

Indicators of the immune system after correction of climacteric syndrome in women with uterine leiomyoma and endometrial hyperplasia

L.I. Butina, L.P. Shelestova, F.A. Khancha, A.L. Ostroukh, P.F. Shahanov
Donetsk National Medical University

The objective: to evaluate the effectiveness of the correction of climacteric syndrome (CS) with the use the method of sequential prevention and treatment of CS in women with uterine leiomyoma (UL) and endometrial hyperplasia (EH) based on studies of indicators of the immune system.

Materials and methods. On the basis of prognosis using a mathematical model some groups of women with UL and EH in the period of before and after menopause, with the risk of development of disorders in menopause were chosen and the state of the immune system before and after the correction of climacteric syndrome with the use the method of sequential prevention and treatment of CS were evaluated.

The prevention of CS was carried out in 184 women aged 40 to 53 years with the presence of signs of UL and EH, in which after menstruation was delayed for 3–6 months, uterine bleeding and symptoms of CS were observed. These women underwent CS prevention for one year with the use of a contraceptive containing of the natural estrogen estradiol valerate and gestagen dienogest. The women were divided into groups depending on the presence or absence of signs of CS, UL and EH: women with UL and CS (n=60), women with UL without CS (n=37), women with EH and CS (n=37), women with EH without CS (n=25), women with CS without UL and EH (n = 25). Women with UL and CS who constituted the main group (n=60), additionally used an immunomodulator that contains meglumine acridonacetate and suppositories containing recombinant alpha interferon β . The control group consisted 50 women of the same age category without the presence of CS, UL and EH

After the prevention in 24 women of the main group (n=60), the menstrual function was recovered and the symptoms of CS disappeared. In remaining 36 women the menopause was developed and they amounted to 1 treatment-and-prophylactic (1-T-P) group of women who were prescribed the treatment complex developed and proposed by us. In these women we investigated the effectiveness of the correction of climacteric syndrome with the use the method of sequential prevention and treatment of symptoms of CS.

The treatment of CS, which included a complex of drugs: a combined herbal preparation containing cimicifuga, a preparation from the microalgae *Spirulina platensis*, pectin and a drug with the active substance mebicar, was carried out for one year in 193 women aged 48 to 60 years. These women consisted of women with UL and CS after prophylaxis – 1 treatment-and-prophylactic (1-T-P) group (n=36), of women without prior prevention: women with UL, CS and natural menopause – 1-treatment (1-T) group (n=31), women of 2 – treatment (2-T) group with UL without CS (n=40), women of 3 – treatment (3-T) group with EH and CS (n=25), women of 4 – treatment (4-T) group with EH without CS (n=27), women of 5 – treatment (5-T) group with CS without UL and EH (n=34). The control group consisted of 35 women of the same age category without the presence of UL, EH and CS. The signs of uterine leiomyoma (UL) and endometrial hyperplasia (EH) were determined according to ultrasound examination of the uterine and the results of histological investigations of the endometrium. The intensity of the symptoms of CS was evaluated using a modified Cooperman index (MCI).

To assess the effectiveness of correction of CS in women with UL and EH by an enzyme immunoassay, the level of Ig A, G, M, interleukins 1 and 2 (IL-1, IL-2) of tumor necrosis factor (TNF) was studied before and after the use of prevention and treatment of CS. Group comparisons were performed using the angular Fischer transform. Parametric indicators at normal distribution were compared using Student's t criterion. In the work, their quantitative values are given in the form of arithmetic mean and its error.

Results. After the treatment in women with EH and CS (n=25) in women with CS without UL and EH (n=34) indicators of humoral immunity IgA, IgM, IgG, IL-1, IL-2 and TNF did not significantly differ from those in healthy women in the menopause ($p>0,05$). In women after consistent prevention and treatment of CS of 1 T-P group (n=36), we observed the increase of the level of IgA for 29%, IgM for 25%, decrease the level of IL-1 to 1,3 times, and TNF level – to 1,8 times. In women without prophylaxis of CS of 1-T group (n=31) we observed the increase of the level of IgA for 25%, IgM for 19%, compared with the indicators before the treatment ($p<0,05$), and the IgG and TNF level after the treatment does not differ from the indicators in healthy women in the menopause ($p>0,05$), the level of the IL-1 remained to 1,6 times higher compared with healthy women ($p<0,05$). The consistent use of prevention and treatment by our worked out method allows to reduce the intensity of CS in women with UL and CS after prevention (n=36) according to the MCI data by 1,26 times in comparison with women in the group with CS, UL and natural menopause (n=31), by 1,28 times in comparison with women in the group with EH and CS (n=25), by 1,39 times in comparison with women in the group with CS without UL and EH (n=25) after treatment according to our method, without previous prevention.

Conclusions. The application of the correction of CS with the use of the method of consistent prevention and treatment of CS allows to reduce the intensity of symptoms of CS in women with UL and CS according to the MCI data by 1,26–1,39 times, recover the indicators of humoral link of immune system and prevent the exhaustion of antitumor protection factors.

Keywords: climacteric syndrome, prevention, treatment, uterine leiomyoma, endometrial hyperplasia, immune system.

Показники імунної системи після корекції клімактеричного синдрому у жінок з лейоміомою матки та гіперплазією ендометрія

Л.І. Бутіна, Л.П. Шелестова, Ф.О. Ханча, А.Л. Остроух, П.Ф. Шаганов

Мета дослідження: оцінювання ефективності корекції клімактеричного синдрому (КС) шляхом застосування методу послідовної профілактики та лікування КС у жінок з лейоміомою матки (ЛМ) та гіперплазією ендометрія (ГЕ) на підставі дослідження показників імунної системи.

Матеріали та методи. На підставі прогнозування за використанням математичної моделі у жінок з ЛМ та ГЕ в період пре- і постменопаузи відібрано пацієнток групи ризику щодо розвитку КС і вивчено стан їхньої імунної системи до та після застосування корекції КС шляхом послідовної профілактики та лікування.

Профілактику симптомів КС проводили у 184 жінок віком від 40 до 53 років з наявністю ознак ЛМ та ГЕ, у яких при затримках менструації на 3–6 міс спостерігались симптоми КС і маткова кровотеча. Їм протягом одного року проводили профілактику КС з використанням контрацептивного препарату, який містить натуральний естроген естрадіолу валерат та гестаген дієногест. Пацієнтки були розподілені на групи залежно від наявності або відсутності ознак ЛМ, ГЕ та КС: жінки з ЛМ та КС (n=60), жінки з ЛМ без КС (n=37), жінки з ГЕ та КС (n=37), жінки з ГЕ без КС (n=25), жінки з КС без ЛМ та ГЕ (n=25). Пацієнткам з ЛМ та КС (n=60), які увійшли до основної групи, додатково застосовували імуномодулятор, що містить меглюміну акридоніацетат, та свічки, які містять інтерферон рекомбінований альфа-2β. До контрольної групи увійшли 50 жінок тієї самої вікової категорії без наявності ЛМ, ГЕ та КС.

Після профілактики у 24 жінок основної групи відновився регулярний менструальний цикл і зникли симптоми КС, в інших 36 жінок розвинулась менопауза, і вони увійшли до 1-ї лікувально-профілактичної (1-Л-П) групи пацієнток, яким призначили розроблений та запропонований нами лікувальний комплекс і у яких дослідили ефективність корекції КС шляхом застосування методу послідовної профілактики та лікування симптомів КС.

Лікування КС, яке включало комплекс препаратів: комбінований рослинний препарат, що містить у складі циміцифугу, препарат з мікрородості *Spirulina platensis*, пектин, та анкіолітичний засіб з діючою речовиною мебікар, проводили протягом одного року у 193 жінок віком від 48 до 60 років. Цих жінок було розподілено на групи: жінки з ЛМ після профілактики КС входили до 1-ї Л-П групи (n=36); жінки без застосування попередньої профілактики КС: пацієнтки з ЛМ, КС та природною менопаузою увійшли до 1-ї лікувальної (1-Л) групи (n=31), жінки з ЛМ без КС увійшли до 2-ї лікувальної (2-Л) групи (n=40), жінки з ГЕ та КС – до 3-ї лікувальної (3-Л) групи (n=25), жінки з ГЕ без КС – до 4-ї лікувальної (4-Л) групи (n=27), жінки з КС без ЛМ та ГЕ – до 5-ї лікувальної (5-Л) групи (n=34). До контрольної групи включено 35 жінок тієї самої вікової категорії без наявності ЛМ, ГЕ та КС.

Наявність ознак ЛМ та ГЕ визначали за даними ультразвукового дослідження матки за результатами гістологічного дослідження ендометрія. Інтенсивність симптомів КС оцінювали за допомогою модифікованого індексу Купермана (МІК). Для оцінювання ефективності послідовної профілактики та лікування КС у жінок з ЛМ та ГЕ імуноферментним методом досліджували рівень IgA, IgG, IgM, інтерлейкінів-1 і 2 (ІЛ-1, ІЛ-2), фактора некрозу пухлини (ФНП) до та після застосування профілактики та лікування КС. Порівняння у групах проводили за допомогою кутового перетворення Фішера. Параметричні показники при нормальному розподіленні порівнювали за допомогою t-критерію Стьюдента. У роботі їхні кількісні значення наведені у формі середнього арифметичного та його помилки.

Результати. Після лікування у жінок з ГЕ та КС (n=25) та у жінок з КС без ЛМ та ГЕ (n=34) показники гуморального імунітету IgA, IgG, IgM, ІЛ-1, ІЛ-2 та ФНП вірогідно не відрізняються від показників у здорових жінок (p>0,05). У жінок з ЛМ та КС 1-Л-П групи (n=36), яким застосовували профілактику КС, після лікування спостерігалось статистично значуще підвищення рівня IgA – на 29%, IgM – на 25%, зниження рівня ІЛ-1 в 1,3 разу, а ФНП – в 1,8 разу. А у жінок 1-Л групи (n=31), яким профілактику КС не проводили, спостерігалось підвищення рівня IgA на 25%, IgM – на 19% порівняно з показниками до лікування (p<0,05). Їхній рівень, так само, як і рівень IgG та ФНП після лікування, статистично не відрізняється від цих показників у здорових жінок у період менопаузи (p>0,05), а рівень ІЛ-1 залишився в 1,6 разу вищий, ніж у здорових жінок (p<0,05).

Послідовне застосування профілактики та лікування КС за розробленим нами методом дозволяє знизити інтенсивність симптомів КС у жінок з ЛМ та КС (n=36) після профілактики за даними МІК в 1,26 разу порівняно з жінками в групі з ЛМ, КС та природною менопаузою (n=31), в 1,28 разу порівняно з жінками з ГЕ та КС (n=25), в 1,39 разу порівняно з жінками з КС без ЛМ та ГЕ (n=34) після лікування за запропонованим нами методом без проведення попередньої профілактики.

Заключення. Корекція КС шляхом застосування запропонованого методу послідовної профілактики та лікування дозволяє зменшити інтенсивність симптомів КС у жінок з ЛМ та КС за даними МІК в 1,26–1,39 разу, відновити показники гуморальної ланки імунної системи і попередити виснаження факторів протипухлинного захисту.

Ключові слова: клімактеричний синдром, лейоміома матки, гіперплазія ендометрія, профілактика, лікування, імунна система.

Показатели иммунной системы после коррекции климактерического синдрома у женщин с лейомиомой матки и гиперплазией эндометрия

Л.И. Бутина, Л.П. Шелестова, Ф.А. Ханча, А.Л. Остроух, П.Ф. Шаганов

Цель исследования: оценка эффективности коррекции климактерического синдрома (КС) путем применения метода последовательной профилактики и лечения КС у женщин с лейомиомой матки (ЛМ) и гиперплазией эндометрия (ГЭ) на основе исследования показателей иммунной системы.

Материалы и методы. На основе прогнозирования с применением математической модели у женщин с ЛМ и ГЭ в период пре- и постменопаузы отобраны пациентки группы риска по развитию нарушений в менопаузе и изучено состояние их иммунной системы до и после коррекции КС путем применения метода последовательной профилактики и лечения.

Профилактику менопаузальных вазомоторных симптомов КС проводили у 184 женщин в возрасте от 40 до 53 лет с наличием симптомов ЛМ и ГЭ, у которых при задержке менструации на 3–6 мес наблюдались симптомы КС и маточное кровотечение. Им в течение одного года проводили профилактику КС с использованием контрацептивного препарата, который содержит натуральный эстроген эстрадиола валерат и гестаген диеногест. Пациентки были разделены на группы в зависимости от наличия или отсутствия признаков КС, ЛМ и ГЭ: женщины с ЛМ и КС (n=60), женщины с ЛМ без КС (n=37), женщины с ГЭ и КС (n=37), женщины с ГЭ без КС (n=25), женщины с КС без ЛМ и ГЭ (n=25). Пациенткам с ЛМ и КС (n=60), которые вошли в основную группу, дополнительно применяли иммуномодулятор, который содержит меглюмина акридоніацетат, и свечи, которые содержат интерферон рекомбинированный альфа-2β. В контрольную группу вошли 50 женщин той же возрастной категории без наличия ЛМ, ГЭ и КС.

После профилактики у 24 женщин основной группы восстановился регулярный менструальный цикл и исчезли симптомы КС, у остальных 36 женщин развилась менопауза, и они вошли в 1-ю лечебно-профилактическую (1-Л-П) группу пациенток, которым назначили разработанный и предложенный нами лечебный комплекс. У них изучили эффективность коррекции КС путем применения метода последовательной профилактики и лечения симптомов КС.

Лечение КС, которое включало применение комплекса препаратов: комбинированный растительный препарат, содержащий в составе циміцифугу, препарат из микрородості *Spirulina platensis*, пектин, и препарат с действующим веществом мебікар, проводили в течение одного года у 193 женщин в возрасте от 48 до 60 лет. Эти женщины были разделены на группы: женщины с ЛМ и КС после профилактики вошли в 1-ю лечебно-профилактическую (1-Л-П) группу (n=36); женщины без применения предварительной профилактики КС: пациентки с ЛМ, КС и природной менопаузой вошли в 1-ю лечебную (1-Л) группу (n=31), женщины с ЛМ без КС вошли во 2-ю лечебную (2-Л) группу (n=40), женщины с ГЭ и КС – в 3-ю лечебную (3-Л) группу (n=25), женщины с ГЭ без КС – в 4-ю лечебную (4-Л) группу (n=27), женщины с КС без ЛМ и ГЭ – в 5-ю лечебную (5-Л) группу (n=34). В контрольную группу включены 35 женщин той же возрастной категории без наличия ЛМ, ГЭ и КС.

Наличие признаков ЛМ и ГЭ определяли по данным ультразвукового исследования матки и результатам гистологического исследования эндометрия. Интенсивность симптомов КС оценивали при помощи модифицированного индекса Купермана (МІК). Для

оценки эффективности коррекции КС у женщин с ЛМ и ГЭ иммуноферментным методом исследовали уровень IgA, IgG, IgM, интерлейкинов-1 и 2 (ИЛ-1, ИЛ-2), фактора некроза опухоли (ФНО) до и после применения профилактики и лечения КС. Сравнение в группах проводили при помощи углового превращения Фишера. Параметрические показатели при нормальном распределении сравнивали при помощи t-критерия Стьюдента. В работе их количественные значения приведены в форме среднего арифметического и его ошибки.

Результаты. После лечения у женщин с ГЭ и КС (n=25) и у женщин с КС без ЛМ и ГЭ (n=34) показатели гуморального иммунитета ИЛ-1, ИЛ-2 и ФНО достоверно не отличались от показателей у здоровых женщин (p>0,05). У женщин 1-Л-II группы (n=36), которым применяли профилактику КС, наблюдалось статистически значимое повышение уровня IgA – на 29%, IgM – на 25%, снижение уровня ИЛ-1 в 1,3 раза, а ФНО – в 1,8 раза. А у женщин 1-Л группы (n=31), которым профилактику КС не проводили, наблюдалось повышение уровня IgA на 25%, IgM на 19% по сравнению с показателями до лечения (p<0,05). Их уровень так же, как и уровень IgG и ФНО, после лечения статистически не отличался от этих показателей у здоровых женщин в период менопаузы (p>0,05), а уровень ИЛ-1 остался в 1,6 раза выше, чем у здоровых женщин (p<0,05).

Последовательное применение профилактики и лечения КС по разработанному нами методу позволяет снизить интенсивность симптомов КС у женщин с ЛМ и КС (n=36) после профилактики по данным МИК в 1,26 раза в сравнении с женщинами в группе с ЛМ, КС и с природной менопаузой (n=31), в 1,28 раза в сравнении с женщинами с ГЭ и КС (n=25), в 1,39 раза в сравнении с женщинами с КС без ЛМ и ГЭ (n=34) после лечения по предложенному нами методу без проведения предварительной профилактики.

Заключение. Коррекция КС путем применения метода последовательной профилактики и лечения позволяет уменьшить интенсивность симптомов КС у женщин с ЛМ по данным МИК в 1,26–1,39 раза, восстановить показатели гуморального звена иммунной системы и предупредить истощение факторов противоопухолевой защиты.

Ключевые слова: климактерический синдром, лейомиома матки, гиперплазия эндометрия, профилактика, лечение, иммунная система.

In the whole world and in Europe the number of women with menopause increases rapidly, today 10% of the world population is the women in climacteric age. Every year this population will grow for 25 mln. Different in degrees of difficulties the signs of neurovegetative and psychoemotional disorders such as climacteric syndrome (CS) is present among 26–48% of women [5, 7].

Usually we appoint the treatment of these disorders after their appearance and use the substitutive hormone therapy by estrogen preparations. But for women with hyperproliferative processes of the reproductive system, including uterine leiomyoma and endometrial hyperplasia, the appointment of estrogenous preparations is forbidden, because it may lead to the activation of proliferative processes [11].

In perspective there is the formation of groups of risk in the development of menopausal vasomotor symptoms of CS the development and application within these patients the method of prevention disorders long before the menopause period. This will help to prepare a woman for this period and help her to enter the menopause gradually without dishormonal disorders, which form the conditions for the development of menopause disorders. This method will help to raise the effectiveness of treatment menopause disorders.

That's why, to our mind, it's very important to forecast the possibilities of the development of disorders in menopause in women with uterine leiomyoma and endometrial hyperplasia 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 uterine leiomyoma and endometrial hyperplasia and evaluate its efficiency.

Taking into consideration the fact that there are activity reduction data of immune system in women with uterine leiomyoma and endometrial hyperplasia [10,13], and paying attention to the conclusions that the changes of immunological reactivity increases the degree of climacteric syndrome (CS), because the triggers of the development of pathological passage of premenopausal period are the changes in immunoreaction and in the processes of body immunoregulation [9]. We think it's necessary to add preparations for the correction of the immunity state in the complex method of consistent prevention and treatment of CS in women with uterine leiomyoma (UL) and endometrial hyperplasia (EH). That's why to evaluate the efficiency of the proposed method of consistent prevention and treatment of CS in women with uterine leiomyoma and endometrial hyperplasia we decided to investigate the indicators of immune system before and after

the implementation of the method of consistent prevention and treatment of CS.

The objective: to evaluate the effectiveness of the correction of climacteric syndrome (CS) with the use the method of sequential prevention and treatment of CS in women with uterine leiomyoma (UL) and endometrial hyperplasia (EH) based on studies of indicators of the immune system.

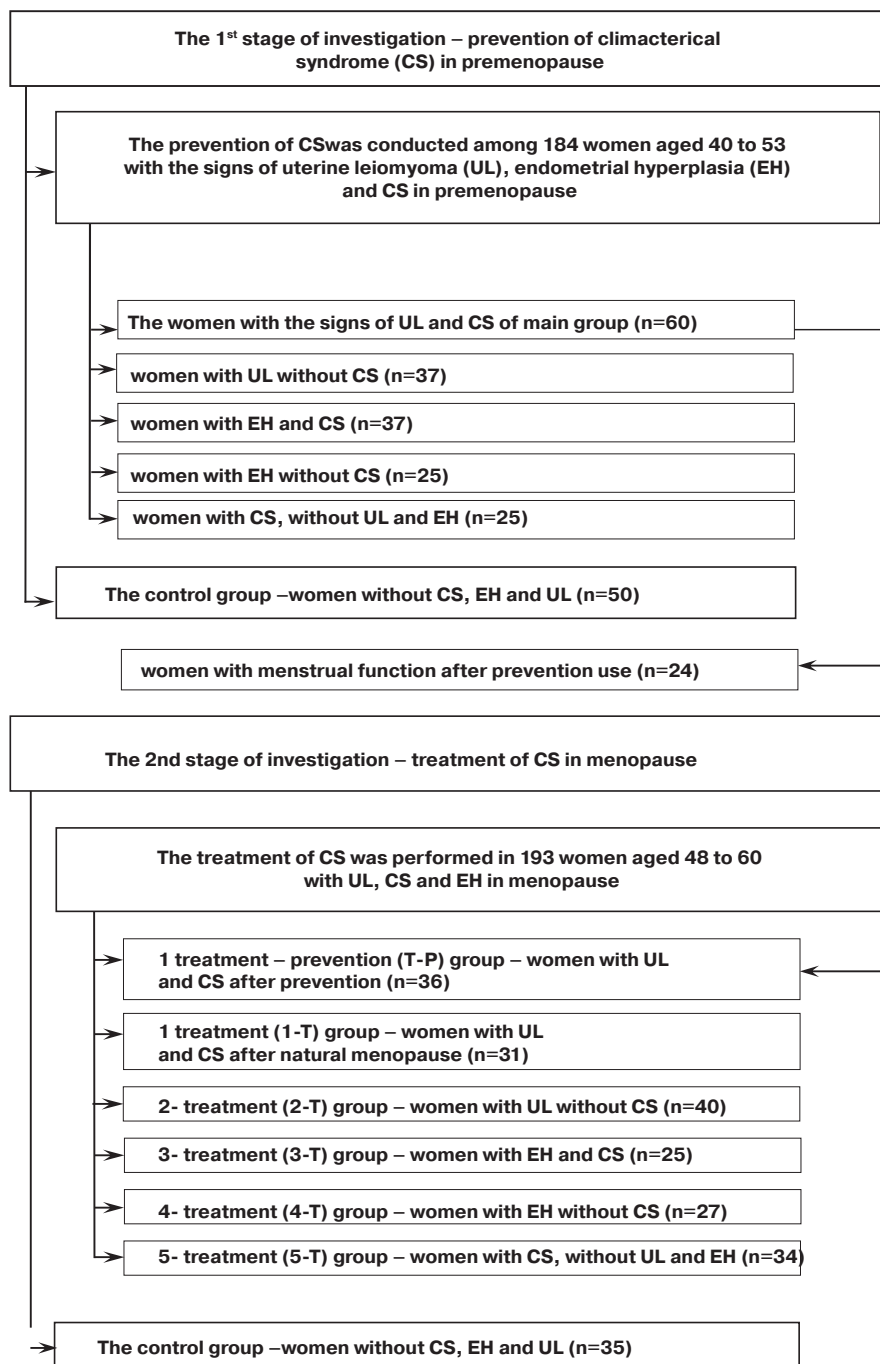
MATERIALS AND METHODS

On the basis of prognosis using a mathematical model some groups of women with uterine leiomyoma (UL) and endometrial hyperplasia (EH) in the period of before and after menopause, with the risk of development of CS were chosen [1] and the state of the immune system before and after the correction of climacteric syndrome with the use the method of sequential prevention and treatment of CS were evaluated.

The prevention of climacteric syndrome (CS) was carried out in 184 women aged 40 to 53 years with the presence of signs of uterine leiomyoma (UL) and endometrial hyperplasia (EH), in which after menstruation was delayed for 3-6 months, uterine bleeding and symptoms of CS were observed. These women underwent CS prevention for one year with the use of a contraceptive containing of the natural estrogen estradiol valerate and gestagen dienogest. The women were divided into groups depending on the presence or absence of signs of CS, UL and EH: women with UL and CS (n=60), women with UL without CS (n=37), women with EH and CS (n=37), women with EH without CS (n=25), women with CS without UL and EH (n=25). Women with UL and CS who constituted the main group (n=60), additionally used an immunomodulator that contains meglumine acridonacetate and suppositories containing recombinant alpha interferon 2β [3]. The control group consisted 50 women of the same age category without the presence of CS, UL and EH

After the prevention in 24 women of the main group (n=60), the menstrual function was recovered and the symptoms of CS disappeared. In remaining 36 women the menopause was developed and they amounted to 1 treatment-and-prophylactic (1-T-P) group of women who were prescribed the treatment complex developed and proposed by us. In these women we investigated the effectiveness of the correction of climacteric syndrome with the use the method of sequential prevention and treatment of symptoms of CS.

The treatment of CS, which included a complex of drugs: a combined herbal preparation containing cimicifuga, a preparation from the microalgae *Spirulina platensis*, pectin and a drug with the active substance mebicar, was carried out for one year in 193 women aged 48 to 60 years [2].



Picture 1. The stage of investigation

These women consisted of women with UL and CS after prophylaxis – 1 treatment-and-prophylactic (1-T-P) group (n=36), of women without prior prevention: women of 1 – treatment (1-T) group with UL, CS and natural menopause (n=31), women of 2 – treatment (2-T) group with UL without CS (n=40), women of 3 – treatment (3-T) group with EH and CS (n=25), women of 4 – treatment (4-T) group with EH without CS (n=27), women of 5 – treatment (5-T) group with CS without UL and EH (n=34). The control group consisted of 35 women of the same age category without the presence of UL, EH and CS.

The signs of uterine leiomyoma (UL) and endometrial hyperplasia (EH) were determined according to ultrasound examina-

tion of the uterine [12] and the results of histological investigations of the endometrium [15]. The intensity of the symptoms of CS was evaluated using a modified Cooperman index (MCI) [14].

To assess the effectiveness of correction of CS in women with UL and EH by an enzyme immunoassay, the level of IgA, IgG, IgM, interleukins 1 and 2 (IL-1, IL-2) of tumor necrosis factor (TNF) was studied before and after the use of prevention and treatment of CS. Group comparisons were performed using the angular Fischer transform. Parametric indicators at normal distribution were compared using Student's t criterion. In the work, their quantitative values are given in the form of arithmetic mean and its error [8].

RESULTS OF THE STUDY

Influence of a prophylactic complex on immunological indicators.

On the basis of prognosis some groups of women with UL and EH in the period before and after menopause, with the risk of the development of CS were chosen, and the state of the immune system was studied [1].

It's known the role of endogenous stimulants-interleukins and tumor necrosis factor in uterine benign tumor pathogenesis: myoma and endometriosis.

It's observed a synergistic increase of IL-1, IL-2 and the tumor necrosis factor (TNF), that demonstrates both the mechanism of tumor development and body defense reaction and witnesses the state of the «immune stress» in women with uterine benign tumor [13].

There are investigations that prove: the development of pathological variant of premenopause is closely connected with the changes in the immune system. The characteristic features are: the activation of T-lymphocytes, the imbalance of immune regulatory cells, an increase in the number of cells with suppressor

and cytotoxic features among lymphocytes, and also anti-inflammatory cytokine producers [9].

We decided to investigate the role of immunoglobulins and endogenous immunomodulators IL-1, IL-2 and the TNF with uterine leiomyoma and endometrial hyperplasia during the development of CS in premenopausal period and find out pathogenetically based directions of prevention activities.

In women with UL, EH and CS in premenopause the level of IgA increased for 22-38%. The level of IgG, increased for 21% in women with UL and CS, in women with UL and EH as with CS and without CS the level of IgM decreased on 22–37%. (p<0,05) (Table 1).

Indicators of immunoglobulin level in women with uterine leiomyoma (UL), endometrial hyperplasia (EH), climacteric syndrome (CS) before and after prophylaxis of CS and disorders of menstrual function (MF) in the premenopause (M±m)

Indicators	Groups						
	Women with UL and CS n=60	Women with UL without CS n=37	Women with EH and CS n=37	Women with EH without CS n=25	Women with CS without UL and EH n=25	Women without UL, EH, CS n=50	
	before prophylaxis						
Ig A (g/l)	(2,4±0,07)*	(1,8±0,03)	(1,9±0,02)*	(1,6±0,03)	(1,7±0,05)	(1,5±0,05)	
Ig G (g/l)	(9,57±0,38)*	(8,1±0,2)	(8,3±0,2)	(8,1±0,03)	(7,9±0,4)	(7,6±0,2)	
Ig M (g/l)	(1,14±0,03)*	(1,18±0,08) ^o	(1,3±0,02)*	(1,4±0,03) ^Δ	(1,5±0,02)	(1,8±0,03)	
	after prophylaxis						
	with MF n=24	without MF n=36	n=37	n=37	n=25	n=25	n=50
Ig A (g/l)	(1,99±0,06)*	(2,37±0,08)*	(1,7±0,03)	(1,60±0,03)	(1,63±0,02)	(1,57±0,03)	(1,5±0,05)
Ig G (g/l)	(8,35±0,5) ^o	(10,4±0,6)*	(8,0±0,2)	(7,6±0,02)	(7,9±0,03)	(7,5±0,4)	(7,6±0,2)
Ig M (g/l)	(1,12±0,04)*	(0,93±0,03)*	(1,21±0,03) ^o	(1,5±0,05)	(1,43±0,003)	(1,7±0,01)	(1,8±0,03)

Note: * – difference of indicators in women with UL and CS before and after prophylaxis and in women without CS, UL and EH. p<0,05

^o – difference of indicators in women with UL without CS before and after prophylaxis and in women without CS, UL, EH. p<0,05.

* – difference of indicators in women with EH and CS before prophylaxis and in women without CS, UL and EH p<0,05.

^Δ – difference of indicators in women with EH without CS before prophylaxis and in women without CS, UL and EH p<0,05.

^o – difference of indicators in women with MF after prophylaxis and in women with UL and CS before prophylaxis p<0,05

In women with UL and EH in premenopause the indicators of humoral link of immune system increases. The presence of hyperproliferative processes in endometrium with morphological signs of chronic inflammation [6] 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 [9].

In women with UL and EH as with CS and without CS in premenopause. the level of IL-1 increased to 1,4–2,6 times up, IL-2 – 1,5–2,6 times up and TNF 22–47% up (p<0,05), as compared with healthy women without UL, CS and EH (Table 2). In women with UL and EH in premenopause the indicators of the immunity in organism increases that testifies about the activation of adaptation system of the antinoplastic defense. The hyperproduction of cytokine (IL-1, IL-2, TNF) may increase the severity of the course of menopause vasomotor symptoms of CS in menopause.

A synergistic increase of IL-1, IL-2 and TNF in uterine leiomyoma may demonstrate both pathological development and body defense reaction. Thanks to its ability to stimulate gene expression of releasing factors, IL-1 may influence the central biological mechanism of body homeostasis way to level up the level of corticotropin releasing factor, that increases the production of adrenocorticotrophic hormone and gonadotropic hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH) that provoke the development of menopause vasomotor symptoms of CS in premenopausal period. The release of hypothalamic monoamines and neuropeptides under the influence of great concentrations of endogenous IL-1 may cause disorders in gonadotropic and sex hormones. The increase of FSH and LH production will cause hyperestrogenia that is one of the pathogenesis links of the development of uterine hyperplastic processes. At the same time the increased concentrations of IL-1 and TNF may cause antitumor effect. In this aspect the ability of cytokine to influence the cells apoptosis plays an important role. On the one hand it's a physiological reaction, based on the diversity of cytokine mechanisms and an attempt to launch

the apoptosis programme, but on the other hand this reaction is not good and safe, because there is a break of balance between control and uncontrol, benefit and harm of immune answers. The surplus of cytokine is a decisive factor in supporting and gaining pathological processes: chronic inflammation and proliferation [13].

So the premises for the development of disorders in menopause are formed in women with UL and EH in premenopause, which results in changes of immunoreactivity and processes of immunoregulation of organism. No doubt, they need correction.

For the first time the scientifically based method of prevention of CS in menopause using the hormone and immunocorrection therapy has been developed and applied in premenopause in women with UL and EH on the basis of the results obtained. The effectiveness of this prevention was evaluated

After prevention use in 24 women in the main group (n=60) the menstrual function (MF) was recovered and the symptoms of CS disappeared. So the prevention of symptoms of CS was perceived among 40% of women

It was installed in women with UL and CS with MF (n=24) the level of IgG decreases for 24% (p<0,05) compared with the indicators before prophylaxis (Table 1), the level of IgA increases for 25%, and the level of IgM decreases for 39% compared with healthy women (p<0,05). In women with UL and CS with MF the level of IL-1 decreases to 2,4 times (p<0,05), it was not different from the indicators in healthy women (p>0,05). The level of IL-2 decreases for 43%, the TNF level decreased for 28% compared with level before prophylaxis, but the level was increased for 34% and 26% compared with healthy women according to (p<0,05) (Table 2).

In women without menstrual function after prophylaxis the level of IgA and IgG does not change and remain increased to 1,6 times and to 1,4 times up compared with healthy women according to. The level of IgM remains lower to 2 times (Table 1), but the level of IL-2 – is higher to 2,2 times compared with healthy women (p<0,05). The level of IL-1 increased to 1,6 times and, the TNF level – to 1,6 times and it exceeds the indicators in the healthy women to 4,1 times and to 2,9 times according to (p<0,05). That indicators were increased compared with the results, which we received in women with menstrual function (n=24): IL-1 – to 3,75 times, IL-2 – to 1,5 times, the TNF to 2,2 times (p<0,05). In wom-

Indicators of cytokine level in women with uterine leiomyoma (UL), endometrial hyperplasia (EH), climacteric syndrome (CS) before and after prophylaxis of CS and disorders of menstrual function (MF) in the premenopause (M±m)

Indicators	Groups						
	Women with UL and CS n=60		Women with UL without CS n=37	Women with EH and CS n=37	Women with EH without CS n=25	Women with CS without UL and EH n=25	Women without CS UL and EH, n=50
	before prophylaxis						
interleukin 1 (pg/ml)	(12,4±0,2)*		(9,4±0,3)°	(8,7±0,3)*	(6,6±0,5) ^Δ	(6,5±0,5) [□]	(4,7±0,6)
interleukin 2 (pg/ml)	(10,7±1,6)*		(7,9±0,4)°	(8,1±0,5)*	(6,3±,4) ^Δ	(6,1±0,3) [□]	(4,1±0,5)
tumor necrosis factor (pg/ml)	(25,8±1,2)*		(20,3±1,3)°	(19,5±1,5)*	(18,1±1,3) ^Δ	(17,8±1,3) [□]	(13,9±1,8)
	after prophylaxis						
	with MF n=24	without MF n=36	n=37	n=37	n=25	n=25	n=50
interleukin 1 (pg/ml)	(5,1±1,8) [⊛]	(19,3±0,9)*	(8,9±0,3)°	(6,5±0,3)*	(5,6±0,2)	(4,9±0,4)	(4,7±0,6)
interleukin 2 (pg/ml)	(6,1±0,4) [⊛]	(9,02±0,2)*	(7,5±0,3)°	(6,0±0,4)*	(5,3±0,3) ^Δ	(4,3±0,2)	(4,1±0,5)
tumor necrosis factor (pg/ml)	(18,7±1,5) [⊛]	(41,1±1,6)*	(19,4±1,3)°	(17,6±1,2)*	(15,3±1,2)	(14,3±1,5)	(13,9±1,8)

Note: * – difference of indicators in women with UL and CS before prophylaxis, in women without MF after prophylaxis and in women without CS, UL and EH in the premenopause p<0,05.

⊛ – difference of indicators in women with and without MF after prophylaxis and in women without CS, UL, EH p<0,05.

° – difference of indicators in women with UL without CS before and after prophylaxis and in women without CS, UL, EH p<0,05.

Δ – difference of indicators in women with EH and CS before and after prophylaxis and in women without CS, UL and EH p<0,05.

Δ – difference of indicators in women with EH without CS before and after prophylaxis and in women without CS, UL, EH p<0,05.

□ – difference of indicators in women with CS without UL, EH before prophylaxis and in women without CS, UL, EH p<0,05.

en with UL without CS and in women with EH as with CS, and without CS the level of IL-2 increased for 23–46%, the TNF level for 22–29%, IL-1 remains increased in women with UL without CS to 1,9 times (p<0,05) (Table 2).

So in women with UL and EH in menopause the activity of humoral link of immune system and adaptation system of the antinoplastic defense increases, as compared with healthy women in premenopause.

Influence of the prophylactic complex on the course of CS in premenopausal women with UL and EH.

The use of prevention of CS among women with UL and EH with the menstrual function, reduces the exertion of immunologic reaction and reduces the risk of denutrition of their compensatory possibilities. and allows to liquidate the symptoms of CS for 40% of women with UL in the period of premenopause.

In 36 (60%) women with UL the menstrual function was absent and they have disorders in menopause, but the use of prevention of CS reduces the intensity of the symptoms of CS. 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 Cooperman index (MCI) is (22,8±1,5). This intensity of the menopausal vasomotor symptoms of CS corresponds to the middle degree of the course of disorders in menopause [4].

The effect of treatment and prevention complex on the immune system in women with UL and EH in menopause.

In women without menstrual function after prophylaxis 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%, as compared with the healthy women in menopause (p<0,05) (Table 3).

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 becomes to 2,95 times higher (n=36) and to 1,8 times higher (n=31). The level of TNF remains

high to 1,4 times, compared with healthy women in menopause. All these factors testify for activation of antitumor protection (Table 4).

In women with UL without CS and EH as with CS and without CS it's observed the decrease of the level of IgA for 25–36% and the level of IgM for 19–30% (Table 3), the level of IL-2 decreased for 19–24%, the level of IL-1 increased for 19–29%, the level of TNF increased for 20–22% compared with healthy women (p<0,05) (Table 4).

So we can trace the decline of humoral link of immunity and activation of antitumor protection in women with UL and EH, compared with healthy women in the menopause. 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 consistent prevention and treatment of the menopausal vasomotor symptoms of CS in women with UL and EH.

After the treatment in women with UL without CS and EH as with CS and without CS the concentration of IgA and IgM the same as IgG level, IL-1. IL-2, TNF level in women doesn't differ from the indicators of healthy women in the menopausal period (p>0,05).

In women after consistent prevention and treatment of CS of 1-L-P group (n=36), we observed the increase of the level of IgA for 29%, IgM for 25% (Table 3), decrease the level of IL-1 to 1,3 times, and TNF level – to 1,8 times (Table 4), in women without prophylaxis of CS – 1-L group (n=31) we observed the increase of the level of IgA for 25%, IgM for 19%, compared with indicators before the treatment (p<0,05) (Table 3). The level of IgA and IgM as the level of IgG and TNF level after the treatment does not differ from the indicators in healthy women in the menopause (p>0,05), the level of the IL-1 remains to 1,6 times higher as compared with healthy women (p>0,05) (Table 3, 4).

The level of IL-1 decreased as compared with the data before treatment, but it remains higher compared with the data of healthy women. (p<0,05) This is due to the fact, that there are

Table 3

Indicators of immunoglobulin level in women with uterine leiomyoma (UL) without of menstrual function (MF) after prophylaxis in the premenopause, in women with UL and natural menopause (NM), endometrial hyperplasia (EH) and climacteric syndrome (CS) in the menopause before and after treatment CS (M±m)

Indicators	Groups						
	Women with UL and CS without MF n=36	Women with UL, CS and NM n=31	Women with UL without CS n=40	Women with EH and CS n=25	Women with EH without CS n=27	Women with CS without UL and EH n=34	Women without UL, EH, CS n=35
	before treatment						
Ig A (g/l)	(2,37±0,08) ^Δ	(2,14±0,03) [◊]	(2,31±0,02) [*]	(2,53±0,03) [*]	(2,68±0,03) [▼]	(2,73±0,04) [◻]	(3,6±0,05)
Ig G (g/l)	10,4±0,6	(9,29±0,6)	(8,61±0,3) [*]	(8,52±0,02) [*]	(9,08±0,0,4)	(8,71±0,5)	(10,9±0,4)
Ig M (g/l)	(0,91±0,03) ^Δ	(0,9±0,04) [◊]	(0,93±0,04)	(0,98±0,04) [*]	(1,03±0,05) [▼]	(1,1±0,05) [◻]	(1,3±0,02)
	after treatment						
Ig A (g/l)	(3,3±0,03) ^{Δ*}	(3,1±0,04) ^{Δ*}	(3,5±0,02)	(3,4±0,03)	(3,1±0,03)	(3,2±0,04)	(3,6±0,05)
Ig G (g/l)	(10,7±0,5)	(10,2±0,2)	(9,3±0,3)	(9,5±0,5)	(9,2±0,3)	(10,2±0,3)	(10,9±0,4)
Ig M (g/l)	(1,2±0,02) ^{Δ*}	(1,1±0,02) ^{Δ*}	(1,2±0,02)	(1,3±0,03)	(1,1±0,03)	(1,4±0,02)	(1,3±0,02)

Note: ^Δ – difference of indicators in women with UL, CS without MF before treatment and in women without CS, UL, EH p<0,05.
[◊] – difference of indicators in women with UL, CS and NM before treatment and in women without CS, UL and EH p<0,05.
^{*} – difference of indicators in women with UL without CS before treatment and in women without CS, UL and EH p<0,05.
[▼] – difference of indicators in women with EH and CS before treatment and in women without CS, UL and EH p<0,05.
[◻] – difference of indicators index in women with EH without CS before treatment and in women without CS, UL and EH p<0,05.
[◻] – difference of indicators in women with CS without UL, EH before treatment and in women without CS, UL, EH p<0,05
^{Δ*} – difference of indicators in women with UL, CS without MF and with NM before and after treatment p<0,05.

Table 4

Indicators of cytokine level in women with uterine leiomyoma (UL) without of menstrual function (MF) after prophylaxis in the premenopause, in women with natural menopause (NM) and UL, endometrial hyperplasia (EH) and climacteric syndrome (CS) in the menopause before and after treatment CS (M±m)

Indicators	Groups						
	Women with UL and CS without MF n=36	Women with UL, CS, NM n=31	Women with UL without CS n=40	Women with EH and CS n=25	Women with EH without CS n=27	Women with CS without UL and EH n=34	Women without UL, EH, CS n=35
	before treatment						
interleukin 1 (pg/ml)	(19,2±0,9) ^{Δ*}	(11,5±0,9) [◊]	(9,1±0,3) [*]	(8,9±0,4) [*]	(8,1±0,2) [▼]	(8,3±0,2) [◻]	(6,5±0,5)
interleukin 2 (pg/ml)	(9,2±0,2) ^Δ	(8,6±0,2) [◊]	(9,0±0,2) [*]	(8,7±0,5) [*]	(9,1±0,4) [▼]	(8,9±0,3) [◻]	(11,3±0,3)
tumor necrosis factor (TNF)(pg/ml)	(41,1±1,6) ^{Δ*}	26,8±1,9	(34,4±1,8) [*]	(29,3±1,1)	(32,5±1,3)	(36,3±1,3) [◻]	(28,7±1,2)
	after treatment						
interleukin 1 (pg/ml)	(14,7±1,8) ^Δ	(10,6±0,9)	(7,3±0,8)	(8,1±0,3) [*]	(7,5±0,3)	7,4±0,5)	(6,5±0,5)
interleukin 2 (pg/ml)	10,8±0,4	(9,8±0,2)	(10,2±0,5)	(9,9±0,3)	(10,3±0,4)	(11,1±0,2)	(11,3±0,3)
TNF (pg/ml)	(22,9±1,5) ^Δ	(24,6±1,6)	(23,8±1,7) [◻]	(27,3±1,5)	(29,3±1,5)	(30,3±1,3)	(28,7±1,2)

Note: ^Δ – difference of indicators in women with UL, CS without MF before and after treatment and in women without CS, UL, EH p<0,05.
[◊] – difference of indicators in women with UL, CS and NM before treatment and in women without CS, UL, EH p<0,05.
^{*} – difference of indicators in women with UL without CS before treatment and in women without CS, UL, EH p<0,05.
[▼] – difference of indicators in women with EH and CS before treatment and in women without CS, UL, EH p<0,05.
[◻] – difference of indicators in women with EH without CS before treatment and in women without CS, UL, EH p<0,05.
[◻] – difference of indicators in women with CS without UL and EH before treatment and in women without CS, UL, EH p<0,05
^{Δ*} – difference of indicators in women with UL and CS without MF and in women with UL, CS, NM before treatment p<0,05.

places of hyperproliferation among tested women, and the activity of antitumor protection factors (IL-1, TNF) remains in tense condition, compared with the healthy women, which may lead to denutrition. Evidently the TNF level decreased to 1.8 times, compared to the data before treatment (p<0,05), so it was for 21% less than with healthy women in menopause (p<0,05). IL-2 level increased (p<0,05) (Table 4) as compared with the level before treatment, as a result the denutrition activity of apoptosis inhibitor was restored, which testifies about the decrease of the hyperprolif-

erative activity in reproductive system because the dimensions of uterine leiomyoma after prophylaxis decrease for 15% [4], and the decline of tension on the antitumor protection system.

The effect of treatment and prevention complex on the symptoms of CS in women with UL and EH in menopause.

After consistent prevention and treatment of CS the intensity of the symptoms of CS declines and a modified Cooperman index (MCI). in women after the usage of our medical prognostication complex (n=36) is to 2,5 times less than before treatment, but

in women with natural menopause MCI is to 2,1 times less than before treatment, in women with EH and CS MCI is to 2 times less than before treatment, in women with CS without UL and EH MCI is to 1,9 times less than before treatment [4].

Consistent application of prevention and treatment by our worked out method allow to decrease the intensity of CS in women with UL and CS (n=36) according to the MCI data to 1,26 times as compared in women with natural menopause (n=31), to 1,28 times as compared in women with EH and CS (n=25), to 1,39 times as compared in women with CS without LU and EH (n=34), after treatment according our method without previous prevention [4].

CONCLUSIONS

In women with UL and EH in premenopause the indicators of humoral link of immune system increases and the indicators of the immunity in organism increases, that testifies about the activation of adaptation system of the antinoplastic defense.

So the premises for the development of CS in menopause are formed in women with UL and EH in premenopause, which results in changes of immunoreactivity and processes of immunoregulation of organism

The use of prevention of CS using the hormone and immunocorrection therapy among women with UL and EH reduces the

strain of immunologic reaction and reduces the risk of denutrition of their compensatory possibilities and allows to liquidate the symptoms of CS for 40% of women in the period of premenopause.

In 60% women the use of prevention of CS reduces the intensity of the symptoms of CS and the frequency of heavy degree of the course of CS in menopause decreased to 6 times compared with the results of prognostication.

So we can trace the decline of humoral link of immunity and activation of antitumor protection in women with CS, UL and EH, compared with healthy women.

Consistent application of prevention and treatment of CS by our worked out method allow to decrease the intensity of symptoms of CS in women with UL and CS according to the MCI data to 1,26–1,39 times as compared in women with UL and natural menopause, EH and CS, after treatment according our method, without previous prevention.

The application of the correction of CS with the use of the method of consistent prevention and treatment of CS allows to recover the indicators of humoral link of immune system and to prevent the exhaustion of the antitumor protection factors which testifies the decrease of the hyperproliferation activity in reproductive system and the decline of tension on the antitumor protection system, as a result of the application of immune response modifier.

Сведения об авторах

Бутина Людмила Ивановна – Кафедра акушерства и гинекологии Донецкого национального медицинского университета, 84404, Донецкая область, г. Лиман, ул. Привокзальная, 27; тел.: (050) 247-24-88, (097) 323-41-39. E-mail: lydmilabutina@gmail.com
ORCID iD 0000-0002-8360-3573

Шелестова Лариса Петровна – Кафедра акушерства и гинекологии Донецкого национального медицинского университета, 84404, Донецкая область, г. Лиман, ул. Привокзальная, 27

Ханча Федор Александрович – Кафедра акушерства и гинекологии Донецкого национального медицинского университета, 84404, Донецкая область, г. Лиман, ул. Привокзальная, 27

Остроух Алла Леонидовна – Кафедра акушерства и гинекологии Донецкого национального медицинского университета, 84404, Донецкая область, г. Лиман, ул. Привокзальная, 27

Шаганов Павел Федорович – Кафедра акушерства и гинекологии Донецкого национального медицинского университета, 84404, Донецкая область, г. Лиман, ул. Привокзальная, 27

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