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## VITAMIN D EFFECT ON THE SEVERITY OF CHRONIC PELVIC PAIN IN PATIENTS WITH OVARIAN ENDOMETRIOSIS COMBINED WITH PELVIC INFLAMMATORY DISEASES

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**Abstract.** Numerous publications in recent years indicate the impact of vitamin D deficiency on the course and severity of a number of gynecological diseases, including endometrial disease. As this transmitter is associated with immune disorders, its involvement in local immunosuppression in the progression of the systemic inflammatory response in the case of endometrial disease is not excluded. Considering the pathogenetic links between vitamin D metabolism and the severity of pelvic pain, it became appropriate to study the relationship between this parameter and the intensity of pelvic pain in patients with ovarian endometriomas associated with chronic pelvic inflammatory diseases, which was **the objective of this research. Materials and methods of research.** The study included 90 patients with ovarian endometriosis aged 20 to 41 years. The main group consisted of 44 patients with endometrioma combined with pelvic inflammatory diseases; the comparison group consisted of 46 patients with isolated ovarian endometrioma. The control group included 30 relatively healthy women without gynecological and somatic pathology. At the initial stage, the level of 25-hydroxyvitamin-D3 (25 (OH) D) was determined in patients of the three groups by mass spectrometry using standard methods. **Analysis and discussion of research results.** Patients with ovarian endometrial cysts on the background of pelvic inflammatory disease were statistically significantly older compared with the group of isolated endometriomas; more than half of the observations were patients aged 36-40 years ( $p < 0.05$ ). Laparoscopic diagnostic and therapeutic techniques allowed to present objective signs of combination of ovarian endometrioma with manifestations of external genital endometriosis: severe manifestations of external genital endometriosis were diagnosed in 31.8% vs. 15.21% in the comparison group. Depending on the severity of the pain syndrome according to VAS, patients of the main group were stratified as follows: 22.7% noted pelvic pain of low intensity, 40.9% – moderate pain, 25.0% – severe pain; in the comparison group there were no manifestations of severe pelvic pain. The combination of pelvic inflammatory disease with ovarian endometriosis was accompanied by an increase in the share of vitamin D deficiency – in 38.64% and the share of severe pain – in 25.0%.

**Conclusion.** A significantly moderate inverse correlation was found between the verification of the manifestations of external genital endometriosis and the level of vitamin D in the blood serum. The obtained data dictated the need to assess the therapeutic potential of vitamin D in combination with nonsteroidal anti-inflammatory drugs to enhance the analgesic effect and reduce the drug load.

**Key words:** *ovarian endometriosis; pelvic inflammatory disease; pelvic pain syndrome; vitamin D concentration.*

**Резюме.** Багаточисленні публікації останніх років свідчать про вплив дефіциту вітаміну D на перебіг та тяжкість проявів ряду гінекологічних захворювань, зокрема, і ендометріїдної хвороби. Так як даний трансмітер пов'язаний із імунними порушеннями, не виключена його участь у місцевій імуносупресії при прогресуванні системної запальної відповіді у випадку ендометріїдної хвороби. Враховуючи існуючі патогенетичні ланки між метаболізмом вітаміну D та ступенем вираженості тазового болю, доцільним стало дослідження взаємозв'язку даного параметру та інтенсивності тазового болю у пацієток з ендометріомами яєчника, асоційованими із хронічними запальними процесами органів малого тазу, що і стало **метою** даного наукового пошуку. **Матеріали та методи дослідження.** У дослідження включили 90 пацієток з ендометріозом яєчників віком від 20 до 41 року. Основну групу склали 44 пацієтки з ендометріомами, поєднаними із запальними захворюваннями геніталій, групу порівняння - 46 пацієток з ізольованими ендометріомами яєчників. У контрольну групу включили 30 умовно здорових жінок без гінекологічної та соматичної патології. Пацієткам трьох груп на вихідному етапі визначали рівень 25-гідроксिवітаміну-D3 (25(OH)D) методом мас-спектрометрії за стандартними методиками. **Аналіз та обговорення результатів дослідження.** Пацієтки з ендометріїдними кістами яєчників на тлі запальних процесів органів малого тазу були статистично значимо старші у порівнянні з групою ізольованих ендометріом, більше половини спостережень серед цих пацієток становила вікова категорія 36-40 років ( $p < 0,05$ ). Лапароскопічні діагностично-лікувальні техніки дозволили представити об'єктивні ознаки поєднання ендометріоми яєчника з проявами зовнішнього генітального ендометріозу: тяжкі прояви зовнішнього генітального ендометріозу були діагностовані у 31,8 % проти 15,21 % - у групі порівняння. В залежності від вираженості болевого синдрому за ВАШ пацієтки основної групи були стратифіковані наступним чином: 22,7 % відмічали тазовий біль слабкої інтенсивності, 40,9 % - помірну біль, 25,0 % – виражену, у групі порівняння не відмічено проявів вираженого

тазового болю. Поєднання запальних процесів органів малого тазу та ендометріозу яєчника супроводжується зростанням частки дефіциту концентрації вітаміну D - у 38,64 % та вираженого болювого синдрому – у 25,0 %.

**Висновок.** Встановлено достовірно помірну зворотню кореляцію між верифікацією проявів зовнішнього генітального ендометріозу та рівнем вітаміну D у сироватці крові. Отримані дані диктують необхідність оцінки терапевтичних можливостей використання вітаміну D у комплексі із нестероїдними запальними середниками з метою посилення протиболівого ефекту та зниження медикаментозного навантаження.

**Ключові слова:** ендометріоз яєчника, запальні захворювання органів малого тазу, синдром тазового болю, концентрація вітаміну D.

**Problem statement and analysis of the latest research.** The development of endometrioid disease does not depend on race, socioeconomic status and age. It affects both adolescents and 60-70-year-old women. Every 10th woman of reproductive age complains of this disease manifestations. Prolonged chronic pelvic pain, infertility, loss of work ability, deterioration of all parameters of quality of life create difficulties for social adaptation and realization of the female potential in the family and society [1, 3, 10].

Numerous publications in recent years indicate the impact of vitamin D deficiency on the course and severity of a number of gynecological disorders, including endometrial disease [1, 3]. There is scientific evidence of vitamin D indirect effects on the results of in vitro fertilization, the pathogenesis of polycystic ovary syndrome, steroidogenesis and folliculogenesis, the course of gestation [5, 7]. Studies have shown a direct relationship between the level of this vitamin and metabolic disorders, insulin resistance and carbohydrate metabolism [5, 7]. As this transmitter is associated with immune disorders, its participation in local immunosuppression in the progression of the systemic inflammatory response in women with endometrial disease is not excluded [6, 9].

In this stream of literature, there are publications indicating a decrease in vitamin D levels in patients with genital endometriosis and chronic pelvic pain [3, 9]. Ciavattini et al. [2] in his study assessed the level of vitamin D in the serum of women with isolated unilateral ovarian endometrioma. He assessed the possible correlation between the size of the endometrioma and the level of this marker. The author found an 85.7% increase in the size of the endometrioma up to 40.2±22.6 mm in the case of vitamin D deficiency in the serum against 26.7±12.1 mm – in the case of its normal reference values [2]. This provided an opportunity to establish a significant linear correlation between the level of vitamin D and the diameter of the ovarian endometrioma [2].

According to domestic and foreign sources, the role of vitamin D, as a necessary component of a wide range of physiological processes and the optimal state of metabolic homeostasis has been established during large-scale scientific research [7, 9]. Vitamin D deficiency have been proved to be involved in maintaining immune homeostasis, playing an important role in the polymorphism of enzymes in the pathogenetic chain of chronic inflammation [6, 8, 9]. Chronic inflammatory processes are accompanied by excess production of the

activated immune system, primarily its mononuclear phagocytic link, and various inflammatory proteins [6]. In contrast to acute inflammatory response, when the secretion of such proteins increases tens to hundreds of times, it increases only 5-6 times in case of chronic inflammatory systemic response. The literature presents results of epidemiological studies, which reveal an inverse relationship between levels of 25(OH)D3 and inflammation markers– C-reactive protein and interleukin (IL)6 [8, 9]; several in vitro studies have shown that calcitriol inhibits inflammation in adipose tissue [3, 6]. The idea of vitamin D effect on the development and progression of endometriosis, modulating the proliferative mechanisms of endometrial cells in the abdominal cavity, was first expressed by Italian scientists [9]. The authors found that the average levels of 25-hydroxyvitamin-D3 in patients with endometriosis were higher than in women without this clinical pathology, increasing the risk of this disease if vitamin D levels exceeded 28.2 ng/ml [1, 3, 7, 9]. Other studies have shown controversial results regarding the increased risk of endometriosis if its levels are low [8, 9]. The problem is getting worse due to the fact that vitamin D deficiency in the modern world has become pandemic [1, 3, 10], and among the population of Ukraine vitamin D deficiency is found in 81.8% [1, 3, 7, 9]. Controversial and contradictory scientific positions in this area reasonably arouse interest in studies on the role of this transmitter in the pathogenesis of endometrial disease, as this clinical condition is associated with the function of the endocrine system, immune system and severe inflammatory response [4, 6]. Recent data have convincingly demonstrated the high content of 25-hydroxyvitamin-D3 in the endometrium, serum and peritoneal fluid in patients with genital endometriosis, which is explained by the local activity of immune cells and cytokines and insufficient stimulation of macrophages [4, 6].

Considering the existing pathogenetic links between vitamin D metabolism and the severity of pelvic pain, it became appropriate to study the relationship between this parameter and the intensity of pelvic pain in patients with ovarian endometrioma associated with chronic pelvic inflammatory disease, which was **the objective of the research.**

#### Materials and methods of research

The study included 90 patients with ovarian endometriosis aged 20 to 41 years. The main group consisted of 44 women with endometrioma combined

with pelvic inflammatory disease; the comparison group consisted of 46 patients with isolated ovarian endometrioma. The control group included 30 relatively healthy women without gynecological and somatic pathology. The diagnosis of ovarian endometrioma was verified using instrumental methods (ultrasound, MRI, etc.). A visual analog scale (VAS) was used to determine the intensity of pelvic pain. Inclusion criteria were the following: ovarian endometriosis, pelvic pain syndrome, reproductive age, pelvic inflammatory disease. Exclusion criteria were the following: proliferative changes in pelvic organs, adhesions, irritable bowel syndrome, psychogenic pain, severe somatic pathology or acute gynecological disorder, refusal to participate in the study. At the initial stage, the level of 25-hydroxyvitamin-D3 (25 (OH) D) was determined in patients of three groups by mass spectrometry using standard methods. Vitamin D deficiency was diagnosed when the concentration of 25-hydroxyvitamin-D3 was below 20 ng/ml (50 nmol/l), insufficiency in the range of 20-30 ng/ml (50-75 nmol/l), while the concentration of 30-60 ng/ml (75-150 nmol/l) corresponded to the reference limits. The type and strength of the correlation between VAS and serum vitamin D levels were determined using the Pearson correlation coefficient. Statistical significance of the data was measured using Pearson's chi-squared test. Systematization and correction of the source digital information and graphical visualization of the obtained data were performed in Office Excel 2010 spreadsheets. Statistical processing of the material was performed using the Microsoft Excel application program using the package "STATISTICA – 6.0".

### Analysis and discussion of research results

The mean age of women in the main group was  $34.9 \pm 2.3$  years, which was more significant than in the comparison group, namely  $27.8 \pm 1.8$  years ( $p < 0.05$ ) and in the control group, namely  $28.0 \pm 2.4$  years ( $p < 0.05$ ). More than half of patients with endometrioid ovarian cysts on the background of inflammatory processes of the pelvic organs were at the age of 36-40 years ( $p < 0.05$ ).

The main complaints included menstrual irregularities, pelvic pain syndrome, infertility, and psycho-emotional symptoms. Laparoscopic diagnostic and therapeutic techniques allowed to present objective signs of a combination of ovarian endometrioma with manifestations of external genital endometriosis: severe manifestations of external genital endometriosis were diagnosed in 14 women of the main group (31.8%), 7 women of the comparison group (15.21%) and 18 patients of the main group; 16 patients of the comparison group had external genital endometriosis of 1-2 degrees of severity (40.91% and 34.78%, respectively).

Depending on the severity of the pain syndrome according to VAS, patients of the main group were stratified as follows: 10 women (22.7%) had pelvic pain of low intensity (1-3 points), 18 (40.9%) patients had moderate pain (4- 6 points), and 11 women (25.0%) suffered from severe pain (7-10 points). In

the comparison group, there were no manifestations of severe pelvic pain; 10 patients (21.7%) did not feel pain at all, while the proportion of mild and moderate symptoms was comparable without statistical deviations (36.9% and 39.1%, respectively). It should be emphasized that the proportion of patients who did not feel pain was 1.9 times higher in the comparison group (21.73% vs. 11.36%,  $p < 0.05$ ).

The average level of vitamin D constituted  $23.28 \pm 2.12$  ng/ml in all patients with the ovarian endometrial disease,  $22.19 \pm 1.84$  ng/ml in the main group,  $24.37 \pm 2.12$  ng/ml in the comparison group, which corresponded to the reference limits of vitamin D deficiency. The content of vitamin D was  $29.12 \pm 2.64$  ng/ml in the control group, which met the criteria of insufficiency, and the proportion of women with normal concentrations of this marker was 43.33% (13 patients). According to Table 1, only 6 women (13.63%) of the main group had normal parameters of vitamin D vs. 13 women (28.26%) in the comparison group, which was 2.1 times more ( $p < 0.05$ ). Deficiency of this transmitter was revealed in one-third of patients of the main group, in 17 patients (38.63%), the most significant in the case of severe pelvic pain –  $19.06 \pm 4.01$  ng/ml.

According to the results obtained, the following should be noted. The combination of pelvic inflammatory disease and ovarian endometriosis, which exacerbates the systemic inflammatory response due to a complex pathogenetic chain of hormonal and alternative effects, was accompanied by an increase in the number of patients with vitamin D deficiency (more than one third of cases – 38.64%) and severe pain syndrome – in every fourth patient (25.0%). The number of women with normal levels of vitamin D decreased up to 13.63% of observations in the main group, up to 28.26% – in the comparison group vs. 43.33% – in the control group ( $p < 0.05$ ). A significant negative moderate-strength correlation between the value of the visual-analog scale and the level of vitamin D in the serum was established ( $r = -0.412$ ;  $p < 0.05$ ).

According to the literature, endometriosis is currently considered as a variant of autoimmune pathology. An inflammation on the ion of immune regulation is an important link in its pathogenesis [9]. Recent scientific studies have demonstrated a proven antiproliferative, anti-inflammatory, and immunomodulatory effect of vitamin D, its significant effect on the mechanisms of proinflammatory cytokine synthesis, strong modulating effect on the immune system, and aggressive development of systemic inflammatory response in case of its deficiency [1, 3, 6, 7, 9]. Considering the distorted inflammatory response and enhanced neoangiogenesis in case of endometrial disease, the study of vitamin D levels in patients with endometriomas associated with chronic pelvic inflammatory diseases, as well as the rationale for correcting its deficiency in this group of patients is a promising direction of optimization of therapeutic options.

### Conclusion

Patients with the endometrial ovarian disease



**Table 1.** Level of vitamin D in women of the study groups related to the severity of pelvic pain, n=90, abs. number, %

Severity of pelvic pain	Vitamin D level					
	Insufficiency		Deficiency		Normal	
	Abs. n.	%	Abs. n.	%	Abs. n.	%
Main group, n=44						
Absence, n=5	3	6.82*	-	-	2	4.54
Weak, n=10	6	13.64	-	-	4	9.09
Moderate, n=18	10	22.72*	8	15.91*	-	-
Severe, n=11	2	4.54*	9	22.73*	-	-
Comparison group, n=46						
Absence, n=10	7	15.22	-	-	3	6.52
Weak, n=17	9	19.57	-	-	8	17.39
Moderate, n=19	17	36.95	-	-	2	4.35

Note. \*the difference is significant compared to the data of the comparison group ( $p < 0.05$ ).

are characterized by a decrease in vitamin D levels to the values that meet the criteria of insufficiency. In case of endometrioma and pelvic inflammatory disease combination in one third of observations, a decrease in the level of this transmitter to the limit parameters of its deficiency (more than in one third of cases) was observed. A significantly moderate inverse correlation was revealed between the verification of the manifestations of external genital endometriosis and the level of vitamin D in the serum.

The obtained data dictated the need to assess the therapeutic potential of vitamin D in combination with nonsteroidal anti-inflammatory drugs to enhance the analgesic effect and reduce the drug load.

**Ethics policy.** All researches involving participants were conducted in accordance with the World Medical Association Declaration of Helsinki. All patients have signed an informed consent before involvement into the study.

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**Conflict of Interest.** The authors stated no conflict of interest.

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