



## **FEATURES OF UTERINE FIBROID VASCULARIZATION IN WOMEN WITH VITAMIN D DEFICIENCY**

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<b>Article history:</b>	<b>Abstract:</b>
<b>Received:</b> September 7 <sup>th</sup> 2023 <b>Accepted:</b> October 7 <sup>th</sup> 2023 <b>Published:</b> November 11 <sup>th</sup> 2023	Uterine fibroids are the most common pathology among women. We examined 200 women at the Multidisciplinary Clinic of the Tashkent Medical Academy. We studied the saturation of the body with vitamin D (25(OH)D) in patients with uterine fibroids (UF) and healthy women, moreover in order to identify ultrasound parameters in the studied women with UF, we performed color duplex scanning of the vessels of the internal iliac artery. In less than half of women with symptomatic fibroids, deficiency and severe deficiency of vitamin D prevails. In 1/3 of women with the symptomatic UF group, intense central blood flow was observed in the PP; in women with asymptomatic fibroids, with an avascular type of blood flow, in more than half of the women, the sizes of the uterus and nodes were minimal. The more pronounced the deficiency of this vitamin D, the more neoangiogenesis develops, leading to increased vascularization of the myomatous node, its growth, and the manifestation of clinical symptoms in these women.

**Keywords:** uterine fibroids (UF), leiomyoma, symptomatic fibroids, asymptomatic fibroids, vitamin D (prohormone D), color duplex scanning (CDS), linear blood flow rate (LBFR), resistance index (RI), pulsation index (PI), perifibroid plexus (PP).

**INTRODUCTION.** In the world, including Uzbekistan, in recent years there has been a tendency for the spread of hormone-dependent tumors in women, and in the gynecological practice uterine fibroids (UF) is dominant. The increase in the incidence of UF, in particular in socio-economically active women of the late reproductive and perimenopausal period, takes a second place by frequency after inflammatory diseases of the genitals [1, 9, 20]. The frequency of UF in the structure of gynecological diseases among women is 20-77% [33, 37].

Throughout the world, modern scientific research pays special attention to the study of the etiology and pathogenesis of UF, so as early diagnosis, effective treatment methods and preventive measures, taking into account predictors of the disease are important in personalized medicine. Ultrasound examination (ultrasound) is currently one of the leading research methods for uterine leiomyoma. Despite the predominance of the surgical method of treating patients with UF, the search for conservative methods of therapy for this disease continues [5]. Color duplex sonography (CDS) is an informative ultrasound that allows you to determine the course of intratumoral vessels [11]. CDS involves visualization of vessels located deep under the layer of skin, subcutaneous tissue and internal organs [6] and identifies even very small vessel segments [16].

Vitamin D, as a steroid hormone, plays a huge role in a woman's reproductive health [4, 21]. Today, WHO experts assess vitamin D deficiency as a new pandemic of the 21st century [38].

Scientists have proven a clear relationship between reduced levels of vitamin D in blood plasma and a higher risk of developing UF [3, 13, 29, 31, 32,34]. The protective role of vitamin D against leiomyomas has been demonstrated in several in vitro experimental studies [14, 23], as well as in a number of in vivo studies [12]. As a result of research, the mechanism of vitamin D action on the development of UF has been studied [15].

Data support the hypothesis that vitamin D deficiency is associated with the etiology of fibroids, but prospective clinical studies involving direct measurement of vitamin D levels in women with UF and studying the angioarchitecture of UF are needed.

The purpose of the study was to identify the level of vitamin D provision in women with uterine fibroids and to study the features of the angioarchitecture of the uterine arteries in this pathology.

**THE SUBJECTS OF THE STUDY** were 200 women of reproductive and premenopausal age, observed from 2021 to 2022, in the Department of Gynecology and the Women's Health Center of the Tashkent Medical Academy Multidisciplinary Clinic. The work was carried out at the Department of Obstetrics and Gynecology in



Family Medicine of the Tashkent Medical Academy. The women were divided into 2 groups: the main group, (n=102) patients with UF, which in turn was divided into 2: with symptomatic (n=53) and asymptomatic (n=49) UF, and a control group, (n=98), which consisted of healthy women.

When working with women, the ethical principles required by the World Medical Association Declaration of Helsinki "Ethical Principles of Scientific and Medical Research Involving Human Subjects" (revision 2013) [39] and diagnostic measures were observed, in accordance with the National Protocol of the Ministry of Health of the Republic of Uzbekistan [10].

Inclusion criteria: patients diagnosed with uterine fibroids with symptomatic and asymptomatic course and age from 18 to 54 years, apparently healthy women without UF of comparable age, presence of menstruation, informed consent of the woman for examination.

Exclusion criteria: women under 18 and over 54 years of age, pregnant women, patients registered at a dispensary; alcohol abuse, drug use, the presence of malignant neoplasms, chronic diseases in the stage of decompensation or exacerbation, a woman's refusal to participate in the study.

**RESEARCH METHODS.** All examined women underwent a comprehensive examination, which included general clinical and special research methods: sociological, biochemical, instrumental (ultrasound + CDS), statistical. In all women were performed collection of complaints and anamnesis, general and gynecological examinations.

Determination of the blood serum concentration as the marker of body saturation with vitamin D - 25(OH)D - was carried out in peripheral venous blood from the ulnar vein of the examined women on 5-7 days of the menstrual cycle, by using the quantitative ELISA method - chemiluminescent microparticle analysis (CMIA).

Association of Endocrinologists (2020) by determining the content of 25(OH)D in the blood serum (I A) (Table 1). Determination of vitamin D levels was carried out by IFA testing using an enzyme-linked immunosorbent assay based on the principle of competitive binding. At the outset, samples were pretreated with denaturing buffer to extract the analyte, since most circulating 25(OH)D is naturally bound to VDBP (vitamin D binding protein) in the blood. After neutralization, biotinylated 25(OH)D (enzyme conjugate) and peroxidase-labeled streptavidin (enzyme complex) were added. The resulting solution, after gentle mixing, was transferred into the wells of a microplate. Endogenous 25(OH)D from the sample competed with biotinylated 25(OH)D3 for binding to VDBG, which was adsorbed in the microplate wells. To detect bound 25(OH)D, the enzyme complex was used to incubate, followed by washing of unbound components. The color reaction was started with the addition of enzyme substrate and ended after a fixed time. The color intensity of the obtained samples was inversely proportional to the concentration of 25(OH)D. Inclusion criteria for study women to determine 25(OH)D: the last 6 months have not consumed vitamin D or calcium supplements, absence of pregnancy and lactation, malabsorption, or parathyroiditis [27].

Ultrasound of the pelvic organs was carried out according to standard methods using Sono-Scape S-50 ultrasound machines using a convex transabdominal sensor with a frequency of 3.5 MHz and a vaginal sensor with an operating frequency of 7.5 MHz (China) in real time. The study protocol included the length, width, anteroposterior size of the uterus, and also determined the condition of the uterine appendages: ovaries - size, volume, follicular apparatus and tubes. To assess the endometrium, the following were determined: anteroposterior size of the M-echo - thickness (expanded, linear cavity); degree of expression (evenly, unevenly); echostructure; echogenicity; contours at the border with the myometrium (clear, unclear), determined the localization of myomatous nodes, their number and volume. The volumes of the uterus and myomatous node during ultrasound of the uterus and appendages were calculated using the formula of Brunn (1981): (Length\*Width\*Height) \*0.457. All patients of both groups underwent ultrasound CDS using the Sono-Scape SSI-5000 device (China).

**RESEARCH RESULTS.** The analysis of the age characteristics of the studied women showed that the average age was 18-54 years. The highest average age was observed in women of the main group: with asymptomatic fibroids 42.6±1 years (n=49) and with

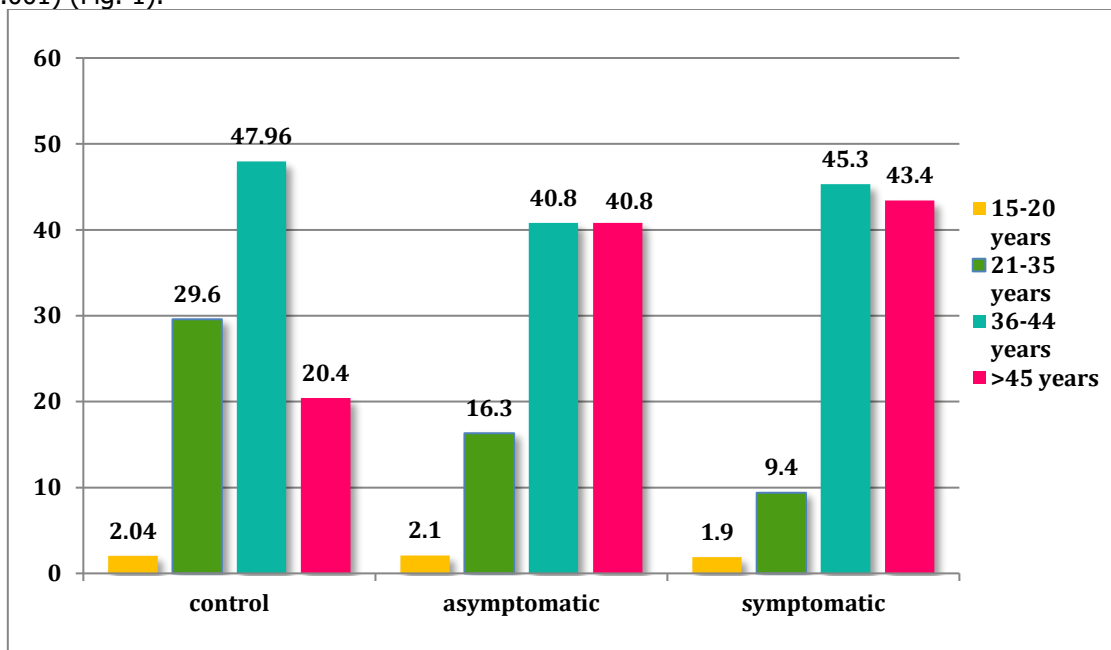
**Table 1.**

**Criteria for the provision of vitamin D in blood serum [2]**

Classification	Level of 25(OH)D in blood	
	ng/ml	nmol/l
Severe vitamin D deficiency	<10	<25
Vitamin D deficiency	<20	<50
Vitamin D deficiency	20–30	50 - 75
Adequate Vitamin D Levels	>30-100	>75-250
Toxic Vitamin D Levels	>150	> 375

Assessment of vitamin D status was carried out according to the recommendations of the Russian

symptomatic fibroids –  $43.5 \pm 0.2$  years ( $n=53$ ), while in the control group ( $n=98$ ) average age was  $38.7 \pm 0.9$  years ( $p < 0.001$ ) (Fig. 1).



**Picture 1. Age of examined patients, %.**

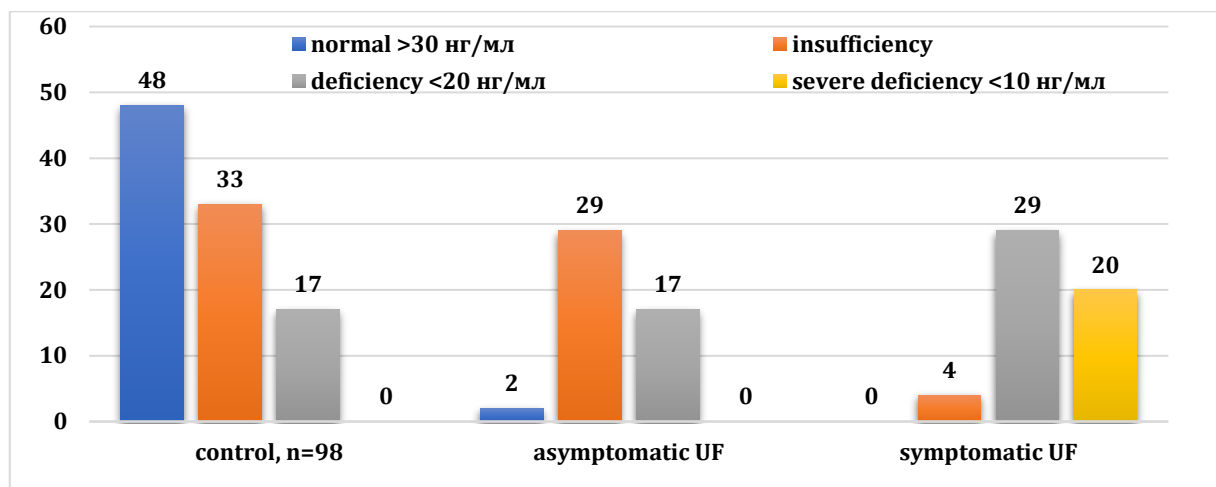
A study of the examined women's age showed that in the main group the majority of patients were in late reproductive age (40.8% and 45.3%, respectively) and perimenopausal age (40.8% and 43.4%, respectively), while in the control group late reproductive age prevailed (47.9%).

When analyzing nationality, the majority of the studied women were Uzbeks, both in the control group (93.9%) and in the main group (93.9% and 96.2%, respectively).

Urban residents prevailed over rural residents in the group with asymptomatic UF (57.1%), while among women with symptomatic UF, rural residents predominated (56.6%). In the control group, the ratio of rural and urban women was equal (50%:50%). Women with symptomatic UF of the main group ( $n=53$ ) presented with various clinical manifestations: the symptom of bleeding and anemia was more prevalent in 86.8% ( $n=46$ ), of which 18.9% of women underwent blood transfusion due to severe anemia; symptom of rapid growth - 11.3% ( $n=6$ ), symptom of pelvic pain ( $n=5$ ) 9.4% and symptom of infertility in 7.5% ( $n=4$ ). Analysis of the initial content of vitamin D in the blood showed that in the group of women with UF its values

ranged from 4 to 36 ng/ml and averaged  $16.7 \pm 1.8$  ng/ml, which turned out to be significantly lower than in healthy women ( $p < 0.001$ ). The blood level of vitamin D in women with symptomatic UF averaged  $11.84 \pm 0.46$  ng/ml and in women with asymptomatic UF -  $21.54 \pm 0.04$ , while in the control group -  $29.83 \pm 1.13$  ng/ml (Fig. 3.6). At the same time, a pronounced deficiency of vitamin D was detected in the group of symptomatic UF  $6.62 \pm 0.9$  ng/ml in 37.7% of women with obvious clinical menorrhagia (in 100% of women) and recurrent course of the disease, and in the group of asymptomatic UF in 1/3 patients (36.7%) had a vitamin D deficiency of  $16.7 \pm 1.6$ . The prohormone values in the control group were significantly different ( $p < 0.001$ ).

When comparing vitamin D levels between groups in the main group, statistical differences were significant, indicating the presence of a relationship between the level of vitamin D saturation in women with UF and the clinical manifestations of the disease. The distribution of women according to the level of vitamin D supply, based on its content in the blood (Fig. 2), showed a significant difference between the main and control groups.



**Picture 2. Vitamin D provision in the studied women, abs**

In the main group of women with asymptomatic UF, normal values of vitamin D were only 4.1% of cases, insufficiency - in more than 1/2 (59.2%) and deficiency - in 1/3 (34.7%) of women, while in the study group of women with symptomatic UF, normal values of the prohormone were not detected, a deficiency was detected in more than 1/2 (54.7%) of women in this group and a pronounced deficiency was found in 1/3 (37.7%) of women, which is 2.88 times more than in group of asymptomatic UF and 5.4 times compared to the control group.

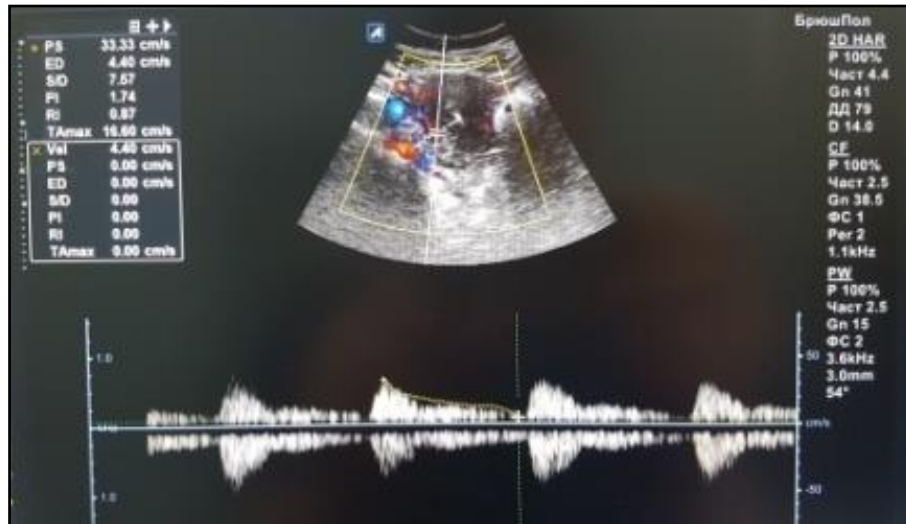
It is noteworthy that, despite the absence of the disease, 52% of healthy women in the control group had insufficient levels and deficiency of vitamin D in the blood, in a country with sufficient insolation, which may be due to the presence of modifying risk factors in these women. The target serum 25(OH)D level should be 40–60 ng/ml [4]. When analyzing the OR of UF, it was revealed that in women with insufficiency and/or deficiency of vitamin D, the chances of developing UF are 16.13, which proves that the factor of prohormone deficiency is a strong provoking factor for the development of the disease.

We analyzed the relationship between the number and location of myomatous nodes and the presence or absence of clinical fibroids. In women with symptomatic UF (n=53), 1/3 (32.1%) had multiple UF (more than 2 myomatous nodes) and 2/3 (67.9%) had a solid tumor,

while in those studied with asymptomatic multinodular UF was diagnosed 2 times less compared to symptomatic UF (14.3% and 85.7%, respectively). The number of myomatous nodes in the studied women of the main group with multiple nodes varied from 2 to 6 nodes.

According to the localization of the myomatous node in the thickness of the uterus in both groups of the main group, the intramural node prevailed (71.7% and 63.2%, respectively, groups), submucosal (7.15% and 6.12%) nodes in equal proportions and subserous (7, 15% and 24.5%) – 3 times more often detected in women with asymptomatic UF. Mixed myomatous nodes in women with symptomatic UF were 2 times more coUFon than in women with asymptomatic UF (13.2% and 6.12%, respectively).

During CDS, we analyzed the blood flow velocity curves in the IIA, UA, OA and in the dominant myomatous node, determining the diameter of the vessels, LBFR, RI, PI and the type of angioarchitecture of the PP. In the studied women, the diameter of the studied vessels varied slightly: in the main group, the diameter of the IPA was 1.14 UF larger than in the control group, which averaged  $7.5 \pm 1.31$  UF (5.1-11.3 UF) and  $6.36 \pm 0.67$  UF (5.2-7.8UF) according to the groups. When measuring the diameter of the UA and OA arteries, no significant differences were revealed in the groups ( $p < 0.001$ ) (Fig. 3).



**Picture 3. Patient R. with asymptomatic UF, right UA, avascular type of PP (No. 12420).**

According to the CDS data, we identified differences in the LBFR: this IIA indicator was found to be within normal limits in all groups, but in the UA the blood flow was significantly increased in women with symptomatic UF ( $144.3 \pm 24.8$  cm/s) ( $p < 0.001$ ). In the control group, the LBFR numbers were within normal limits. We studied LBFR in the perifibroid plexus and found that in the first group it was 1.16 times higher than in the second ( $72.09 \pm 22.1$  cm/s and  $62.17 \pm 5.07$  cm/s, respectively) ( $p < 0.01$ ).

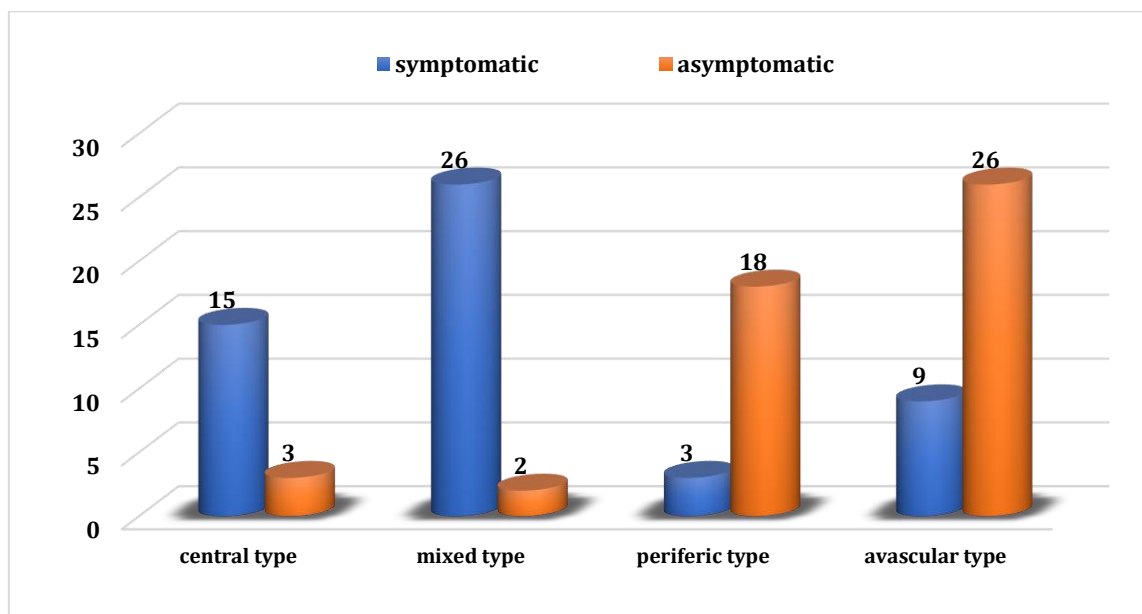
Thus, the blood flow velocity in UF is significantly higher in UA and PS than in the control group, which indicates increased blood supply to the uterus in the presence of a tumor ( $p < 0.001$ ).

Studying the PI index, we found that its decrease in all vessels of the IIA basin was observed in women with UF, especially in the group of symptomatic UF ( $p < 0.01$ ); PI in the perifibroid plexus within the main group did not reveal any significant differences ( $1.63 \pm 0.14$  and  $1.67 \pm 0.05$ , respectively). In UF, PI in the uterine arteries, compared with similar parameters in healthy women, turned out to be significantly low ( $p < 0.001$ ).

The results of RI indicators we obtained: in all the studied vessels, no significant differences in the RI

indicator were detected, while in the main group we noted vascular resistance in the PP with a decrease in RI up to 1.1 times compared to the RI of other studied vessels. RI in the PP of the first subgroup was  $0.76 \pm 0.03$  and in the second –  $0.75 \pm 0.03$  ( $p < 0.01$ ). According to the analysis of RI values in the PP, depending on the vascularization of the myomatous node, with intensively vascularized myomatous nodes (with mixed and central types of angioarchitecture), RI averaged 0.72 in the main group and 0.83 in the control group, which revealed several decreased RI in patients with UF compared to healthy women.

During CDS of PP in women with UF, we identified 4 types of angioarchitecture in different proportions (Table 2). In the group with symptomatic UF ( $n=53$ ), in half of the women examined the mixed type prevailed (49.05%,  $n=26$ ) and in 1/3 - the central type of blood supply to the perifibroid plexus (28.3%,  $n=15$ ), then in the group with asymptomatic UF ( $n=49$ ), more than half of the women had a predominant avascular (53.06%,  $n=26$ ) type of perifibroid blood flow. The pronounced proliferative potential of the myometrium in these types of angioarchitecture can be evidenced by the presence of UF symptoms in the first group (Fig. 4).



**Picture 4. Type of angioarchitecture of perifibroid blood flow in women of the main group, n=102, abs.**

**DISCUSSION.** In women with symptomatic myoma, a duplex study revealed an increase in LBFR in the UA and PP by 1.3 times ( $p < 0.001$ ), a prevalence of mixed (49.05%) and central type of PP (28.3%) and in women with asymptomatic - avascular (53.06%) type of PP. Severe vitamin D deficiency was detected in 37.7% of women with symptomatic fibroids ( $6.62 \pm 0.9$  ng/ml), and in asymptomatic women, its deficiency was found in 1/3 of patients ( $16.7 \pm 1.6$  ng/ml).

We came to the conclusion that with the peripheral type of angioarchitecture of PP, conservative tactics for managing patients are possible. Analysis of blood flow velocity curves made it possible to establish that in patients with UF, PI and RI indices in the uterine arteries and perifibroid plexus are reduced compared to healthy women.

From the data presented, we can conclude that UF is more often diagnosed in women of late reproductive and perimenopausal age, and AUB most often manifests itself. Women with UF have a high frequency of burdened premorbid background, severe vitamin D deficiency, clear clinical signs and complications, which often lead to a deterioration in the quality of life of women due to radical operations. According to the analysis of duplex blood flow studies, we can come to the conclusion that LBFR and RI in the studied vessels depend on the degree of the proliferative process of the myomatous node. Depending on the type of blood supply to the PP, a dynamic assessment of the growth of the myomatous node is possible, thereby providing a differentiated approach to management and treatment tactics.

The study of the effect of vitamin D deficiency on women's health has great potential for the basis of modern personalized medicine, since it makes it possible to predict the development of the disease, the nature of the course and the risk of possible complications. Epigenetic risk factors for the development of UF, identified at this stage of our scientific work, require a connection with the genetic determinants of this disease.

**CONCLUSION.** Thus, analysis of the clinical picture showed that patients with severe vitamin D deficiency in the group of symptomatic UF ( $< 10$  ng/ml) had clear clinical manifestations of the disease: menorrhagia leading to anemia in women of this category, rapid growth of the myomatous node against the background of critical deficiency vitamin D and accompanying pelvic pain, infertility. It was also found that in women with symptomatic UF, vitamin D levels were significantly lower compared to the asymptomatic UF group. Our data coincide with the results of foreign studies [17, 29, 37].

In women with an established diagnosis of uterine fibroids, it is necessary to conduct a duplex scan of the vessels of the IIA. Depending on the type of blood supply, it is possible to assess the growth of fibroids, which will provide a differentiated approach to diagnosis and treatment. When identifying central and mixed types of perifibroid plexus, the need for active management of patients with conservative and ineffective surgical therapy is obvious.



Women with UF need to determine the initial level of vitamin D deficiency and/or deficiency and the relationship between the degree of prohormone deficiency and the clinical manifestations of the disease. Determination of this marker in the blood of women with UF can be used in practical medicine as a predictor for preclinical prediction of disease symptoms and further management of women on this continent, which requires the need to include women with UF in the standard examination. Screening, supplementation, treatment recommendations, and public health strategies for vitamin D deficiency in women with UF, as well as in women at high risk of developing fibroids, may have a potential impact on reducing fibroid growth and UF symptoms.

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