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## QUALITY OF LIFE AND PLASMA LEVELS OF MELATONIN AND STEROID HORMONES IN WOMEN WITH UTERINE LEIOMYOMA

### Summary

*Uterine leiomyoma is the most common neoplasm of the female reproductive system, consisting of smooth muscle cells. This proliferative pathology accounts for up to 30 % of gynecological diseases, ranking second after pelvic inflammatory processes. The appearance of clinical symptoms of uterine leiomyoma negatively affects the quality of life of such patients. It is also known that uterine leiomyoma is associated with changes in hormonal regulation in the female body; in particular, many researchers have noted an increase in blood levels of reproductive hormones, namely estradiol, in comparison with healthy women. However, the role of such an important hormone as melatonin, which has antioxidant properties and is capable of activating the processes of physiological apoptosis, in this disease is not fully understood. These processes require the most detailed study.*

**The aim of the study** was to estimate the quality of life and levels of melatonin and steroid hormones in women of reproductive age diagnosed with uterine leiomyoma.

**Materials and methods.** 60 women of reproductive age diagnosed with uterine leiomyoma were studied. The control group consisted of 20 apparently healthy women of the same age. Quality of life was assessed using the UFS-QOL questionnaire. The level of melatonin in the women's blood was determined once, on an empty stomach, at 8 o'clock in the morning, using the Human MT (melatonin) ELISA kit; also, the blood plasma concentrations of reproductive steroid hormones (estradiol and progesterone) in the follicular phase (5th day of the menstrual cycle) were measured using the MAGLUMI diagnostic kits for immunochromoluminescence analysis. Statistical processing was performed using the MedCalc software package.

The study was approved by the Commission on Biological and Medical Ethics of the Higher State Educational Institution of Ukraine «Bukovinian State Medical University» (Minutes № 4 of December 22, 2020) and was conducted in strict accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. All patients signed an appropriate informed consent.

The publication is a fragment of the research work of the Department of Obstetrics and Gynecology of Bukovinian State Medical University «Preserving and restoring of the reproductive health of women and girls with obstetric and gynecological pathology». State registration number: 0121U110020. Period of conduction: 01.01.2021-12.2025.

**Results.** It was found that patients of reproductive age with uterine leiomyoma have a probable decrease in overall self-assessment of quality of life ( $28.71 \pm 14.65$  points according to the UFS-QOL questionnaire, in the control group  $98, 15 \pm 3.45$  points,  $p < 0.01$ ), sexual function ( $32.50 \pm 16.63$  points, control group  $99.38 \pm 2.80$  points,  $p < 0.01$ ), and internal well-being ( $29.83 \pm 17.76$  points, control group  $99.90 \pm 0.45$  points,  $p < 0.001$ ). We also found that the level of melatonin in the blood of women of reproductive age suffering from uterine leiomyoma probably decreased by 27.6 % ( $111.08 \pm 18.54$  ng/ml, in the control group  $153.50 \pm 8.47$  ng/ml  $\pm 3.17$  pg/ml). The severity of the symptoms of the disease depends on the level of estradiol in blood plasma, which is described by the linear regression equation.

**Conclusions.** 1. Patients of reproductive age diagnosed with uterine leiomyoma have a significant decrease in general self-assessment of quality of life, sexual function, and internal well-being compared to healthy women of the same age group. 2. The level of melatonin in the blood of women of reproductive age suffering from uterine leiomyoma significantly decreases (by 27.6 %), and the concentration of estradiol in such patients significantly increases (by 2.97 times), compared to healthy women of the same age group. 3. In women of reproductive age suffering from uterine leiomyoma, the severity of symptoms of the disease depends on the level of estradiol in blood plasma. This relationship is described by a linear regression equation that may have prognostic value in predicting the severity of disease symptoms.

**Key words:** Uterine Leiomyoma; Quality of Life; Survey; Melatonin.

### Introduction

The demographic situation of a country is an important indicator. Therefore, the issue of women's health and ability to perform reproductive functions is significant and urgent. Protection of women's reproductive health is of great medical and social importance in Ukraine, which is connected with low birth rate and negative changes in population dynamics. According to the data of the State Statistical Service, there is currently a serious demographic crisis characterized by depopulation in connection with the crisis socio-economic situation. In such conditions, preservation of women's reproductive health is an important state priority for restoring high indicators of the demographic situation in Ukraine. An important task is timely diagnosis and prevention of diseases affecting

fertility [1, 2]. The study and analysis of women's health indicators, in particular, the evaluation of the effectiveness of family planning services and awareness is a necessary and urgent measure [1].

The most common neoplasms of the female reproductive system are smooth muscle tumors of the uterus, including uterine leiomyoma and its variants, smooth muscle tumors of uncertain malignant potential, uterine fibroids, and leiomyosarcomas. Accurate diagnosis is determined by nuclear atypia, the number of mitoses, and the presence or absence of tumor cell necrosis, a process that is often difficult and subjective [3]. Uterine leiomyoma is the most common benign proliferative pathology, accounting for up to 30 % of gynecologic diseases, second only to pelvic inflammatory disease [1, 2]. Unfortunately, currently there

are no statistical data on the incidence in Ukraine, but it is believed that its occurrence in the female population of Ukraine corresponds to that in the world. According to a recent study, the estimated incidence of uterine leiomyoma is 20 to 77 %, and the prevalence is 40 to 60 % in women under 35 years of age and 70 to 80 % in women over 50 years of age [4]. Classically, uterine leiomyoma is considered to be a disease of premenopausal age because the maximum percentage of morbidity occurs during this period of a woman's life [5]. However, according to many publications, there is a trend of «rejuvenation» of the disease; the prevalence in women under 30 years of age has increased from 2 to 12.5 % [5, 6]. Uterine leiomyoma is detected for the first time in 5-10 % of women during preventive examinations, in 30-35 % of gynecological patients. The average age of women when this disease is detected is 32-33 years. The peak incidence occurs at the age of 35-45 years. Black women have a higher risk of developing uterine leiomyoma than Caucasians because they are characterized by earlier menarche and a tendency to develop obesity [4, 7].

Uterine leiomyoma is a monoclonal tumor arising in the myometrium from smooth muscle tissue, consisting of randomly arranged myofibroblasts embedded in the extracellular matrix, which constitutes a significant part of the tumor volume, regardless of the presence or absence of a fibroplastic component in the tumor nodules and the level of hormone dependence [8]. Despite the fact that uterine leiomyoma is a benign tumor, it often has an asymptomatic clinical course, which worsens timely diagnosis and treatment; later it can cause a number of unpleasant clinical symptoms in a woman's life, including Menstrual cycle disorders – irregular, prolonged and heavy menstrual bleeding; iron deficiency anemia; dysmenorrhea; pelvic pressure and pain; urinary incontinence, frequent urge to urinate; impaired fertility; infertility (primary infertility occurs in 18-24 % of patients, secondary in more than 25 % of cases), early and recurrent miscarriages, etc. Many publications confirm the unfavorable course of pregnancy and postpartum period in women with fibroids, namely: complicated course of pregnancy, reproductive losses, abnormalities of labor activity and postpartum complications [9-12].

The quality of life of patients with uterine leiomyoma is a very important criterion that is primarily determined by the presence and severity of clinical symptoms. However, this criterion is difficult to measure. In order to objectify the quality of life of patients with uterine leiomyoma, various questionnaires have been developed around the world. One of the most popular questionnaires is the UFS-QOL, which is widely used in this pathology, especially to evaluate the effectiveness of surgical and medical treatment of uterine leiomyoma [13]; this questionnaire was selected by us for our study.

The role of melatonin, a hormone secreted by the pineal gland that maintains the circadian rhythm, is well known. Melatonin has a protective effect on the female reproductive system, including protection against breast and ovarian cancer [14]. However, the effect of this hormone on the growth and development of uterine leiomyoma has not been conclusively determined, and

this problem is being actively studied. Scientists establish the role of melatonin as a biochemical agent capable of triggering the mechanisms of apoptosis and autophagy in cells that form the basis of uterine leiomyoma. Thus, in the study of Po-Han Lin and co-authors conducted on mice (2019), it is noted that melatonin has a corresponding effect on ELT3 cells (Eker rat-derived uterine leiomyoma cells) *in vivo*, activating their apoptosis, while the leading role belongs to the effect on MT1-type melatonin receptors localized in the myometrium [14].

In addition, a negative correlation between peak melatonin concentration and 17-beta-estradiol levels has been observed in clinical studies of women of reproductive age [15]. Excessive estrogen secretion, according to several authors, increases and accelerates the growth of uterine leiomyomas and activates signaling pathways necessary for the expression of growth factors of this tumor [16, 17].

Therefore, the definition of etiopathogenesis, i.e. the relationship between the severity of clinical symptoms of uterine leiomyoma and the concentrations in the blood of patients of such important hormones as melatonin and estradiol, is important in the context of expanding diagnostic possibilities and finding new methods of treatment of this disease, which is an urgent problem today.

**The aim of the study.** To determine the quality of life and levels of melatonin and steroid hormones in women of reproductive age diagnosed with uterine leiomyoma.

**Material and methods.** We selected 60 women of reproductive age (research group). Diagnosis, examination and treatment were carried out in accordance with the order of the Ministry of Health of Ukraine from January 25, 2023. No. 147, Standard of medical care «uterine leiomyoma». The control group consisted of 20 practically healthy women of reproductive age. The groups were equal in age and social status. The age of the women in the experimental group ranged from 27 to 46 years, with a mean of  $36.3 \pm 1.81$  years, and the age of the patients in the control group ranged from 24 to 45 years, with a mean of  $35.6 \pm 2.85$  years ( $p=0.20$  according to the t-criterion), which indicates the statistical homogeneity of the age groups. Women with severe extragenital pathology were excluded from the study.

To determine the impact of uterine fibroids on quality of life and to assess symptoms, a specially developed questionnaire, the Uterine Fibroid Symptoms and Quality of Life (UFSQOL) questionnaire, was used. The Ukrainian version of the questionnaire was used [18]. As a result of the study, data were obtained characterizing the general, social, medical, emotional and sexual spheres of life of each patient with uterine leiomyoma. All items are rated on a 5-point Likert scale ranging from «not at all bothersome» to «very much so» for symptom severity items and «never» to «always» for quality of life items. Symptom severity and scale scores were summed and converted to a scale of 0 to 100 points. In the questionnaire used, the quality of life scale associated with each complaint is inversely related to the severity of the symptoms, with higher scores indicating better quality of life. Sections of the questionnaire included questions about general quality of life, severity of uterine

leiomyoma symptoms (pain, menorrhagia, metrorrhagia, feeling of «heaviness» in the small pelvis, etc.), sexual function, and internal well-being (presence or absence of shyness) in relation to the severity of uterine leiomyoma symptoms.

The Human MT (Melatonin) ELISA Kit (country of manufacture – China) was used to determine melatonin levels in the blood serum of the studied patients. Melatonin levels in the blood of women were determined once a day in the fasting state, venipuncture was performed at 8 o'clock in the morning.

Venous blood samples were taken during the follicular phase of the menstrual cycle. We used diagnostic sets of MAGLUMI company «Set of reagents for determination of progesterone», «Set of reagents for determination of estradiol» (country of manufacture – Germany). The concentrations of the specified steroid hormones were measured by the method of in vitro immunochemiluminescence analysis using a fully automated immunochemiluminescence analyzer of the MAGLUMI 1000 series. Blood was collected by venipuncture at 8 o'clock in the morning on the 5th day of the menstrual cycle.

Statistical processing was performed with the MedCalc software package (Ostende, Belgium) using the unpaired

t-test. The difference in results was considered significant at  $p < 0.05$ .

**Ethical approval.** The study was approved by the Commission on Biological and Medical Ethics of the Higher State Educational Institution of Ukraine «Bukovinian State Medical University» (Minutes № 4 of December 22, 2020) and was conducted in strict accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. All patients signed an appropriate informed consent.

**Connection with the scientific work of the department.** The publication is a fragment of the research work of the Department of Obstetrics and Gynecology of Bukovinian State Medical University «Preserving and restoring of the reproductive health of women and girls with obstetric and gynecological pathology». State registration number: 0121U110020. Period of conduction: 01.01.2021-12.2025.

**Results and their discussion**

We found that in women diagnosed with uterine leiomyoma, the results of the questionnaire differed, as expected, from the results of the survey of practically healthy women in the control group (Table 1).

**Table 1.**

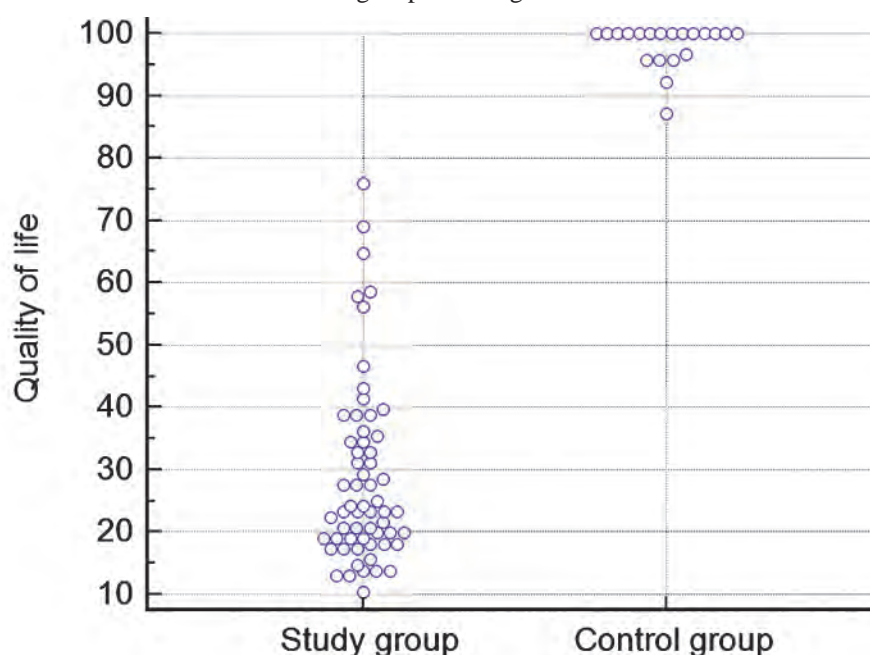
**Results of the survey of women with uterine leiomyoma**

	Study group (n=60)	Control group (n=20)
The general estimation of the quality of life, points	28,71 ± 14,65*	98,15 ± 3,45
Sexual function, points	32,50 ± 16,63*	99,38 ± 2,80
Internal well-being, points	29,83 ± 17,76*	99,90 ± 0,45
Expression of the clinical symptoms, points	74,27 ± 15,98*	1,72 ± 3,28

Note: 1. –  $p < 0,01$ , 2. – the standard deviation is indicated in the table.

As can be seen from Table 1, the assessment of quality of life in women of the experimental (study) group was more than three times lower than in the control group.

The distribution diagram of the assessment of quality of life in women with uterine leiomyoma is shown in Figure 1.

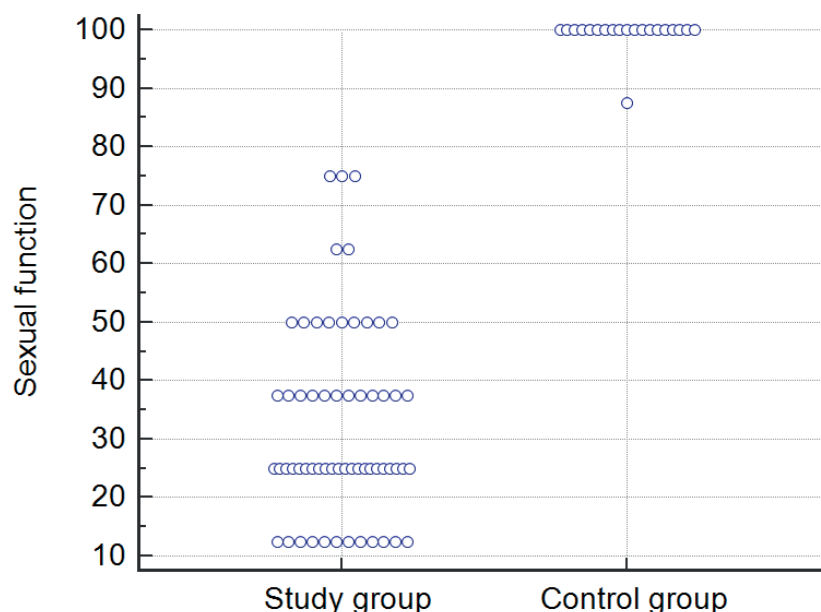


**Fig. 1. Distribution diagram of assessment of quality of life in women with uterine leiomyoma and women of the control group, points.**

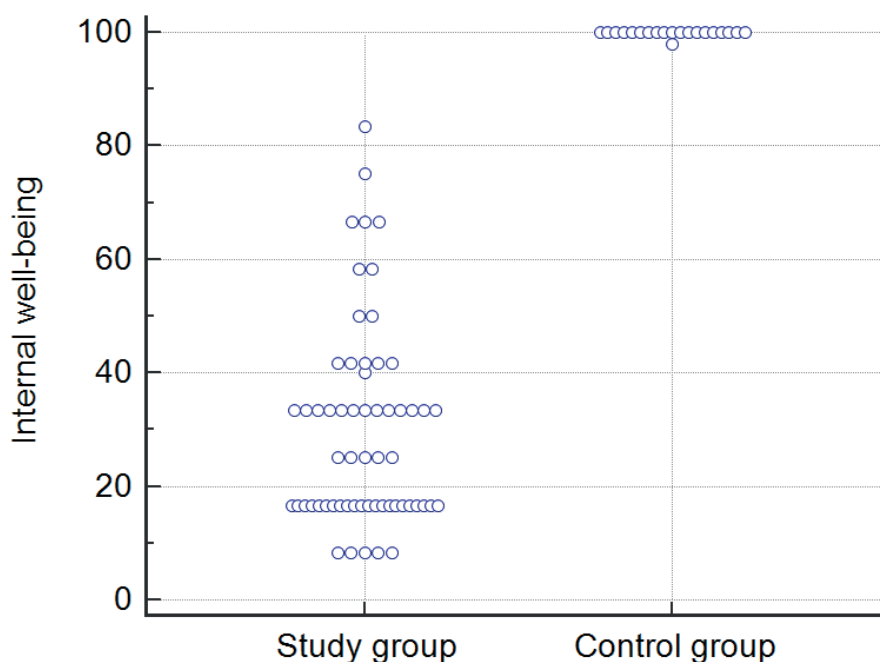
As the patients in the experimental group indicated in the questionnaire, their overall assessment of their own sexual function was also significantly lower than that of the healthy women included in the control group. The distribution diagram of the self-assessment of sexual

function by patients with uterine leiomyoma is shown in Figure 2.

A distribution plot of self-rated internal well-being (presence or absence of the feeling of shyness) in patients with uterine leiomyoma is shown in Figure 3.



**Fig. 2.** Distribution diagram of the self-assessment of sexual function by patients with uterine leiomyoma and women of the control group, points.



**Fig. 3.** Distribution diagram of the self-assessment of internal well-being in patients with uterine leiomyoma and women of the control group, points.

We found the following, in our opinion, very important fact: the level of melatonin in the blood plasma of patients with uterine leiomyoma was significantly

lower than the level of this hormone in practically healthy women (Table 2). The difference was about 27.6 percent.

**Table 2.**

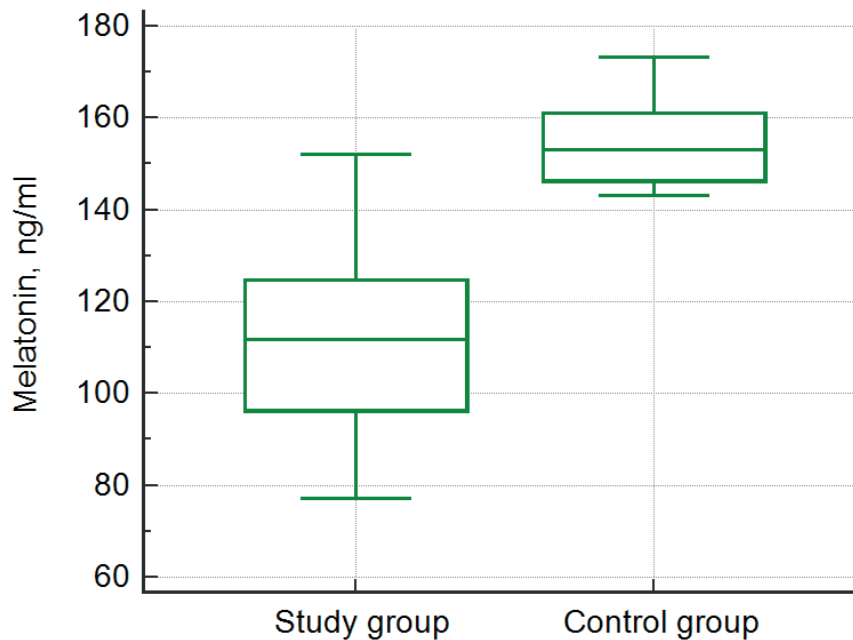
**The levels of melatonin in the blood plasma in women diagnosed with uterine leiomyoma**

	Study group (n=60)	Control group (n=20)
Melatonin, ng/ml	111,08 ± 18,54*	153,50 ± 8,47

Note: 1. –  $p < 0,01$ , 2. – the standard deviation is indicated in the table.

Figure 4 shows a graphical presentation (in the form of a comparative diagram) of the difference in melatonin concentrations between the experimental and control groups of examined patients.

Levels of steroid hormones (estradiol and progesterone) were measured in patients with uterine leiomyoma and in practically healthy women included in the control group. The results are shown in Table 3.



**Fig. 4. Comparative chart of melatonin concentrations in blood plasma of women with uterine leiomyoma and of practically healthy women, ng/ml.**

**Table 3.**

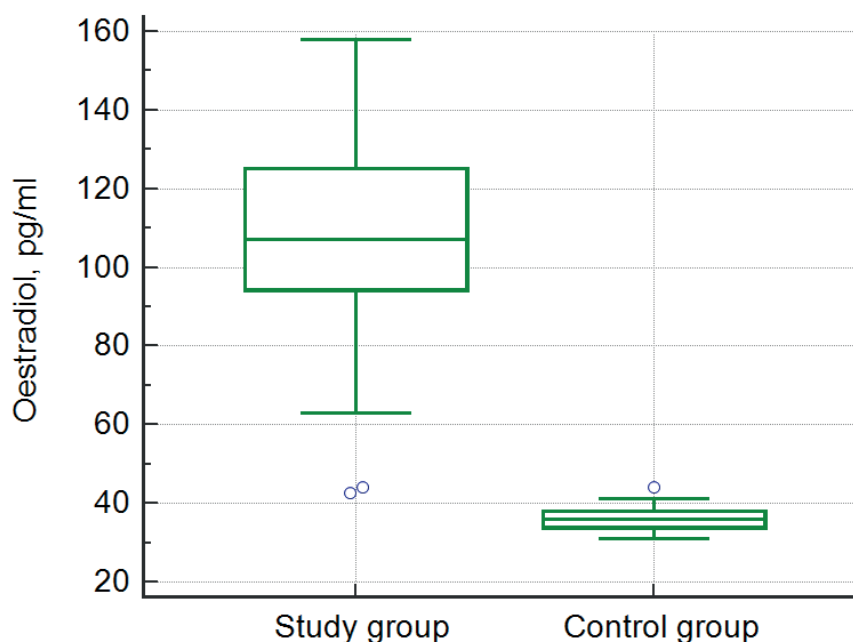
**Concentrations of estradiol and progesterone measured in the blood plasma of women diagnosed with uterine leiomyoma**

	Study group (n=60)	Control group (n=20)
Estradiol, pg/ml	107,38 ± 25,25*	36,15 ± 3,17
Progesterone, ng/ml	2,06 ± 0,43	1,13 ± 0,50

Note: 1. –  $p < 0,01$ , 2. – the standard deviation is indicated in the table.

We found no statistically significant differences in progesterone concentrations between the study groups. Instead, we found that the blood level of estradiol in

women with uterine leiomyoma was almost three times (2.97 times) higher than in the apparently healthy patients included in the control group (Figure 5).

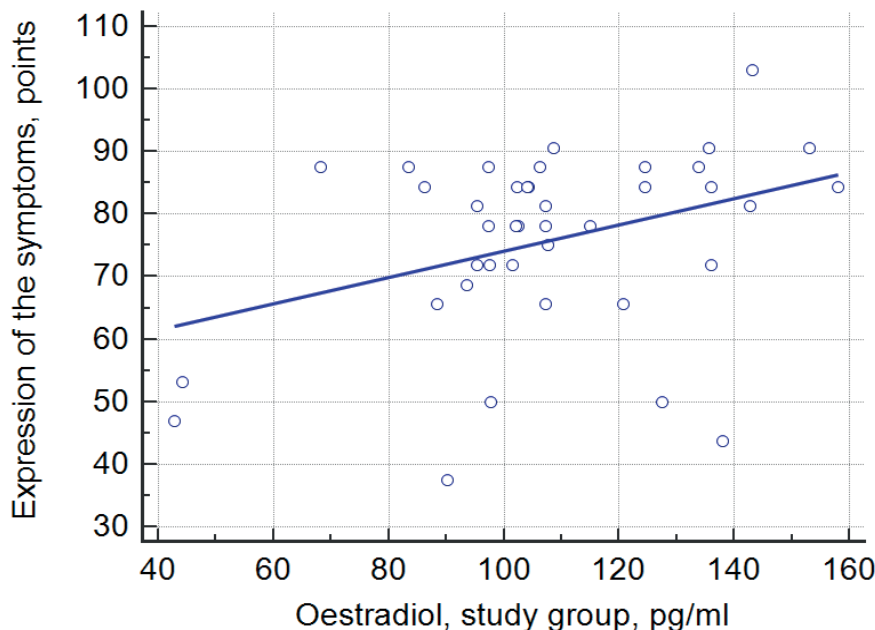


**Fig. 5. Comparative chart of estradiol concentrations in blood plasma of women with uterine leiomyoma and practically healthy women.**

We were also able to derive a regression equation that describes the relationship between the concentration of estradiol in the blood of patients with uterine fibroids and the severity of their symptoms, according to the results of the survey. The equation is the following:

$$y = 53,0655 + 0,2108 x$$

where  $x$  is the concentration of estradiol (pg/ml),  $y$  is the severity of complaints in points, according to the questionnaire used ( $p=0,022$ ). Figure 6 shows a scatter plot with a regression line for the derived equation.



**Fig. 6. Scatterplot with regression line describing the relationship between plasma estradiol concentrations in women with uterine leiomyoma and the severity of their complaints.**

In discussing the results obtained, we note that the severity of symptoms in uterine leiomyoma has long attracted the attention of researchers and clinicians. Attempts to objectify and digitize women's complaints are described in many scientific papers [13, 17]. The severity of symptoms directly affects the ability of women of reproductive age to work and causes significant economic damage even in developed countries [13, 18]. For example, patients surveyed in France in 2016 with a diagnosis of uterine leiomyoma emphasized that this disease of theirs had a significant (from moderate to severe) impact on their quality of life in more than 64 % of cases, and seriously (on average by 28-33 %) worsened their internal well-being, sexual function, and general condition in these patients [18]. This is in general agreement with our data. However, we were unable to find in the literature studies similar to ours that correlated the severity of symptoms with hormone levels in the blood of patients of reproductive age diagnosed with uterine leiomyomas.

The results of our research are largely consistent with those reported in the literature. In particular, a statistically significant increase in the concentration of estradiol in the blood plasma of women of reproductive age with uterine leiomyoma compared to practically healthy women was observed in the groups studied by us. In our opinion, a decrease in the level of melatonin in the patients included in the study group prevents the protective effect of this hormone on the myometrium, which results not only in a more pronounced proliferation of smooth muscle cells [19], but also in the accumulation under the influence of estrogens at the site of the tumor of extracellular matrix, in particular of collagen, fibronectin and proteoglycans [14, 20-23], which causes a rapid increase in tumor volume and

provokes the appearance of complaints in such patients. We have been able to describe this pathophysiological pathway, which links the concentration of estradiol in the blood plasma of women with uterine leiomyoma and the severity of their complaints, using a linear regression equation, which, we believe, may have prognostic value regarding the clinical course of this pathology, particularly in predicting the severity of disease symptoms.

### Conclusions

1. Patients of reproductive age diagnosed with uterine leiomyoma have a significant decrease in general self-assessment of quality of life, sexual function, and internal well-being compared to healthy women of the same age group.
2. The level of melatonin in the blood of women of reproductive age suffering from uterine leiomyoma significantly decreases (by 27.6 %), and the concentration of estradiol in such patients significantly increases (by 2.97 times), compared to healthy women of the same age group.
3. In women of reproductive age suffering from uterine leiomyoma, the severity of disease symptoms depends on the level of estradiol in blood plasma. This relationship is described by a linear regression equation that may have prognostic value in predicting the severity of disease symptoms.

**Prospects for further research** are to establish the pathophysiological mechanisms of the development of uterine leiomyoma in women of reproductive age, in particular, the processes of lipid peroxidation and angiogenesis. The influence of melatonin on these processes deserves special attention. These can be useful for the development of new mechanisms of treatment of the studied pathology.

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## ЯКІСТЬ ЖИТТЯ ТА РІВНІ МЕЛАТОНІНУ ТА СТЕРОЇДНИХ ГОРМОНІВ В ПЛАЗМІ КРОВІ У ЖІНОК З ЛЕЙОМІОМОЮ МАТКИ

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### Резюме.

Лейоміома матки є найпоширенішим новоутворенням жіночої статеві системи, що складається з клітин гладких м'язів. Ця проліферативна патологія складає до 30 % гінекологічних захворювань, займаючи друге місце після запальних процесів органів малого тазу. Поява клінічних симптомів лейоміоми матки негативно впливає на якість життя таких пацієнток. Також

відомо, що при лейоміомі матки відбуваються зміни гормональної регуляції в жіночому організмі, зокрема, багато дослідників відзначали збільшення рівнів репродуктивних гормонів, а саме, естрадіолу, порівняно зі здоровими жінками. Однак не до кінця з'ясовано при даному захворюванні залишається роль такого важливого гормону, як мелатонін, який володіє антиоксидантними властивостями та здатен активізувати процеси фізіологічного апоптозу. Ці процеси потребують якнайдетальнішого вивчення.

**Метою дослідження** було визначити якість життя та рівні мелатоніну та стероїдних гормонів у жінок репродуктивного віку, у яких діагностовано лейоміому матки.

**Матеріали і методи дослідження.** Обстежено 60 жінок репродуктивного віку, у яких було діагностовано лейоміому матки. Контрольну групу склали 20 практично здорових жінок тієї ж вікової групи. Визначення якості життя проводилося за допомогою опитувальника UFS-QOL. Рівні мелатоніну в крові жінок встановлювалися однократно, натще, о 8-й годині ранку, для чого використовувався набір Human MT (Melatonin) ELISA Kit; також за допомогою діагностичних наборів фірми MAGLUMI для імунохемолумінесцентного аналізу вимірювали концентрації в плазмі крові репродуктивних стероїдних гормонів (естрадіолу та прогестерону) у фолікулярній фазі (5-й день менструального циклу).

Статистичну обробку виконували за допомогою програмного пакету MedCalc (Ostende, Бельгія) з використанням t-тесту для неоднакових вибірок. Різницю в результатах вважали вірогідно значимими при  $p < 0,05$ .

Дослідження було схвалено Комісією з біологічної та медичної етики Вищого державного навчального закладу України «Буковинський державний медичний університет» (протокол № 4 від 22 грудня 2020 р.) і проводилась в суворих відповідно до Етичного кодексу Всесвітньої медичної асоціації (Гельсінська декларація) для експериментів із залученням людей. Всі пацієнтки підписували відповідну інформовану згоду.

Публікація є фрагментом науково-дослідної роботи кафедри акушерства і гінекології Буковинського державного медичного університету «Збереження та відновлення репродуктивного здоров'я жінок та дівчат при акушерській і гінекологічній патології». Державний реєстраційний номер: 0121U110020. Термін виконання: 01.2021-12.2025 рр.

**Результати.** Встановлено, що у пацієнток репродуктивного віку з лейоміомою матки спостерігається вірогідне зниження загальної самооцінки якості життя ( $28,71 \pm 14,65$  бали згідно опитувальника UFS-QOL, у контрольній групі  $98,15 \pm 3,45$  бали,  $p < 0,01$ ), сексуальної функції ( $32,50 \pm 16,63$  бали, в контрольній групі  $99,38 \pm 2,80$  бали,  $p < 0,01$ ) та внутрішнього самопочуття ( $29,83 \pm 17,76$  бали, в контрольній групі  $99,90 \pm 0,45$  бали,  $p < 0,001$ ). Також нами виявлено, що рівень мелатоніну в крові жінок репродуктивного віку, що хворіють на лейоміому матки, вірогідно знижується на 27,6 % ( $111,08 \pm 18,54$  ng/ml, в контрольній групі  $153,50 \pm 8,47$  ng/ml,  $p < 0,01$ ), а концентрація естрадіолу у таких пацієнток, за нашими даними, достовірно підвищується майже в три рази, порівняно з практично здоровими жінками ( $107,38 \pm 25,25$  pg/ml, у контрольній групі  $36,15 \pm 3,17$  pg/ml). Вираженість симптомів захворювання залежить від рівня естрадіолу в плазмі крові, що описується рівнянням лінійної регресії.

**Висновки.** 1. У пацієнток репродуктивного віку з лейоміомою матки спостерігається вірогідне зниження загальної самооцінки якості життя, сексуальної функції та внутрішнього самопочуття. 2. Рівень мелатоніну в крові жінок репродуктивного віку, що хворіють на лейоміому матки, вірогідно (на 27,6 %) знижується, а концентрація естрадіолу у таких пацієнток достовірно (у 2,97 рази) підвищується, порівняно з практично здоровими жінками. 3. У жінок репродуктивного віку, що хворіють на лейоміому матки, вираженість симптомів захворювання залежить від рівня естрадіолу в плазмі крові. Ця залежність описується рівнянням лінійної регресії, що може мати прогностичне значення для передбачення тяжкості симптомів захворювання.

**Ключові слова:** лейоміома матки; якість життя; опитування; мелатонін.

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