (ФНП) до та після профілактики та лікування. У контрольну групу для профілактики включили 50 жінок, а для лікування – 35 жінок тієї самої вікової категорії без наявності НВПМ та ГППРС.

Результати. Після лікування інтенсивність симптомів НВПМ вірогідно знижується, і МІК у жінок після застосування лікувально-профілактичного комплексу (n=36) становить $9,2 \pm 1,2$, тобто у 2,5 разу менше, ніж до лікування, а у жінок з природною менопаузою (n=31) МІК – $11,6 \pm 1,4$, що у 2,1 разу менше, ніж до лікування. Послідовне застосування ЗГП та лікування за розробленим нами методом дозволяє знизити інтенсивність НВПМ у жінок з ГППРС (n=36), за даними МІК, у 1,26 разу порівняно з жінками у групі з природною менопаузою (n=31) після лікування за запропонованим нами методом без проведення попередньої ЗГП.

Заключення. Застосування запропонованого методу послідовного прогнозування, профілактики та лікування дозволяє уникнути розвитку або зменшити інтенсивність симптомів нейровегетативних та психоемоційних порушень у менопаузі за рахунок зниження рівня продукції гонадотропнів, відновити показники гуморальної ланки імунної системи і попередити виснаження факторів протипухлинного захисту.

Ключові слова: математична модель, порушення у менопаузі, прогнозування, профілактика, лікування, гіперпроліферативні процеси репродуктивної системи, адаптаційна система, гормональний гомеостаз, імунна система.

Прогнозирование, профилактика и лечение нарушений в менопаузе у женщин с гиперпролиферативными процессами репродуктивной системы
Т.Ф. Татарчук, Л.И. Бутина

Цель исследования: оценка эффективности прогнозирования, профилактики и лечения нарушений в менопаузе у женщин с гиперпролиферативными процессами репродуктивной системы (ГППРС).

Материалы и методы. Для выявления факторов, связанных с тяжестью течения климактерического синдрома (КС), и оценки их влияния на развитие тяжелой степени течения нарушений в менопаузе был использован метод построения и анализа многофакторных математических моделей. При построении модели использовали результаты исследования 19 показателей у 124 пациенток в возрасте от 45 до 79 лет с наличием нарушений в менопаузе в форме КС и признаков миомы матки и гиперплазии эндометрия по данным ультразвукового исследования матки и придатков или на основе патогистологического исследования соскоба из полости матки. Заместительную гормональную профилактику (ЗГП) нейровегетативных и психоэмоциональных нарушений в менопаузе (НВПМ) проводили у 60 женщин в возрасте от 40 до 53 лет, а лечение НВПМ проводили у 67 женщин в возрасте от 48 до 60 лет после ЗГП – 1 Л-П группа (n=36) и с естественной менопаузой – 1-Л группа (n=31) с наличием признаков ГППРС по данным УЗИ матки и результатам гистологического исследования соскоба из полости матки. Для оценки эффективности профилактики и лечения НВПМ исследовали уровень гормонов: фолликулостимулирующего (ФСГ), лютеинизирующего (ЛГ), эстродиола (Е), прогестерона (ПГ), тестостерона (ТС), пролактина (ПРЛ), кортизола (КР), инсулина, определяли уровень иммуноглобулинов А, М, G (IgA, IgM, IgG), интерлейкинов-1, -2, (ІЛ-1, ІЛ-2), фактора некроза опухоли (ФНО) до и после профилактики и лечения. В контрольную группу для профилактики включили 50 женщин, а для лечения – 35 женщин той же возрастной категории без наличия НВПМ и ГППРС.

Результаты. После лечения интенсивность симптомов НВПМ достоверно снижается, и МІК после применения лечебно-профилактического комплекса (n=36) составляет $9,2 \pm 1,2$, то есть в 2,5 раза меньше, чем до лечения, а у женщин с естественной менопаузой (n=31) МІК – $11,6 \pm 1,4$, что в 2,1 раза меньше, чем до лечения. Последовательное применение ЗГП и лечения по разработанным нами методом позволяет снизить интенсивность НВПМ у женщин с ГППРС (n=36), по данным МІК, в 1,26 раза по сравнению с женщинами в группе с естественной менопаузой (n=31) после лечения предложенным нами методом без проведения предварительной ЗГП.

Заключение. Применение предложенного нами метода последовательного прогнозирования, профилактики и лечения позволяет избежать развития или уменьшить интенсивность симптомов нейровегетативных и психоэмоциональных нарушений в менопаузе за счет снижения уровня гонадотропинов, восстановления показателей гуморального звена иммунной системы и предупредить истощение факторов противопухоловой защиты.

Ключевые слова: нарушения в менопаузе, математическая модель, прогнозирование, профилактика, лечение, гиперпролиферативные процессы репродуктивной системы, адаптационная система, гормональный гомеостаз, иммунная система.

Сведения об авторах

Татарчук Татьяна Феофановна – ГУ «Институт педиатрии, акушерства и гинекологии Национальной академии медицинских наук Украины», 04050, г. Киев, ул. Платона Майбороды, 8

Бутина Людмила Ивановна – Кафедра акушерства и гинекологии Донецкого национального медицинского университета, 84404, г. Лиман, ул. Привокзальная, 27.; тел.: (050) 247-24-88, (097) 323-41-39. E-mail: lydmilabutina@gmail.com

LITERATURA

- Butina L.I. 2013 Prevention of disorders in menopause in women with hyperproliferative processes of reproductive system. Medical-social problems of family.4. 50–54.
- Butina L.I. 2013 Mathematical model of prognostication of disorders in the menopause in women with hyperproliferative processes of reproductive system.- Ukrainian journal of telemedicine and medical telematics.11. 2. 162–166.
- Butina L.I. 2017 Treatment of disorders in the menopause in women with hyperproliferative processes of reproductive system.- Reproductive endocrinology. 5(37). 70–74.
- Butina L.I. 2017 Dynamics of index of immune system after prevention of disorders in the menopause in women with hyperproliferative processes of reproductive system.- Health of women. 9(125). 100–104.
- Vykhyayeva E.M. 1997 The postmenopausal syndrome and strategy of the substitutive hormone therapy. Obstetric and gynecology. 5. 51–56.
- Vykhyayeva E.M. 2008. Postmenopausal therapy.M.: MED press-Inform. – 448.
- Petry A., Sabyk K. 2003 Visual statistics in medicine. Translation from English V.P. Leonova.M.: HEOTAR-MED.144.
- Simrok V.V., Simrok D.V., Chominskaya Z.B. 2008 Boom of cytokines in cases of non-malignant processes of uterus News of medicine and pharmacy. 253. 114–117.
- Tatarchuk T.F. 2007 Substitutive hormone therapy. Questions and answers. International endocrinological journal. 4 (10).59-65.
- Shcherbyna Y.N. 2009.Character of immune disorders in premenopause of women. Collection of scientific articles of Association of Obstetric and gynecology of Ukraine. Kiev: «Intermed». 722–726.

Статья поступила в редакцию 13.12.17