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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

**ROLE OF VITAMINS AND MICROELEMENTS IN
HYPERPLASTIC PROCESSES OF THE ENDOMETRIA IN
THE PERIMENOPAUSAL PERIOD**

Speciality: 3215.01 – Obstetrics and gynecology

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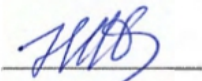
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GENERAL CHARACTERICS OF WORK AND THE DEGREE OF ITS DEVELOPMENT EHP

The actuality of the subject Endometrial hyperplastic processes (EHP) remain one of the most important problems of modern gynecology. This condition is associated with long-term exposure to estrogen, in the absence of treatment, creates the background for the occurrence of endometrial cancer ¹. As you know, EHP is detected in most cases in the perimenopausal period. The main clinical symptom of EHP is abnormal uterine bleeding (AUB). Violation of the mechanisms of the natural physiological rhythm of the cycle of the endometrium, as a rule, causes the appearance of hyperplasia of the endometrium, which causes AUB. Hyperplastic processes of the endometrium are found in 54-62% of women with AUB in premenopause. Anemia caused by uterine bleeding causes nervousness, depression, physical fatigue ^{2,3}. From a modern point of view, hyperplasia of the endometrium is considered a polyetiological pathological process, its occurrence and development depend on various factors. One of such factors is the age of the patient, the perimenopausal period, when as a result of hormonal changes, the initial and stimulating conditions for the emergence of hyperplastic processes in the reproductive system are created ^{4,5}. Research in recent years has shown that a decrease in

¹ Пронин С.М. Применение рилизинг-систем и агонистов гонадотропин-рилизинг-гормона в лечении атипической гиперплазии и начального рака эндометрия / С. М. Пронин, О. В. Новикова, Ю. Ю. Андреева // Онкология. Журн. им. П.А. Герцена. – 2013. №1. – с. 40-43.

² Чернуха Г.Е., Асатурова А.В., Иванов И.А., Думановская М.Р. Структура патологии эндометрия в различные возрастные периоды. Акушерство и гинекология. - 2018. № 8. с.129-34.

³ Karakoç H, Uçtu AK, Özerdoğan N. Genitourinary syndrome of menopause: effects on related factors, quality of life, and self-care power. // Prz Menopauzalny. – 2019. 18(1). – p. 15-22.

⁴ Sanderson P.A., Critchley H.O.D., Williams A.R.W. New concepts for an old problem: the diagnosis of endometrial hyperplasia. // Hum. Reprod. Update. – 2017. 23(2). – p. 232-54.

⁵ Takacs, P.; Damjanovich, P. The effect of oral zinc supplementation on cervicovaginal lavage fluid zinc level. // Eur. J. Obstet. Gynecol. Reprod. Boil. – 2020. 248 - p. 106–109.

vitamin D concentration is also among the risk factors for the development of EHP. As a result of folic acid deficiency, erythropoiesis, the synthesis of nucleic acids, and the reproduction of rapidly proliferating cells are disrupted. This, in turn, increases the rate of development of such pathological processes as increased sweating, fatty infiltration of the liver and atherosclerosis in women in the perimenopausal period. Vitamin B₁₂ deficiency causes fatty degeneration of nerve cells, demyelination of nerve fibers, which leads to neurological changes. Deficiency of Mg and Zn in perimenopausal women leads to decreased quality of life, swelling of the fingers and toes, paresthesia, weakened immunity, dry skin, and depression^{6,7,8,9}. Endless interest in this pathological process is determined by the tendency of EHP to have a long-term relapsing course, the absence of pathological symptoms, as well as the difficulty of differential diagnosis and the difficulty of choosing adequate treatment methods. At the same time, unfortunately, the currently existing methods of treating endometrial hyperplastic processes are not effective enough, as evidenced by the high percentage of relapses.

In modern conditions, prevention, early diagnosis, adequate step-by-step treatment, and restoration of menstrual and reproductive functions are important in the management of patients with HPE^{10,11}.

Timely detection and correction of hypovitaminosis D is one of the areas of comprehensive treatment of perimenopausal symptoms,

⁶ Ganguly A, Tamblyn JA, Finn-Sell S. Vitamin D, the placenta and early pregnancy: effects on trophoblast function. // *J Endocrinol.* –2018. 236, p.93–103.

⁷ Gracia C.R., Freeman E.W. Onset of the menopause transition: the earliest signs and symptoms. // *Obstet Gynecol Clin North Am.* - 2018. 45. – p. 585–597.

⁸ Chasapis, C.T.; Ntoupa, P.S., Spiliopoulou, C.A., et al. Recent aspects of the effects of zinc on human health. // *Arch. Toxicol.* – 2020. 94. – p. 1443–1460

⁹ Alperin M, Burnett L, Lukacz E. et al. The mysteries of menopause and urogynecologic health: clinical and scientific gaps. // *Menopause.* – 2019. 26(1). – p. 103-111.

¹⁰ Kwak J.H., Hong Y.C., Choi Y.H. Serum 25-hydroxyvitamin D and hypertension in premenopausal and postmenopausal women: National Health and Nutrition Examination Surveys 2007-2010. // *Public Health Nutr.* – 2020. Jan 17. – p. 1-11.

¹¹ Ward K., Deneris A. An update on menopause management. // *J Midwifery Womens Health.* – 2018. 63, p.168–177.

designed not only to improve and maintain many health indicators during this period of a woman's life, but also to generally improve the quality of life.

Object of the research. The study included 100 women aged 45 to 55 years (mean age 49.52 ± 1.15 years) who were in the perimenopausal period. The 100 women examined were divided into 3 groups depending on the clinical manifestations of the disease: the main group - 50 women with endometrial hyperplastic processes, accompanied by bleeding in the perimenopausal period; comparison group - 30 women without complaints of bleeding, in whom prophylactic ultrasound revealed thickening of the endometrium in the perimenopausal period. The control group included 20 healthy women who had no complaints during the perimenopausal period and who did not have endometrial thickening according to ultrasound.

The purpose of the research was to determine the risk of hyperplastic processes of the endometrium due to deficiency of vitamins and microelements in the perimenopausal period, assess the quality of life and prepare a set of corrective and preventive measures for women with deficiency.

Research objectives:

1. Assessment of the content of vitamin D, vitamin B₁₂, folic acid and trace elements Ca, Zn, Mg, P in women with endometrial hyperplastic processes in the perimenopausal period.

2. Evaluation of the results of ultrasound examination of the pelvic organs in perimenopausal women against the background of vitamin D and microelements deficiency.

3. Assessment of the morphological characteristics of the endometrium in women with hyperplastic processes in the perimenopausal period against the background of deficiency of vitamin D, vitamin B₁₂, folic acid and microelements.

4. Assessment of the quality of life of women with endometrial hyperplasia in the perimenopausal period.

5. Increasing the effectiveness of treatment, improving the quality of life and optimizing the prevention of late metabolic disorders in hyperplastic processes of the endometrium in the perimenopausal period.

pausal period, as well as deficiency of vitamin D, vitamin B₁₂, folic acid and trace elements Ca, Zn, Mg, P.

Research methods. In the complex studies carried out, a number of modern examination methods were used, including: clinical, laboratory, instrumental, morphological (macroscopic, cytological, histological), statistical and experimental psychological studies (assessment on the MENQOL scale).

The main provisions submitted to the defence:

1. Inflammatory diseases in the perimenopausal period in women are accompanied by morphological and functional changes in the endometrium, which undergoes dystrophic and hormonal changes.

2. The severity of menopausal symptoms, a number of neurovegetative and psycho-emotional disorders, as well as main indicators of quality of life depend on the level of vitamins and microelements in the blood serum of women with HPE.

3. Complex therapy increases the effectiveness of traditional treatment of endometrial hyperplasia, improves the quality of life of women and reduces the manifestations of menopausal symptoms in the early period of perimenopause with a deficiency of vitamins and microelements.

Scientific novelty of the research:

For the first time, a quantitative analysis of the content of vitamin D, vitamin B₁₂, folic acid and trace elements Ca, Zn, Mg, P in the blood serum of women with endometrial hyperplastic processes in the perimenopausal period was carried out. Analysis of the results showed that in 76.0±6.0% of cases in the perimenopausal period, the level of 25(OH)D of patients corresponded to hypovitaminosis D (10-29 ng/ml), severe vitamin D deficiency was detected in 18.0±5.4% of patients (<10 ng/ml).

For the first time, the quality of life indicators of women with endometrial hyperplasia in conditions of deficiency and severe deficiency of vitamin D, vitamin B₁₂, folic acid and microelements Ca, Zn, Mg, P were studied in a comparative manner.

For the first time, the feasibility of complex treatment of processes has been substantiated in order to prevent clinical manifesta-

tions of perimenopausal syndrome, late metabolic disorders and improve the quality of life, as well as increase the effectiveness of treatment of hyperplastic endometrium in women with vitamin D deficiency in the perimenopausal period.

Practical significance of the research. This study examined the results of determining the content of vitamin D, folic acid, vitamin B₁₂, Ca, Zn, P, Mg in the blood during endometrial hyperplastic processes in the perimenopausal period. Thanks to the examinations carried out, the role of changes occurring in women with a deficiency of vitamins and microelements was determined. The results of an examination of women with HPE in the early period of perimenopause showed a high prevalence of hypovitaminosis D in these patients. A set of pathogenetically based therapeutic and preventive measures has been developed for women with a deficiency of vitamins and microelements due to hyperplastic processes of the endometrium in the perimenopausal period. A set of preventive measures has been developed to improve the quality of life of women during perimenopause. The results of the study on the examination of patients suffering from HPE and the prevention of complications can be regarded as an addition to the treatment of this pathology.

Approbation of the work. The dissertation materials were discussed: at the conference of the XXIII Republican Scientific Conference of Graduate Students and Young Scientists (Baku, 2019), at the online conference “From Scientific Research to Ensuring a Healthy Future” (Baku, 2020), at the international scientific a practical conference dedicated to the 90th anniversary of the Azerbaijan Medical University “Current problems of medicine” (Baku, 2020), at an international scientific and practical conference dedicated to the 100th anniversary of Tamerlan Aliyev “Current problems of medicine” (Baku, 2021); at the international scientific and practical conference dedicated to the 100th anniversary of the birth of Heydar Aliyev “Current problems of medicine” (Baku, 2023). The dissertation materials were reported and discussed at an interdepartmental meeting held jointly by specialized departments of the Azerbaijan Medical University (Baku, 05.06.2023, protocol No. 10), at a scientific semi-

nar of the approbation commission at the dissertation council of the Azerbaijan Medical University (Baku, 04.12.2023, protocol No.4)

The dissertation materials are used in the educational process at the Department of Obstetrics and Gynecology, Oncology of the AMU, the proposed practical recommendations are applied in practice.

The name of the organization where the dissertation has been accomplished. The dissertation work was carried out at the II Department of Obstetrics and Gynecology and at the Department of Oncology of Azerbaijan Medical University.

Publications. 19 scientific works on the topic of the dissertation have been published. 6 of them are articles, 13 theses, including 2 articles (Scopus index in data base) and 2 thesis published in a foreign publishing house.

The structure and scope of the dissertation. The dissertation is presented on 161 pages of computer text and consists of an introduction (213 530), entry (11 450), chapter I (64 300), chapter II (13 500), chapter III (43 600), chapter IV (25 300), chapter V (25 280), chapter VI (30 100), conclusions, practical recommendations and literature consists of a list. Bibliography consists of 205 sources, including the works of Azerbaijani authors. Dissertation work contains 15 tables, 14 graphs and 15 pictures.

MATERIAL AND METHODS OF THE RESEARCH

Research work was carried out in 2018-2022 at the II Department of Obstetrics and Gynecology of the Azerbaijan Medical University and on the basis of the Oncology Clinic of the Azerbaijan Medical University. When selecting the material, more than 300 patient criteria were analyzed, for 80 of them it was possible to obtain systematized complete information. Permission from the Ethics Commission was obtained to conduct the study.

100 women in perimenopause were classified, among them: 50 women in the perimenopausal period, accompanied by hyperplastic processes of the endometrium (main group); 30 women in the perimenopausal period without complaints of bleeding, in whom prophy-

lactic ultrasound revealed thickening of the endometrium (comparison group); 20 healthy women without complaints and thickening of the endometrium according to ultrasound data. Planned hospitalization was performed on 30 patients, emergency hospitalization was performed on 50 patients. According to the inclusion criteria, the study included women with endometrial hyperplastic processes in the perimenopausal period. Exclusion criteria were acute inflammatory processes of the endometrium, signs of endometrial cancer and tumor-like processes of the ovaries.

When collecting an obstetric and gynecological history, we studied the clinical picture of the disease, the duration of symptoms, the number of pregnancies, births and abortions, and the duration of menopausal changes. The objective examination included both general clinical, laboratory, and instrumental studies. During the gynecological examination, the condition of the external genitalia and pelvic floor muscles, the degree of puberty, examination of the vagina and cervix in speculum, and bimanual examination were assessed.

The content of FSH, LH, Prolactin, Estradiol in blood serum was determined using an IMMULITE2000 XPI analyzer from Siemens. Prothrombin time and INR were determined using an automatic coagulometer analyzer. A blood test was also carried out for the presence of infections using the CLIA method on the ARCHITECT i 1000 SR immunological analyzer, owned by ABBOTT. Analyzes for vitamin D and folic acid were processed by the CLIA method on the ARCHITECT i1000 SR immunoassay analyzer from Abbott. Vitamin B₁₂ tests were carried out using the ECLIA method on a COBAS E 411 analyzer owned by ROSCHE. The contents of Ca, Mg, P and Zn were studied by the colorimetric method in COBAS C 501, the biochemical module of the COBAS 6000 analyzer. The MENQOL scale was used to assess the quality of life of women during menopause.

Methods of statistical processing. All numerical indicators obtained during our study were analyzed in Microsoft Excel 2013 and STATISTICA 7.0 (Statsoft Inc, USA) using the method of biomedical statistics, taking into account modern recommendations.

RESULTS OF OWN RESEARCH AND THEIR DISCUSSION

100 women in the perimenopausal period we examined were distributed by age as follows: 35 women (35.0±4.7%) aged 45-47 years, 55 women (55.0±4.9%) - 48-51 years, 10 women (10.0±3.0%) aged 52-55 years; thus, the majority of women were aged 48-51 years (Table 1). Of the women in this age group (48-51 years old), 30 (60.0±6.9%) made up the main group, 13 (43.33±9.0%) - the comparison group and 12 - the control group (60,0±10,9%). In the age group of 45-47 years, the main group included 15 (30.0±6.5%) women, the comparison group - 14 (46.67±9.1%) and the control group - 6 (30.0± 10.2%) women ($p>0.05$). It is worth noting that the proportion of women aged 52-55 years in different groups was the same (10.0±4.2%, 10.0±5.5% and 10.0±6.7%, respectively; $p>0.05$).

Table1.
Age characteristics of women in the perimenopausal period

Age /group	45- 47 yaş		48 – 51 yaş		52 – 55 yaş	
	abs	%	abs.	%	abs.	%
The main group (n=50)	15	30,0±6,5	30	60,0±6,9	5	10,0±4,2
Comparative group(n=30)	14	46,67±9,1	13	43,33±9,0	3	10,0±5,5
Control group (n=20)	6	30,0±10,2	12	60,0±10,9	2	10,0±6,7
Total (n=100)	35	35,0±4,7	55	55,0 ±4,9	10	10,0±3,0

The difference between the indicators by groups is not statistically significant ($p>0,05$)

Of the women included in the main group, 35 (70.0±6.5%) were urban residents, while 15 (30.0±6.5%) were residents. In the comparison group, 24 women (80.0±7.3%) were urban residents, and 6 (20.0±7.3%) were rural residents. When considering the social status of women in all three groups, a predominance of housewives was noted: 38 (76.0±6.0%), 18 (60.0±8.9%) and 13 (65.0±10.7%) respectively ($t=14.24$; $p<0.001$). The proportion of employees was also

quite high: 12 (24.0±6.0) patients of the main group, 12 (40.0±8.9) patients of the comparison group and 7 (35.0±10.7%) women of the control group groups ($t=12.53$; $p<0.001$). All healthy women were those registered in the city.

There were 9 women with higher education in the main group (18.0±5.4%), in the comparison group - 12 (40.0±8.9%), in the control group - 7 patients (35.0±10.7 %) ($t=8.86$; $p <0.001$). The percentage of people with secondary education in the main group was 38 (76.0±6.0%), in the comparison group - 18 (60.0±8.9%) and in the control group 13 patients (65.0±10.7%) ($t=12.85$; $p<0.001$). Housing conditions were satisfactory in 18 (36.0±5.4%) patients of the main group, 14 patients in the comparison group (46.67±9.1%) and 12 patients included in the control group (60.0±10.9%, $t=9.64$; $p<0.001$). Housing conditions were unsatisfactory in 32 (64.0±5.4%) women of the main group, 16 (53.33±9.1%) women in the comparison group and 8 women in the control group (40.0 ±10.9%), ($t=11.38$; $p<0.001$).

The marital status of women was also studied. Thus, the majority of women were married, by group: 43 (86.0±4.9%), 19 (66.67±9.1%) and 18 (90.0±6.7%), respectively. 5 patients of the main group (10.0±4.2% women), 9 patients of the comparison group (23.33±7.8% women) and 1 patient of the control group (5.0%) were not married. 2 patients (4%) from the main group and 3 patients (10.0±5.5%) from the comparison group were single.

Analysis of observations of patients showed that there is a correlation between endometrial hyperplastic processes and BMI (Table 2).

Our study showed that an increase in body mass index leads to a decrease in 25(OH)D levels. The largest group of women in perimenopause are women with a BMI of 25.0–29.9 kg/m²: (48.0±7.1%) in the main group, 50.00±8.9% in the comparison group 63, 33%±10.7% and in the control group. BMI of 30.0–34.9 kg/m² was observed in 34.0±6.7%, 36.67±8.8% and 10.0±6.7% of women in the perimenopausal period, respectively. BMI 35.0 - 39.9 kg/m² was determined in 4.0±2.7% in the main group, 3.33% in the comparison group. In the main group, 4.0±2.7% of women had a BMI of 40.0 -

44.9 kg/m². In patients included in our study groups, a BMI of 18.59-24.99 kg/m² was observed in 10.0±4.2%, 10.0±5.5% and 30.0±10.2% of patients according to groups accordingly.

Table 2.
Anthropometric data of the studied groups general information

Data	Main group (n=50)		Comparative group (n=30)		Control group (n=20)	
	abs.	%	abs.	%	abs.	%
BMI, kg/m ² : 18,59-24,99	5*	10,0±4,2	3	10,0±5,5	6	30,0±10,2
25,0–29,9	24	48,0±7,1	15	50,00±8,9	12	63,33±10,7
30,0–34,9	17*	34,0±6,7	11*	36,67±8,8	2	10,0±6,7
35,0 – 39,9	2	4,0±2,7	1	3,33	-	-
40,0 – 44,9	2	4,0±2,7	-	-	-	-
Height, sm	1,64±0,01		1,61±0,01		1,62±0,01	

*Note: * - The difference in relation to the control group indicator is statistically significant (p<0,05)*

In terms of the timing of menarche in the groups we studied, there was no significant difference between the main group and the comparison group. Women in the main study group had longer periods of menstruation than in the comparison group, but no significant statistical differences were observed. Women in the main and comparative study groups had shorter menstrual cycles than healthy women, which may play a role in the pathogenesis of the disease. Also, when analyzing the anamnestic data in this group of patients, there was no significant difference in the characteristics of dysmenorrhea in reproductive age, especially of an acute nature (p>0.05).

Analysis of the obstetric and gynecological history showed that parity (1-3) in the examined women was 46.3 ± 5.6% in groups of patients (respectively: 56.0 ± 7.0% of patients in the main group, 23.33 ± 7.8% of patients in the comparison group, in the main group the parity number was 4-6 in 26.0±6.2% of patients, in the comparison group - 46.67±9.1%, in the control group - 45.0±11, 1%. And when analyzing the sum of the number of people who gave birth and

those who had an abortion, there was no significant difference in these characteristics between the groups ($p > 0.05$).

When studying the functional state of the cardiovascular, respiratory and excretory systems, concomitant diseases were identified. In patients with endometrial hyperplastic processes, the most common concomitant disease was cardiovascular diseases ($36.3 \pm 5.4\%$), which amounted to $46.0 \pm 6.7\%$ of patients in the main group and $20.0 \pm 7.3\%$ in the comparison group. The data obtained showed that arterial hypertension was observed in $26.3 \pm 4.9\%$ of all concomitant diseases, which was a coincidence in $26.0 \pm 6.2\%$ of cases in the main group and in $26.67 \pm 8.0\%$ of cases in the group comparisons.

Among endocrine diseases, type II diabetes mellitus was observed in $22.0 \pm 5.8\%$ of cases in the main group and in $10.0 \pm 5.5\%$ in the comparison group. Obesity I degree in $34.0 \pm 6.7\%$ of cases in the main group and $36.67 \pm 8.8\%$ in the comparison group, obesity in 4 patients ($8.0 \pm 2.7\%$) and in 1 patient in the corresponding II and III groups was observed in 3.33% of cases.

Autoimmune thyroiditis was observed in 1 (2.0%) patient of the main group. In the main group, degree I anemia was observed in $48.0 \pm 7.1\%$ of women, degree II anemia - in $10.3 \pm 4.2\%$, degree III anemia - in $6.0 \pm 3.3\%$ of women. In the comparison group, $36.7 \pm 8.8\%$ of women had grade I anemia, grade II anemia in $13.3 \pm 6.3\%$, grade III anemia was not observed in the study groups.

A comparative study of the characteristics of the hormonal status of patients in the study groups found that a high level of FSH was observed in $56.0 \pm 7.0\%$ of women in the main group and in $33.3 \pm 8.6\%$ of women in the comparison group. In women in the control group, FSH levels were within normal limits. The presented data showed that LH levels above normal were determined in $28.0 \pm 6.3\%$ of women in the main group, while in the comparison group it was $26.7 \pm 8.1\%$. At the same time, a monotonous decrease in estradiol to 16.0 ± 1.8 pg/ml was observed in $24.0 \pm 6.0\%$ of women in the main group and in $20.0 \pm 7.3\%$ of women in the comparison group. Such a decrease was observed in FSH (in $56.0 \pm 7.0\%$ of women in the main group and in $33.3 \pm 8.6\%$ of women in the comparison group) and LH

(in $28.0\pm 6.3\%$ of women in the main group and in $26.7\pm 8.1\%$ of women in the comparison group).

Also, low estradiol levels were observed in $24.0\pm 6.0\%$ of women in the main group and in $20.0\pm 7.3\%$ of women in the comparison group. In the control group of women, estradiol levels were normal. According to our study, it was found that ultrasound thickness of the endometrium in the main group was 13-17 mm in $52.0\pm 7.1\%$ of cases, 18-21 mm in $38.0\pm 6.9\%$ of cases, and in $10.0\pm 4.2\%$ of cases, recorded in the range of 22-27 mm.

By ultrasound, in $93.34\pm 4.3\%$ of women included in the comparison group, the thickness of the endometrium was in the range of 13-17 mm, in 3.33% of women - 20.9 mm, in 3.33% of women - 24 mm. By ultrasound, the thickness of the endometrium in 100% of women in the control group was estimated to be within 5-9 mm. According to the results of a comprehensive ultrasound examination, endometrial polyps (FIGO-P) were found in $38.0\pm 6.9\%$ of patients included in the main group, and multiple polyps - in $12.0\pm 4.6\%$. Also, $20.0\pm 5.7\%$ of patients had endometrial polyps against the background of submucosal uterine fibroids. $33.33\pm 8.6\%$ of patients included in the comparison group had endometrial polyps, 3.33% of them had multiple polyps, $13.33\pm 6.1\%$ of patients had endometrial polyps in combination with submucosal uterine fibroids.

In our study, $35.00\pm 5.3\%$ of women in both groups were diagnosed with uterine fibroids according to ultrasound examination. According to the results of a detailed ultrasound examination, fibroids were detected in $34.0\pm 6.7\%$ of patients in the main group, and multiple fibroids were detected in $18.0\pm 5.4\%$ of patients. Myoma was detected in $36.7\pm 8.8\%$ of patients included in the comparison group, and multiple fibroids were detected in $13.33\pm 6.1\%$ of them. No ultrasound data on the presence of fibroids was obtained in patients in the control group. According to the results of a comprehensive ultrasound examination, adenomyosis was detected in $28.0\pm 6.3\%$ of patients included in the main group, of which $8.0\pm 3.8\%$ had diffuse adenomyosis.

Adenomyosis was detected in $13.33\pm 6.1\%$ of patients included in the comparison group, of which 3.33% of patients were diagnosed

with diffuse adenomyosis. For the first time, as part of the dissertation work, the amount of vitamin D, folic acid and vitamin B₁₂, as well as the content of calcium, magnesium, phosphorus and zinc in the blood serum was studied in 80 perimenopausal women suffering from endometrial hyperplastic processes and in 20 healthy women.

The examination showed that in the main group a normal level of 25(OH)D (>30 ng/ml) was in a small part - 6.0±3.3% of patients, while in 76.0±6.0% of patients insufficient content was noted (10-29 ng/ml). At the same time, severe vitamin D deficiency (<10 ng/ml) was detected in 18.0±5.4% of women (Table 3).

Table 3.
Comparative characteristic of vitamin D level in patients of the studied groups

Groups	Level of vitamin D					
	>30 ng/ml		10-29 ng/ml		< 10 ng/ml	
	abs	%	abs.	%	abs	%
Main group (n=50)	3*,**	6,0±3,3	38	76,0±6,0	9	18,0±5,4
Comparative groups (n=30)	7	23,3±7,7	23	76,7±7,7	-	-
Control group (n=20)	8	40,0±10,9	12	60,0±10,9	-	-

Note: * - comparison difference in relation to the control group indicator ($p < 0,05$)

When studying the vitamin content in the comparison group, a normal level of 25(OH)D (>30 ng/ml) was determined in 23.3±7.7% of patients; deficiency (10-29 ng/ml) was diagnosed in 76.7±7.7% of patients. Severe vitamin D deficiency (<10 ng/ml) was not reported in this group. In the control group, a sufficient level of 25(OH)D (>30 ng/ml) was observed in 40.0±10.9% of patients, and a deficiency (10-29 ng/ml) was determined in 60.0±10.9% of patients. In this group of subjects, severe vitamin D deficiency (<10 ng/ml) was not observed. Having analyzed the results of the study, we came to the conclusion that there is a correlation between the thickness of the endometrium and the level of vitamin D. Thus, in patients with se-

vere deficiency ($11.3\pm 3.6\%$) and patients with deficiency ($76.3\pm 4.8\%$) the thickness of the endometrium was greater than that of the others. The presented data indicate the important role of vitamin D in women during perimenopause, however, the biological functions of vitamin D are still not fully understood.

Based on our research, we conclude that vitamin D deficiency leads to various pathological conditions that can aggravate the symptoms of menopausal syndrome in perimenopausal women. We consider an important aspect of this work to be the importance of early detection of vitamin D deficiency and its timely correction.

The results of our research showed that $6.0\pm 3.3\%$ of women in the main group of perimenopausal women had a serum folic acid level higher than the norm, while $94.0\pm 3.3\%$ of women were within the norm. 3.3% of the women included in the comparison group had a serum folic acid level higher than normal, and $96.7\pm 3.1\%$ had a normal level. In 100% of women of the control group included in the study, the level of folic acid in blood serum was normal.

The results of our study showed that in 4.0% of women in the perimenopausal period the level of vitamin B₁₂ in the blood serum was above normal, in 2.0% it was below normal, and in $94.0\pm 3.3\%$ normal values were determined. In 100% of women in the comparison group, the level of vitamin B₁₂ in the blood serum was within normal limits. In $85.0\pm 7.9\%$ of women in the control group included in the study, the level of vitamin B₁₂ in the blood serum was normal, and in $15.0\pm 7.9\%$ of women it was elevated.

As can be seen from the presented data, it was shown that the level of Ca in the blood serum in all 3 groups was within normal limits, that is, it was in the range of 8.4 - 10.2 mg/dl. In the main group, normal P levels (2.6 - 4.5 mg/dl) were recorded in $86.0\pm 4.9\%$ of patients, deficiency (<2.6 mg/dl) was determined in $6.0\pm 3.3\%$, an increase in serum P (>4.5 mg/dL) was found in $8.0\pm 3.4\%$. A normal P level (2.6-4.5 mg/dL) was observed in 100% of patients in the comparison group. In the control group, $70.0\pm 10.2\%$ of patients had normal P levels (2.6-4.5 mg/dL), and $30.0\pm 10.2\%$ had high P levels in the blood serum (>4.5 mg/dl). In the main group, a normal level of Zn (0.8-1.2 mg/dl) was detected in $80.0\pm 5.7\%$ of patients, and in

20.0±5.7% of patients an increased level of Zn in the blood serum was detected (>1.2 mg/dl). In the comparison group, 93.3±3.3% of patients had normal Zn levels (0.8-1.2 mg/dL), and 6.7±3.3% had elevated levels (>1.2 mg/dL), 100% of women in the control group had a sufficient level of Zn (0.8-1.2 mg/dl). In the main group, a normal level of Zn (0.8-1.2 mg/dl) was detected in 80.0±5.7% of patients, and in 20.0±5.7% of patients an increased level of Zn in the blood serum was detected (>1.2 mg/dl). In the comparison group, 93.3±3.3% of patients had normal Zn levels (0.8-1.2 mg/dL), and 6.7±3.3% had elevated levels (>1.2 mg/dL), 100% of women in the control group had a sufficient level of Zn (0.8-1.2 mg/dl). The study of the level of magnesium showed that in most cases - 21 (75%) patients had a normal level, and 7 (25%) patients had hypomagnesemia. In the main group, normal magnesium levels (1.6-2.6 mg/dl) were detected in 94.0±3.3% of patients, deficiency (<1.6 mg/dl) - in 6.0±3.3%. In the comparison group, 100% of women had magnesium levels within the normal range (1.6 – 2.6 mg/dL).

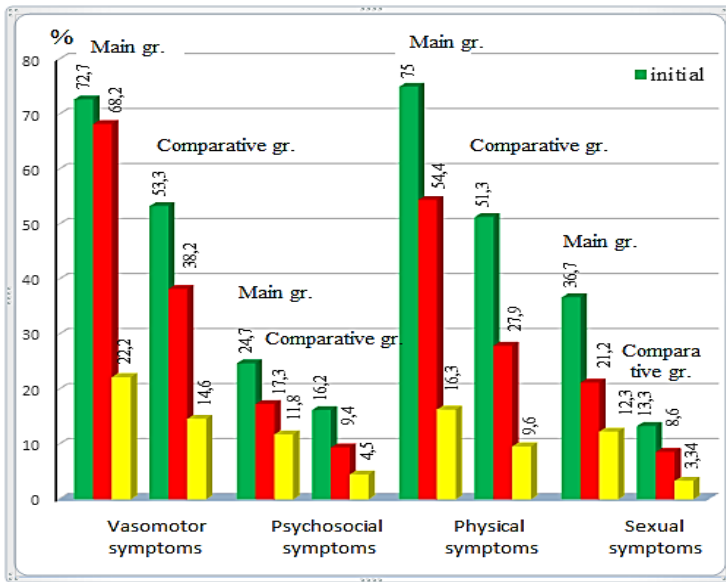
In the control group, 85.0±7.9% of patients had normal magnesium levels (1.6-2.6 mg/dL), and 15.0±7.9% had increased serum magnesium levels (> 2.6 mg/dl). Upon admission to the hospital, all patients underwent histological examination. Indications for their implementation were abnormal uterine bleeding, as well as suspicion of thickening of the endometrium according to ultrasound data. According to the results of histological examination, fibrous (33.3%), adenomatous (20.8%), glandular (16.6%), glandular-cystic (16.6%) and glandular-fibrous (12.7%) endometrial polyps were identified. Glandular endometrial hyperplasia is classified into “active” and “quiet” types depending on the activity of proliferative processes. Glandular hyperplasia of the “active” form of the endometrium (58.33%) is characterized by numerous mitoses of glandular epithelial cells, high alkaline phosphatase activity and the formation of light-colored cells in the glands. The “quiet” form of glandular endometrial hyperplasia (41.67%) is characterized by the fact that the endometrial glands are in a non-functional state due to prolonged exposure to low levels of estrogen (follicular atresia), relative hyperestrogenism, intense staining of the nuclei, mitoses are insignificant or absent.

Evaluation of the histological picture of the endometrium determines the subsequent treatment tactics for the patient.

The increase in women's life expectancy dictates the need for a significant revision of the strategy and assessment of the quality of health at different stages of life. Features in the structure of the disease are characterized by the nature of changes in the course of diseases, their deviation from the natural course.

From this point of view, special attention should be paid to timely assessment of the transition period in a woman's life - the perimenopausal period, improving her balance, increasing adaptogenicity. One of the tasks that we set for ourselves in our research work was to study the quality of life of women in the perimenopausal period. The scale we use assesses the quality of life during perimenopause and menopause in four areas. During the course of my dissertation, it became clear that the use of MENQOL is an effective in the general population. In our study, we found that perimenopausal women experienced a higher degree of vasomotor and physical symptoms, which may be explained by the fluctuations in follicle-stimulating hormone (FSH) and estrogen levels that occur during perimenopause. The majority of women (97.14% overall) experienced at least five or more menopausal symptoms. Vasomotor symptoms were manifested by hot flashes (study group and comparison group: 82.0% and 53.33%, respectively), sweating (74.0% and 63.33%, respectively) and night sweats (62.0% and 43.33% respectively). Most women had such somatic symptoms as frequent back pain (96.0% and 73.33% in the main group and comparison group, respectively), decreased physical strength (92.0% and 73.33%, respectively), general weakness (92.0% and 80.0%, respectively), weight gain (84.0% and 50.0%, respectively), neck pain (90.0% and 70.0%, respectively), muscle pain (90.0%, 0% and 86.67%, respectively), loss of strength, weakness (86.0% and 46.67%, respectively), sleep problems (88.0% and 63.33%, respectively), flatulence (78.0% and 40.0%, respectively), decreased physical activity (92.0% and 73.33%, respectively), changes skin (52.0% and 23.33%), respectively: stress urinary incontinence when laughing or coughing (38.0% and 13.33%, respectively), dry skin (64.0% and 43.33%, respective-

ly), increased urination (32.0% and 20.0%, respectively), swelling (82.0% and 43.33%, respectively), and increased facial hair (58.0% and 33.33%, respectively). Among the participants, depression of unknown cause was observed (respectively: 44.0% and 20.0%), anxiety and irritability (respectively: 24.0% and 16.67%), dissatisfaction with personal life (respectively: 46.0% and 23.33), memory impairment (respectively: 18.0% and 13.33). Various problems were reported to occur in 13.33%, poor health (respectively: 16.0% and 16.67%), impatience and irritability (respectively: 12.0% and 13.33%) (Fig. 1).



Note: * - Comparison in relation to the control group indicator, the difference is statistically significant ($p < 0,05$)

Fig. 1. The frequency of menopausal symptoms in perimenopause

Frequency of menopausal symptoms in perimenopause

Only a few women expressed a desire to be alone most of the time (respectively: 14.0% and 10.0%). Changes in libido (respectively: 32.0% and 20.0%), vaginal dryness (respectively: 64.0% and

10.0%) and sexual problems (respectively: 14.0% and 10.0%) were recorded.

The questionnaire, which included 29 questions grouped into 4 scales, was filled out by patients in the main group and the comparison group before the start of treatment (during the initial examination of patients), then 3 and 12 months after the start of therapy. Patients in the control group completed a questionnaire at the first visit. Comparison of the indicators of 4 scales allowed us to note significant positive changes in the two groups during treatment ($p < 0.001$, $p < 0.001$).

According to the “Vasomotor symptoms” and “Psychological symptoms” scales, a significant improvement was noted after 12 months in the main group and in the comparison group ($p < 0.001$ and $p < 0.001$, respectively). Analysis of the data on “Physical symptoms” and “Sexual symptoms” showed that after three months there was a significant improvement in indicators in the main group and the comparison group ($p < 0.001$ and $p < 0.001$, respectively).

Patients were prescribed 3 different oral doses of vitamin D (2000 IU, 5000 IU or 7000 IU), in the form of liquid drops. As a vitamin D preparation, we chose D-Colerol, drops for oral administration, 50,000 IU/15 ml (vitamin D3), produced in Turkey. We assessed the effect of daily doses of vitamin D greater than 2000 IU for at least 3 months. To prevent and treat vitamin D deficiency, we recommend that patients take the following doses: for patients with a 25(OH)D level > 30 ng/ml - at least 2000 IU of vitamin D per day, for a deficiency of 10-29 ng/ml - vitamin D per day 5000 IU, with severe vitamin D deficiency (< 10 ng/ml) - vitamin D 7000 IU per day. After treatment with D-colerol in the main group, a normal amount of 25(OH)D (> 30 ng/ml) was detected in $78.0 \pm 5.9\%$ of patients, deficiency - in $22.0 \pm 5.9\%$ - in 11 patients (10 -29 ng/ml), severe vitamin D deficiency < 10 ng/ml was not observed in this group of patients. In the comparison group, 26 patients ($86.7 \pm 6.1\%$) had normal levels of 25(OH)D (> 30 ng/ml), 4 patients ($13.3 \pm 6.1\%$) had vitamin D deficiency (10-29 ng/ml). Severe vitamin D deficiency (< 10 ng/ml) was not observed in this group. 8 patients ($16.0 \pm 5.2\%$) and 5 patients (16.6 ± 6.8) in the control group took 5000 IU per day.

When taking a dose of 7000 IU/day, hypercalciuria was observed in $14.0 \pm 4.9\%$ of women. After treatment with D-Colerol at a dose of 5000 IU, 7 women in the main group ($14.0 \pm 4.9\%$) and 3 women in the comparative group ($10.0 \pm 5.5\%$) experienced mild hypercalcemia. This complication was observed when taking a dose of 7000 IU per day in 4 women of the main group ($8.0 \pm 3.8\%$). (Fig. 2).

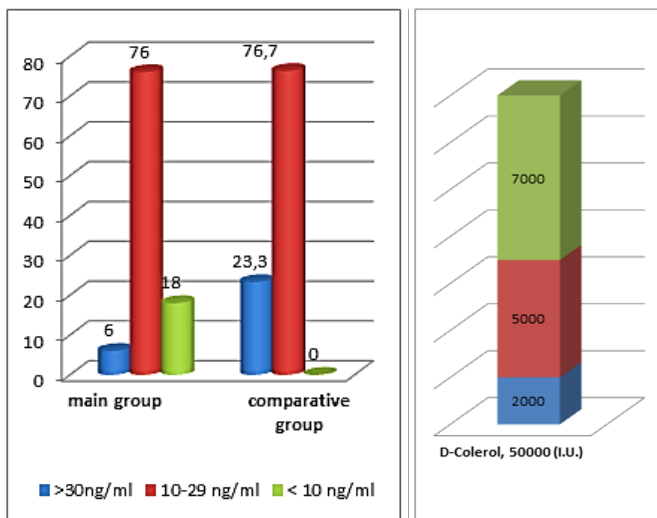


Fig 2. Depending on the vitamin D deficit, D- colerol is 50000 B.V. reception of a dose –dependent drug.

Looking at the results in our main study group, we concluded that serum 25(OH)D levels were lower than in the comparator study group and the endometrium was thicker in cases of severe deficiency. Judging by the results obtained, vitamin D deficiency is observed in both groups and plays a major role in the progression of the disease.

When choosing treatment, we took into account the patient's age, clinical, laboratory and instrumental examination parameters, type of hyperplasia and concomitant diseases. The main type of surgical intervention in patients with endometrial hyperplastic processes is dilation and curettage, which was used in 100% of patients. After timely treatment and a complete examination (hysteroscopy, separate

curettage of the uterus and cervical canal), radical surgery was performed in $22.5\pm 4.7\%$ of cases. Of 80 patients, 39 patients ($48.8\pm 5.6\%$) underwent dilatation and curettage, 18 patients underwent radical surgery ($22.5\pm 4.7\%$), 7 patients ($8.8\pm 3.2\%$) underwent polypectomy, 15 patients - ($18.6\pm 4.4\%$) - TLH and BSO and 1 patient underwent (1.3%) TAH. The main type of surgical operation for hyperplastic processes of the endometrium is “Dilatation and curettage”, which was performed in $46.0\pm 7.0\%$ of patients in the main group and in $53.4\pm 9.1\%$ in the comparison group. Operations of the TLH and BSO type were performed in $16.0\pm 5.2\%$ of patients in the main group and in $23.3\pm 7.7\%$ of patients in the comparison group. In the main group, polypectomy was not performed; in the comparison group, it was performed in 7 patients ($23.3\pm 7.7\%$). In the main group, total hysterectomy was performed in only 18 patients ($36.0\pm 6.7\%$).

Combination treatment included a combination of two or more treatments. In the main group, 6.0% of patients diagnosed with EG after dilatation and curettage of the uterine cavity were introduced to a levonorgestrel-containing intrauterine system (Mirena), $30.0\pm 6.5\%$ of patients received COCs in a 21-day regimen from the 1st day of menstruation for 3 months, $40.0\pm 6.9\%$ of patients received dienogest at a dose of 2.0 mg for 6 months.

The intrauterine system (Mirena) was administered to 6.7% of patients in the comparison group, and dienogest 2.0 mg to $46.7\pm 9.1\%$ of patients.

Management of patients during menopause includes a number of activities. First of all, this means sufficient physical activity, a balanced diet and regular temperature control, as well as treatment of the underlying disease. Based on our research, we suggest medical monitoring of hormonal changes in perimenopausal women, as well as periodic assessment of mineral and vitamin D levels and, if necessary, dosage adjustments to reduce health problems. The diagnostic algorithms we have developed can become an effective tool in the daily clinical practice of a doctor, will contribute to the successful management of patients with menopausal symptoms and will allow women to make a personal contribution to the overall goal of nation-

al well-being. Based on the collected data, an algorithm for early diagnosis in women with endometrial hyperplastic processes in the perimenopausal period was developed. Based on the analysis of the information received, individual diagnostic algorithms for assessing the condition of the endometrium in each patient were developed based on specific principles of functional treatment using modern research methods.

Thus, this strategy makes it possible to increase the efficiency of identifying benign and malignant endometrial diseases, as well as to individualize the tactics of managing perimenopausal women with endometrial pathological processes with the significant involvement of modern diagnostic methods.

CONCLUSIONS

1. In hyperplastic processes of the endometrium in the perimenopausal period, vitamin D deficiency is detected with high frequency. Thus, in the main group, normal levels of vitamin D (>30 ng/ml) were found in $6.0\pm 3.3\%$ of patients, deficiency ($10-29$ ng/ml) in $76.0\pm 6.0\%$ of patients, severe vitamin D deficiency (<10 ng/ml) was found in $18.0\pm 5.4\%$. In the comparison group, the normal level was $23.3\pm 7.7\%$ ($p<0.05$), vitamin D deficiency was observed in $76.7\pm 7.7\%$ of women; there was no severe vitamin D deficiency <10 ng/ml in this group fixed. In hyperplastic processes of the endometrium in the perimenopausal period, no significant differences were found in the content of microelements (Ca, Zn, Mg, P) ($p>0.05$) [15,16,17,18].

2. In patients with severe vitamin D deficiency (9 women, $11.3\pm 3.6\%$), the thickness of the endometrium was higher than in patients with deficiency (61 women; $76.3\pm 4.8\%$), from 13 mm to 27 mm. Thus, in $52.0\pm 7.1\%$ of patients of the main group, the thickness of the endometrium was in the range of 13-17 mm (15.2 ± 0.29), in $38.0\pm 6.9\%$ of patients - in the range of 18-21 mm. (19.6 ± 0.27), and in $10.0\pm 4.2\%$ of patients it was estimated within 22-27 mm (24.5 ± 0.96). In patients included in the comparison group, endome-

trial thickness was assessed as $93.34\pm 4.3\%$, 3.33% and 3.33% , respectively [16,17].

3. In perimenopausal women, endometrial hyperplastic processes occurred in the “active” type (58.33% of cases) and the “quiet” type (41.67% of cases), depending on the activity of proliferation [7,17].

4. When assessing the quality of life according to the results of “Vasomotor, psychological, physical and sexual” symptoms of the MENQOL scale in perimenopausal women, a significant improvement was established in the respondents of the main and comparison groups ($p<0.001$, $p<0.001$, respectively) in the first three months of treatment, which indicates significant positive dynamics [7,13,14].

5. When choosing complex treatment, it is necessary to take into account the age of the patients, clinical, laboratory and instrumental examination parameters, the type of hyperplasia and concomitant diseases. After treatment with D-Colerol, $78.0\pm 5.9\%$ of patients had normal 25(OH)D levels (>30 ng/ml), $22.0\pm 5.9\%$ had a deficiency ($10-29$ ng/ml), severe vitamin D deficiency <10 ng/ml was not observed [17].

PRACTICAL RECOMMENDATIONS

1. Carry out medical monitoring of hormonal changes in perimenopausal women, as well as assess the level of minerals (Ca, Zn, Mg, P) and vitamin D and adjust the dose if necessary once a year

2. When examining patients with endometrial hyperplastic processes in perimenopause, it is recommended to study the level of 25(OH)D in the blood serum along with appropriate blood tests and instrumental examination.

3. For the prevention and treatment of vitamin D deficiency, we recommend the following doses of vitamin D: for patients with a level of 25(OH)D >30 ng/ml - 2000 IU of vitamin D per day, at the level of deficiency. $10-29$ ng/ml - 5000 IU of vitamin D per day, with severe vitamin D deficiency <10 ng/ml - vitamin D 7000 IU per day.

4. In order to prevent possible clinical and chronic degenerative diseases of perimenopausal women, it is recommended to evaluate

and monitor the nutritional status of perimenopausal women (vitamin and microelement value of the food they consume).

5. Patients with endometrial hyperplastic processes in the perimenopausal period are recommended to fill out the MENQOL quality of life questionnaire before the start of treatment; based on the results of the MENQOL survey 3 and 6 months after the start of therapy, it is recommended to evaluate the effectiveness of treatment for perimenopausal disorders and the dynamics of the main indicators of quality of life and, if necessary, individualize the treatment program

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LIST OF ABBREVIATIONS

AMU	–	Azerbaijan Medical University
AUB	–	Abnormal uterine bleeding
BMI	–	Body mass index
BSO	–	Bilateral salpingo-oophorectomy
EH	–	Endometrial hyperplasia
EHP	–	Hyperplastic processes of the endometrium
FSH	–	Follicle stimulating hormone
LH	–	Luteinizing hormone
LNG UDV	–	Intrauterine device containing levonor-gestrel
TAH	–	Total abdominal hysterectomy
TLH	–	Total laparoscopic hysterectomy
TVE	–	Transvaginal echography
TVS	–	Transvaginal sonography
UDV	–	Intrauterine device
Ultrasound	–	Ultrasound examination

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