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Assessment of 25(OH)D status in patients with genital endometriosis and clinical efficacy of cholecalciferol in the treatment of the disease

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AIM: The aim of this study was to determine the 25(OH)D status in patients with genital endometriosis compared to the control group and to analyze the clinical efficacy of cholecalciferol implication as a combined targeted therapy of the disease.

MATERIALS AND METHODS: The main group included 440 patients with genital endometriosis (mean age 33.7 ± 5.8 years) with various degrees of disease prevalence. The control group consisted of 30 women with the normal ovulatory menstrual cycle (mean age 26.3 ± 3.1 years) in whom gynecological pathology was not revealed. Peripheral blood (PB) 25(OH)D level was assessed in all the participants included into the study. In 49 women from the main group, the level of 25(OH)D in the peritoneal fluid (PF) was determined. Comparative evaluation of the clinical efficacy of cholecalciferol intake in combination with gonadotropin-releasing hormone agonist (aGnRH) 3.75 mg injections or with dienogest 2 mg oral administration, as well as monotherapy in comparison with standard hormone-modulating treatment was carried out. Prior to the start of treatment, the patients had pain syndrome of varying severity, which was evaluated using the McGill Pain Questionnaire with the Visual Analogue Scale for pain. The psycho-emotional status was assessed using the Hospital Anxiety and Depression Scale. The Excel, Statistica 10, and Jamovi software programs were used to process the obtained data.

RESULTS: The level of 25(OH)D in PB of patients with endometriosis was significantly lower compared to the control group ($p < 0.001$). Women with Grades III and IV genital endometriosis were characterized by lower PB 25(OH)D levels compared to the patients with Grades I and II of the disease, but the difference was not statistically significant. Relationships were revealed between 25(OH)D levels in the PB and PF ($p < 0.001$), as well as PF 25(OH)D level and the disease prevalence ($p = 0.004$). Significantly more pronounced pain reduction and stabilization of the psycho-emotional status were observed in patients receiving combined therapy with cholecalciferol.

CONCLUSIONS: Insufficient level of vitamin D and vitamin D deficiency can be considered as factors that play a role in the progression of genital endometriosis. The use of cholecalciferol in combination with aGnRH 3.75 mg or dienogest 2 mg may more effectively reduce the severity of pain and stabilize the psycho-emotional status in patients with genital endometriosis compared to standard hormone-modulating therapy.

Keywords: vitamin D; 25(OH)D; cholecalciferol; peritoneal fluid; genital endometriosis.

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Статус 25(OH)D у больных наружным генитальным эндометриозом и клиническая эффективность применения колекальциферола в терапии заболевания

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Цель — определить статус 25(OH)D больных наружным генитальным эндометриозом и проанализировать клиническую эффективность применения колекальциферола в качестве комбинированной таргетной терапии заболевания.

Материалы и методы. В основную группу вошли 440 пациенток (средний возраст — 33,7 ± 5,8 года) с различной степенью распространенности наружного генитального эндометриоза. Контрольную группу составили 30 женщин (средний возраст — 26,3 ± 3,1 года) без гинекологической патологии с овуляторным менструальным циклом. Всем пациенткам определяли уровень 25(OH)D в периферической крови. У 49 женщин из основной группы оценивали уровень 25(OH)D в перитонеальной жидкости. Анализировали клиническую эффективность применения колекальциферола в сочетании с агонистами гонадотропин-рилизинг-гормона в дозе 3,75 мг или диеногестом в дозе 2 мг, а также в качестве монотерапии по сравнению со стандартной гормономодулирующей терапией. До начала лечения у пациенток отмечался болевой синдром различной степени выраженности, который определяли с помощью визуальной аналоговой шкалы боли Мак-Гилла. Психоэмоциональный фон оценивали с применением шкалы тревоги и депрессии. Для обработки полученных результатов использовали программы Excel, Statistica 10, Jamovi.

Результаты. Уровень 25(OH)D в периферической крови больных наружным генитальным эндометриозом был достоверно ниже по сравнению с уровнем у пациентов контрольной группы ($p < 0,001$). У пациенток с наружным генитальным эндометриозом III–IV степеней был более низкий уровень 25(OH)D в периферической крови по сравнению с пациентками с I–II степенями заболевания, но различия не были статистически значимыми. Выявлены зависимости между уровнями 25(OH)D в периферической крови и перитонеальной жидкости ($p < 0,001$) и уровнем 25(OH)D в перитонеальной жидкости и степенью распространенности заболевания ($p = 0,004$). Более выраженное уменьшение болевого синдрома и стабилизация психоэмоционального фона отмечены у пациенток, получавших комбинированную терапию с колекальциферолом.

Заключение. Дефицит и недостаточность витамина D могут рассматриваться как факторы, играющие роль в прогрессировании наружного генитального эндометриоза. Применение колекальциферола в сочетании с агонистами гонадотропин-рилизинг-гормона в дозе 3,75 мг или диеногестом в дозе 2 мг позволяет более эффективно уменьшить выраженность болевого синдрома и стабилизировать психоэмоциональный фон у больных наружным генитальным эндометриозом по сравнению со стандартной гормономодулирующей терапией.

Ключевые слова: витамин D; 25(OH)D; колекальциферол; перитонеальная жидкость; наружный генитальный эндометриоз.

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BACKGROUND

External genital endometriosis (EGE) is a chronic, recurrent, progressive, hormone-dependent disease characterized by an extrauterine benign proliferation of endometrium-like tissue. Clinically, EGE presents with dyspareunia, dysmenorrhea, chronic pelvic pain, abnormal uterine hemorrhage, infertility, and miscarriage.

Controlled studies have revealed that chronic pain syndrome with EGE represents a serious problem for women of reproductive age and can negatively affect the psychoemotional state and quality of life of patients [1]. Moreover, genital endometriosis imposes the same socioeconomic expenses on society as other chronic diseases: type 2 diabetes mellitus, Crohn's disease, and rheumatoid arthritis [2].

There is no unified approach and universal method of treatment that guarantees a complete cure and absence of recurrence of the disease [3]. Surgical treatment of endometriosis significantly reduces the severity of pain and dyspareunia in patients [4]. EGE patients, as a rule, undergo repeated surgical interventions throughout life, primarily on the ovaries. This significantly reduces the ovarian reserve and negatively affects the reproductive function. The concept of the expediency of a single surgical intervention has currently been adopted as a rule, which, in terms of execution time, should be most closely approximated to the stage of pregnancy planning.

In this regard, great importance is attached to hormone-modulating therapy for EGE, which can slow down the disease progression, reduce the severity of pain and improve significantly the quality of life of patients. Most effective hormonal drugs for the treatment of EGE have an antigonadotropic effect, which excludes pregnancy planning at the stage of its use, and hormone-modulating therapy is characterized by a significant number of side effects. The search for an alternative targeted therapy for EGE with such effects remain an urgent task.

Currently, new directions in the treatment of genital endometriosis are being actively studied. One of these promising drugs may be vitamin D. The term "vitamin D" refers to a group of chemical compounds that are similar in structure and function in the body. Vitamin D_3 (colecalciferol) is of key importance in this group, and is considered the "true" vitamin D, while other forms are referred to as modified derivatives. Colecalciferol is produced in the skin by exposure to shortwave ultraviolet radiation. Ergocalciferol (Vitamin D_2) enters the body through plant sources. After two successive hydroxylation reactions in the liver and kidneys, both metabolites are able to transform into $1,25(OH)_2D$ (calcitriol, 1,25-dihydroxyvitamin D_3, 1,25-dihydroxyvitamin D), the active hormonal form whose mechanism of action is similar to that of steroid hormones and is currently the subject of numerous disputes and research.

The use of colecalciferol and its selective agonist elocalcitol in animal models of experimental endometriosis confirms their effect on endometrioid foci as they reduce the area of endometrioid lesions, and in some cases, lead to complete resorption [5–7]. These studies also demonstrated the ability of colecalciferol and elocalcitol to provide nonclassical effects: anti-inflammatory ones by reducing the level of macrophages and pro-inflammatory cytokine, interleukin-1 (IL-1) in the peritoneal fluid [5]; antiproliferative effects through fibrosis and apoptosis in the stromal component of implants [6]; and antiangiogenic effects due to decrease in the levels of vasculoendothelial growth factor (VEGF), matrix metalloproteinase-9 (MMP-9), and the ability to increase the content of tissue inhibitor of metalloproteinase-2 (TIMP-2) [7].

According to our own research conducted in the D.O. Ott Scientific Research Institute of Obstetrics, Gynecology, and Reproduction, the use of oral cholecalciferol as a monotherapy for endometriosis in an experimental model on Wistar rats was comparable in efficiency to the use of dienogest, which is currently considered as a "specific" therapy for the disease. It should be noted that the use of colecalciferol had a dose-dependent effect, and a higher dose was associated with greater efficacy of treatment [8].

Previously, we studied the expression of vitamin D receptors (VDR) in patients with EGE and found a significant decrease in VDR expression in endometrioid heterotopies compared to the endometria of the control group in the secretory phase and of EGE patients in both the proliferative and secretory phases of the menstrual cycle. The results obtained demonstrated the absence of cyclic changes in VDR expression in the endometrium of EGE patients compared to the endometrium of patients in the control group, thereby indicating changes in endometrial receptivity characteristic of patients with EGE and influencing the pathogenesis of the disease. Therefore, the absence of cyclic changes in VDR expression can be considered as one of the causes of endometriosis-associated infertility [9].

We therefore aimed at determining the 25(OH)D status in patients with EGE and to analyze the clinical efficacy of using cholecalciferol within a combined treatment regimen and as monotherapy.

MATERIALS AND METHODS

The main group included 440 female patients with a diagnosis of I–IV prevalence EGE, whose mean age was 33.7 ± 5.8 years. The diagnosis of EGE was established during the surgical laparoscopy and verified during the morphological examination. Prevalence was assessed according to the revised classification of the American Society for Reproductive Medicine (r-ASRM). The control group for comparing the level of 25(OH)D in the peripheral

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blood consisted of 30 females without gynecological pathology with an ovulatory menstrual cycle, confirmed by determining the level of progesterone in the secretory phase of the menstrual cycle and the presence of a corpus luteum on pelvic ultrasound. In 49 women from the main group, the level of 25(OH)D in the peritoneal fluid was determined. The peritoneal fluid was collected during the surgical laparoscopy. The level of 25(OH)D in peripheral blood and peritoneal fluid was assessed using an enzyme-linked immunosorbent assay (25-OH Vitamin D (total) ELISA, DRG Instruments GmbH, Germany).

Inclusion criteria:

- Signed voluntary informed consent to participate in the study
- Endometriosis-associated pain syndrome
- Reproductive age
- EGE grades I–IV of prevalence, confirmed intraoperatively and histologically

Exclusion criteria:

- The intake of hormonal drugs and cholecalciferol six months or less before inclusion in the study
- Combination of EGE with polycystic ovary syndrome or uterine myoma
- Severe somatic pathology
- Diabetes mellitus

The scheme of using colecalciferol (patent for invention No. 2711658) [10].

After intraoperative and histological verification of the diagnosis of EGE, colecalciferol was prescribed as treatment for endometriosis, in addition to standard regimens or as monotherapy, daily per os at a dose of 4000–10,000 IU for 6 months and more.

Initially, based on the blood level of 25(OH)D, the status of vitamin D in the body was assessed as follows:

- Less than 10 ng/mL (25 nmol/L) indicated severe deficiency
- Less than 20 ng/mL (50 nmol/L) indicated deficiency
- 21–30 ng/mL (51–75 nmol/L) indicated insufficiency
- More than 30 ng/mL (75 nmol/L) indicated an adequate level

The daily dose was selected individually, considering the baseline level of 25(OH)D in the peripheral blood and the mean values of changes in its blood concentration based on daily consumption according to the GrassrootsHealth algorithm (Table 1).

When prescribing the drug, preference was given to the highest effective doses. The recommended level of 25(OH)D to achieve the expected effect was 40–60 ng/mL (100–150 nmol/L). Patients received a daily dose once or in divided doses. Three months after the start of treatment, the biochemical parameters (activity of alanine aminotransferase, aspartate aminotransferase, bilirubin level) and the level of 25(OH)D were monitored; and adjustments were made on the daily doses of the drug where necessary.

After the stage of surgical treatment, 217 patients of the main group received colecalciferol in addition to the standard hormone-modulating therapy regimens: 104 patients received it in combination with a gonadotropin-releasing hormone agonist (aGnRH) at a dose of 3.75 mg intramuscularly for 6 months: 113 females received it in combination with dienogest at a dose of 2 mg for 6 months. Colecalciferol was taken as monotherapy by 23 patients who had contraindications to standard hormone-modulating therapy or who refused it. Moreover, 200 women, who made up the comparison subgroup, received standard hormone-modulating therapy, and among them, 103 received aGnRH at a dose of 3.75 mg intramuscularly once every 28 days for 6 months, and 97 patients received dienogest at a dose of 2 mg for 6 months.

Before the start of therapy, patients in all groups had pain syndrome of varying severity. In order to objectively assess the severity of pain, the McGill visual analog pain scale was used. To assess the psycho-emotional condition, we used the Zigmons and Snaith scale of anxiety and depression.

Statistical analysis

Data were processed in Excel, Statistica10, and Jamovi programs. Normally-distributed variables were described through mean and standard deviation; and median, 25th and 75th quartiles in the case were variables were not normally-distributed. To test the hypotheses, nonparametric tests

Table 1. Mean values of changes in blood concentration of 25(OH)D based on daily consumption according to the GrassrootsHealth algorithm (Public Health Promotion Organization)

Expected level, ng/mL / Initial level, ng/mL	20	30	40	50	60
	Recommended daily dose of cholecalciferol, IU				
10	2000	4000	**6000**	**10 000**	**10 000**
15	1000	3000	**6000**	**9000**	**10 000**
20		2000	**5000**	**8000**	**10 000**
25		1000	**4000**	**7000**	**10 000**
30			**3000**	**6000**	**10 000**
35			**1000**	**5000**	**9000**
40				**3000**	**9000**

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Table 2. Level of 25(OH)D in peripheral blood in patients with external genital endometriosis and in controls

	EGE grades I–IV $n = 440$	EGE grades I–II $n = 157$	EGE grades III–IV $n = 283$	Control group $n = 30$
Level of 25(OH)D in peripheral blood, ng/mL	**22.1 (17.1; 28.0)**	**23.6 (20.4; 28.4)**	**20.6 (16.2; 27.6)**	36.0 (19.6; 52.8)
	$p_{1-4} < 0.001$	$p_{2-4} < 0.001$	$p_{3-4} < 0.001$	

Note. EGE — external genital endometriosis.

Table 3. Level of 25(OH)D in peripheral blood and peritoneal fluid in patients with external genital endometriosis

25(OH)D level	Main group $n = 49$	EGE grades I–II $n = 24$	EGE grades III–IV $n = 25$
In peripheral blood	27.5 (20.4; 34.9)	27.9 (22.3; 34.9)	23.1 (13.4; 35.2)
In the peritoneal fluid	6.9 (3.7; 9.1)	10.2 (4.9; 11.7)	3.3 (0; 5.2)
	$p_{1-2} < 0.001$	**$p_{1-2} < 0.001$**	**$p_{1-2} = 0.001$**

Note. EGE — external genital endometriosis.

were used, namely Wilcoxon test for dependent samples, Mann–Whitney and Kruskal-Wallis tests to assess the differences between independent samples.

RESULTS

All patients underwent surgery using a laparoscopic approach. Grade I EGE was established in 10.2% ($n = 45$) females, grade II was detected in 25.5% ($n = 112$), grade III was revealed in 17.7% ($n = 78$), and grade IV was diagnosed in 46.6% ($n = 205$).

The median value of the 25(OH)D level in the peripheral blood in patients with EGE was 22.1 (17.1; 28.0) ng/mL and was significantly lower (Mann–Whitney; $p < 0.001$) than that in the control group; 36.0 (19.6; 52.8) ng/mL (Table 2). In patients with advanced endometriosis (grade III–IV EGE), the level of 25(OH)D was lower compared to that in patients with milder forms of the disease (grade I–II EGE), though this difference was not significant (Kruskal-Wallis; $p = 0.267$). In females with milder forms of genital endometriosis, the median value of the 25(OH)D level in the peripheral blood was 23.6 (20.4; 28.4) ng/mL, and in patients with generalized forms, it was 20.6 (16.2; 27.6) ng/mL. In each of the groups of patients with EGE, the level of 25(OH)D in the peripheral blood was significantly lower than that in controls (Kruskal-Wallis; $p < 0.001$).

In the group of patients whose level of 25(OH)D in the peritoneal fluid was determined ($n = 49$), the median value of 25(OH)D in the peripheral blood was 27.5 (20.4; 34.9) ng/mL (Table 3), while it was 27.9 (22.3; 34.9) ng/mL in patients with grade I–II EGE, and 23.1 (13.4; 35.2) ng/mL in patients with grade III–IV. The average level of 25(OH)D in the peritoneal fluid was 6.9 (3.6; 9.1) ng/mL, while the level of 25(OH)D was 10.2 (4.9; 11.7) ng/mL in patients with milder forms of EGE, and 3.32 (0; 5.2) ng/mL in patients with generalized forms. In 24.5% of patients with EGE, the level of 25(OH)D in the peritoneal fluid was below the analytical sensitivity threshold of the method, therefore we considered it to be 0 ng/mL.

A relationship was established between the level of 25(OH)D in peripheral blood and peritoneal fluid (Wilcoxon test, $p < 0.001$) (Fig. 1); in the case of division into mild

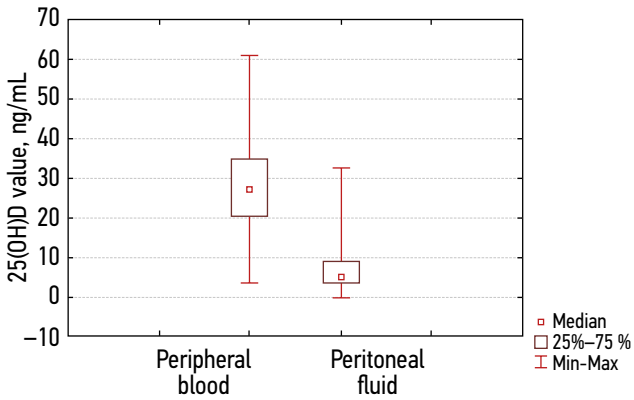

Fig. 1. Level of 25(OH)D in peripheral blood and in peritoneal fluid in patients with external genital endometriosis of grades I–IV

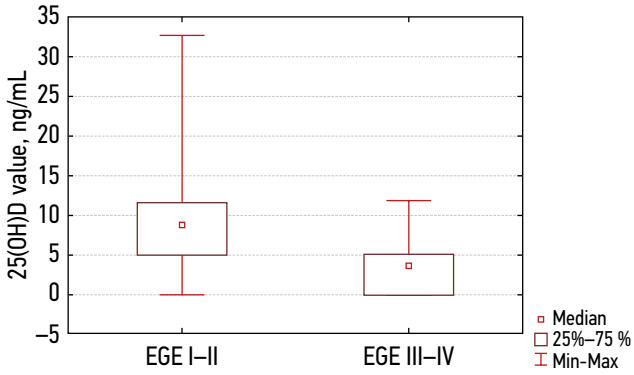

Fig. 2. The relationship between the level of 25(OH)D in the peritoneal fluid and the prevalence of the disease when divided into milder forms of external genital endometriosis (grades I–II) and generalized endometriosis (grades III–IV)

endometriosis and generalized endometriosis, the dependence persisted (Wilcoxon test, $p < 0.001$, $p = 0.001$).

The level of 25(OH)D in peripheral blood did not depend on the prevalence of EGE (Mann–Whitney test, $p = 0.19$); however, between the level of 25(OH)D in the peritoneal fluid and the degree of prevalence of the disease, a significant relationship was found (Mann–Whitney test, $p = 0.004$) (Fig. 2).

Literature data on the role of vitamin D in the pathogenesis of EGE and our results enabled the use colecalciferol as a new pathogenetically justified therapy of the disease. After surgical treatment, colecalciferol was prescribed to patients with EGE according to the previously presented scheme, both in addition to hormone-modulating therapy and as a monotherapy for at least six months. The clinical efficacy of the combined use of cholecalciferol was compared with standard hormonal therapy with aGnRH or dienogest at a dose of 2 mg.

Based on the assessment of pain syndrome on a visual analog scale, a more pronounced decrease in pain syndrome was noted in patients receiving combination therapy with cholecalciferol. Pain was absent in 77.7% of patients who received only aGnRH, and in the case of combined use of aGnRH with cholecalciferol, it was absent in 92.3% of cases. In the monotherapy group with dienogest at a dose of 2 mg, pain was absent in 74.2% of cases compared with the group receiving combined therapy with dienogest and colecalciferol (90.3%).

As a result of assessing the psycho-emotional condition, symptoms of anxiety and depression were registered in 59.6% of patients. We implemented aGnRH and colecalciferol as EGE therapy in 52 patients, while 2 g-dose of dienogest with colecalciferol was administered to 77 female patients, and colecalciferol monotherapy in six patients. The comparison subgroup consisted of 61 and 66 female patients who received aGnRH at a dose of 3.75 mg once every 28 days and dienogest at a dose of 2 mg, respectively.

Based on the scale of anxiety and depression, stabilization and improvement of the psycho-emotional condition were registered in most patients who took vitamin D: 67.3% of patients when colecalciferol was combined with aGnRH; and in 80.5% of patients when colecalciferol was prescribed with dienogest at a dose of 2 mg. However, in patients who used only aGnRH, stabilization and improvement of the psycho-emotional condition were achieved in only 42.7% of cases, and in patients who took only dienogest at a dose of 2 mg, it was registered in 72.2% of cases.

All females tolerated the study drug well. One patient with EGE had an allergic reaction to cholecalciferol, and the drug was discontinued.

DISCUSSION

A number of studies revealed the absence of relationship between the level of 25(OH)D in peripheral blood and endometriosis [11–14], while the results of other studies demonstrated significantly lower levels of 25(OH)D in groups of EGE patients [15–18]. In our study, we revealed that the median value of the level of 25(OH)D in peripheral blood in patients with EGE meets the criteria for insufficiency, and patients with generalized forms of the disease were characterized by the lowest level of 25(OH)D compared with patients with milder forms.

Certain changes that occur in the composition of the peritoneal fluid of patients with EGE are well known. Available literature provides little or no focus on the study of the level of 25(OH)D in the peritoneal fluid in patients with EGE. In our study, relationships were established between the levels of 25(OH)D in peripheral blood and peritoneal fluid, as well as between the level of 25(OH)D in the peritoneal fluid and the prevalence of the disease. Generalized forms of the disease were characterized by a lower level of 25(OH)D in the peritoneal fluid compared with mild forms of the disease. The results obtained indirectly reveals that an increase in the concentration of 25(OH)D in the peripheral blood leads to an increase in the level of 25(OH)D in the peritoneal fluid as a result of which calcitriol will have a local effect on endometrioid lesions. Hence, we can conclude that it is advisable to use the highest permissible doses in patients with advanced endometriosis compared with patients with milder forms of the disease.

Information on the use of colecalciferol for pain syndrome is controversial. Almassinokiani et al. conducted a double-blind clinical study and found no significant differences in reduction of the severity of chronic pelvic pain and dysmenorrhea after treatment with cholecalciferol or placebo [19]. Lasco et al., on the contrary, revealed that colecalciferol with a single dose of 300,000 IU led to a significant pain reduction 5 days before the expected menstruation, compared with placebo in patients with endometriosis-associated primary dysmenorrhea [20]. The decrease in the intensity of pain syndrome is probably associated with the ability of calcitriol, by suppressing cyclooxygenase-2, to influence the synthesis of prostaglandins in the endometrium and inactivate them due to increased regulation of 15-hydroxyprostaglandin dehydrogenase [21]. Our results reveal that patients who received aGnRH at a dose of 3.75 mg or dienogest at a dose of 2 mg and colecalciferol noted a more pronounced decrease in pain syndrome and stabilization of the psycho-emotional condition compared with standard hormone-modulating therapy.

CONCLUSION

Thus, our study revealed that the level of 25(OH)D in patients with EGE meets the criteria for insufficiency, and were significantly lower than those in the control group. When analyzing indicators such as the absence of the disease recurrence and an improvement in the quality of

life, the combined treatment with aGnRH or dienogest at a dose of 2 mg in combination with cholecalciferol were most effective. In patients with contraindications to standard hormone-modulating therapy and in those receiving colecalciferol monotherapy, no cases of the disease relapse were registered, and an improvement in overall well-being and quality of life was noted.

The use of colecalciferol in patients with EGE is an effective method of treating genital endometriosis, both as monotherapy and as supplementation to standard treatment regimens. Given the good tolerance, efficacy, relatively low cost, the possibility of long-term use of cholecalciferol and its prescription as an anti-relapse therapy, including at the stage of pregnancy planning in patients with EGE, the drug is a promising one that can be employed as substantiated targeted therapy for EGE.

ADDITIONAL INFORMATION

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Author contributions. *M.I. Yarmolinskaya, A.S. Denisova* created the concept and design, and wrote the text. *A.S. Denisova* and *N.N. Tkachenko* collected and processed the material. *A.S. Denisova* analyzed data. *M.I. Yarmolinskaya* edited the text.

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