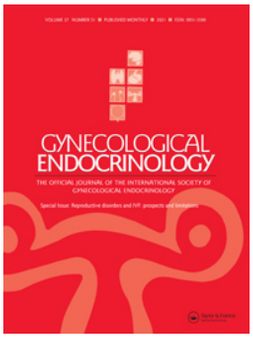

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ORIGINAL ARTICLE

Features of the 1st trimester of pregnancy course with severe deficiency of 25(OH)D

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ABSTRACT

Introduction: The course of physiological pregnancy is provided by many complementary factors. Thus, a deficiency in one of the links of the metabolic network contributes to the development of an imbalance in the work of the whole organism, which ensures the growth and development of the embryo from the first days of gestation. It has been demonstrated that vitamin D can act as an immune regulator during implantation, providing a protective effect in the entire period of pregnancy.

Objective: The aim of this study is to assess the features of the course of pregnancy in patients with different levels of vitamin D in the blood in the first trimester.

Materials and methods: A prospective multicenter randomized study was conducted in the North-West region of the Russian Federation among 88 pregnant women in the first trimester of gestation (up to 13 weeks). All patients were divided into 3 groups depending on the initial level of vitamin D (group 1–14 women with a 25(OH)$D < 10$ ng/ml, group 2–62 pregnant women from 10 to 30 ng/ml, group 3–12 pregnant women with a vitamin D content >30 ng/ml).

Interventions: Criteria of inclusion: pregnant women from 20 to 44 years of the first trimester of gestation (up to 13 weeks) with the studied level of vitamin D in the blood serum; singleton pregnancy; BMI ≤30 kg/m2; signing by the patient of informed consent for inclusion in the study group.

Main outcome measures and results: In group 1, 86% of patients with severe vitamin D deficiency were diagnosed with threatened miscarriage, which is significantly higher than in group 3 (85.7% and 33.3%, $\chi^2 = 7.490$, $p = .007$). At the same time, retrochorial hematoma in group 1 occurred 3.5 times more often than in group 3 (57.1% and 16.67%, respectively, $\chi^2 = 4.473$, $p = .035$). Subsequently, every 4th woman from the group with vitamin D deficiency gave birth earlier than expected, which was not observed among patients from group 3 (25%, 0%, $\chi^2 = 1.231$, $p = .268$).

Conclusion: Prescribing cholecalciferol vitamin replacement therapy as part of complex preserving therapy for threatening miscarriage, followed by monitoring its blood level and deviating from normal parameters, contributing to a favorable course of pregnancy and improving perinatal outcomes.

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Vitamin D; vitamin D receptor; pregnancy; threatening miscarriage; trophoblast

Introduction

The physiological course of the first trimester of pregnancy depends on many factors of the external and internal environment. Only with a combination of the main patterns – the genetic consistency of the embryo with its immunological tolerance, the optimal balance of hormones with receptors sensitive to them, the normal architectonics of the uterus – is pregnancy possible and its successful prolongation. Insufficiency of one of these factors can lead to a malfunction of the mother-placenta-fetus system, which determines the course of pregnancy and can contribute to the development of various obstetric complications, such as: premature termination of pregnancy at any gestational age, preeclampsia, placental insufficiency, Fetal Growth Retardation (FGR), antenatal fetal death.

Throughout the first trimester of gestation, the foundations of 'cooperation' between the two organisms are laid. Thus, the interaction between the cells of the fetus and the mother creates a unique 'trophic' environment, with a special role assigned to its vitamin and micronutrient composition. It determines the adequate work of all metabolic processes in two organisms at once: the growth and proper development of the embryo in the uterus and the protection of the health of the pregnant woman and the fetus from the damaging effects of exogenous and endogenous factors.

A generally accepted indicator of the internal micronutrient composition of the environment is vitamin D, which through its complex multifactorial action has a beneficial effect on metabolic and immune processes in the mother's body [1,2]. In the early stages of pregnancy, the trophoblast simultaneously produces and responds to the effects of vitamin D, which has a local anti-inflammatory response and, in parallel, induces the growth of decidual tissue for a successful pregnancy [3,4]. There is evidence that $1,25(OH)_2D$ regulates the release and secretion of human chorionic gonadotropin in syncytio-trophoblast and increases placental production of sex steroids. There is evidence that calcitriol promotes the transport of calcium to the placenta, stimulates the release of placental lactogen, and also regulates the expression of HOXA10 (a gene that determines the development

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of genital organs) in stromal cells of the human endometrium [4]. Expression of HOXA10 is of some importance for endometrial development and improves susceptibility to implantation. Taken together, the evidence suggests that $1,25(OH)_2D$ helps implant and maintain normal pregnancy, supports fetal growth through calcium delivery, controls the secretion of several important placental hormones, and limits the production of proinflammatory cytokines [5,6].

It has been demonstrated that the placenta forms a physical and functional barrier between maternal and fetal blood flow. Within the mother-placenta-fetus system, $1,25(OH)_2D$ can play an autocrine, paracrine and endocrine role in the regulation of immune defense, trophoblast invasion, metabolism of nutrients and gases, hematopoiesis, hormone production, growth, and development of the fetus [7–9]. The immunosuppressive effects of vitamin D during pregnancy and, in particular, during implantation have been postulated many years ago and may help prevent the maternal immune response against an embryo carrying paternal genes [10,11]. Therefore, during pregnancy, decidual synthesis of vitamin D can modulate uNK cells, DCs, macrophages and T cells, leading to immune tolerance. Thus, vitamin D inhibits Th1 cytokines, while simultaneously stimulating Th2 cytokines, so it can facilitate the implantation process [12,13].

The problem of threatened miscarriage is relevant, however, standard approaches to the diagnosis and treatment of this pathology have not led to a decrease in its frequency. The role of vitamin D in abortion is widely discussed, but there is not a single study demonstrating its effect on the development of this obstetric pathology.

At present, the insufficiency/deficiency of 25(OH)D has received a global worldwide spread, affecting a large part of the population, regardless of age, sex, place of residence, conditions, and diseases [14]. Thus, pregnant and lactating women are at the highest risk of developing severe vitamin D deficiency <10 ng/ml.

In Russia, a limited number of studies have been conducted on the prevalence of vitamin D deficiency in different population groups. Zazerskaya I.E. et al., 2016 showed that among residents of the North-West region of the Russian Federation aged 18–70 years in the period from September to May, vitamin D deficiency and insufficiency were found in 82.2% of the population [15]. Our study aims to assess the features of the pregnancy in patients with different levels of vitamin D in the blood in the first trimester.

Materials and methods

A prospective randomized study of 88 women in the first trimester of pregnancy (up to 13 weeks) was carried out on the basis of the Scandinavia clinic and the Research Institute of obstetrics, gynecology, and reproductology named after D.O.Ott, St. Petersburg, from 2018 to 2020. All patients were selected by the level of vitamin D in the blood serum.

Blood samples from pregnant women were taken from the cubital vein according to the standard method into a plastic vacuum tube (type of tube 'Becton Dickenson', USA, volume 9 ml) in the morning on an empty stomach and delivered to the laboratory. The serum was separated by centrifugation at 1000 rpm for 10 min and placed in plastic tubes for single-use $1.5cm^3$ micro samples and stored at a temperature of −25 °C until the study. To quantify the level of 25(OH)D, a chemiluminescence method was used using kits and calibrators from Roche Diagnostics (Germany) for an Architect 2000 analyzer (USA).

Table 1. Classification of 25(OH)D levels.

Classification	25(OH)D level in blood serum, ng/ml
Severe deficiency of vitamin D	<10 ng/ml (<25 nmol/l)
Deficiency of vitamin D	<20 ng/ml (<50 nmol/l)
Insufficiency of vitamin D	≥20 and <30 ng/ml (≥50 and <75 nmol/l)
Adequate levels of vitamin D	≥30 ng/ml (≥75 nmol/l)*
Levels with possible vitamin D toxicity	>150 ng/ml (>375 nmol/l)

Recommended laboratory reference interval 30–100 ng/ml (75–250 nmol/L). Recommended target values of 25(OH)D for correcting vitamin D deficiency are 30–60 ng/ml (75–150 nmol/L).

Criteria of inclusion: pregnant women from 20 to 44 years of the first trimester of gestation (up to 13 weeks) with the studied level of vitamin D in the blood serum; singleton pregnancy; BMI $\leq 30\,kg/m^2$; signing by the patient of informed consent for inclusion in the study group. The patients' medical history was checked for infertility, previous abortions, gynecological diseases, and operations. The study excluded patients with multiple pregnancies, severe extragenital diseases of the mother, which are a contraindication for prolongation of pregnancy (congenital or acquired defects of the valvular apparatus of the heart, hypertension II degree or more, chronic diseases in the stage of exacerbation).

All patients were divided into three groups depending on the level of vitamin D (25(OH)D):

- Group 1 ($n = 14$) – pregnant women with severe deficiency at a plasma concentration of 25(OH)D <10 ng/ml.
- Group 2 ($n = 62$) – pregnant women with vitamin D deficiency/insufficiency from 10 to 30 ng/ml.
- Group 3 ($n = 12$) – pregnant women with vitamin D levels >30 ng/ml (Table 1).

The data obtained were evaluated by the methods of variation statistics using the Microsoft Excel software package (2010). To calculate and compare the average values of digital data, as well as to assess the reliability of the results obtained, we used methods for assessing the difference between shares, analyzing average trends (Student's t-test). To identify the relationship between quantitative indicators, Spearman's nonparametric correlation coefficient was calculated. The critical level of reliability of the null hypothesis was taken equal to the probability of at least 95% ($p < .05$). Statistical analysis consisted of comparing two samples for one feature (with or without it).

For the analysis of repeated (dependent) quantitative indicators, the distribution of which differs from normal, the nonparametric Chi-square test of paired comparisons was used. Compilation of tables, graphs, and diagrams was carried out on a personal computer using the Microsoft Office 2010 software package and SPSS Statistics 26.

Results

Among the surveyed pregnant women in the North-West region in the first trimester, only 13.6% had a normal level of vitamin D (30–100 ng/ml). Its insufficiency was diagnosed in 86.4% of pregnant women. At the same time, a severe deficiency was found in 15.9% of patients.

At the same time, the diagnosis of infertility in patients with 25(OH)D deficiency was significantly 4 times more likely than in women with its normal level (66.7% and 16.7%, respectively, $\chi^2 = 4.473$, $p = .035$, Table 2. Also, in the group with severe vitamin D deficiency, the patients had a recurrent miscarriage

Table 2. Characteristics of patients in the study groups.

Параметры	1 group ($n = 14$) 25(OH)$D \leq 10$ ng/ml	2 group ($n = 62$) 25(OH)D 10–30 ng/ml	3 group ($n = 12$) 25(OH)$D \geq 30$ ng/ml	Significant	
Characteristics of groups:					
Age (years)(SD)	35.6 ± 6.1	33.3 ± 4.3	32.0 ± 5.2	t-st = 1.56	$p_{1-3} = .81$
BMI (kg/m2)(SD)	22.9 ± 2.8	22.5 ± 4.4	21.3 ± 2.3	t-st = 1.51	$p_{1-3} = .76$
Self-consistentpregnancy (%)	42.8% (6)	64.5% (40)	66.7% (8)	$\chi^2 = 1.474$	$p_{1-3} = .225$
Anamnesis					
Nulliparous (%)	35.7% (5)	35.4% (22)	50% (6)	$\chi^2 = 1.750$	$p_{1-2} = .186$
Infertility in anamnesis (%)	66.7% (8)	37.1% (23)	16.7% (2)	$\chi^2 = 4.473$	$p_{1-3} = .035$
Missed abortion in anamnesis (%)	14.3% (2)	22.5% (14)	16.7% (2)	$\chi^2 = 0.473$	$p_{1-2} = .492$
Abortions in anamnesis (%)	35.7% (5)	16.1% (10)	8.33% (1)	$\chi^2 = 2.729$	$p_{1-3} = .099$
Recurrent pregnancy loss (%)	14.3% (2)	4.8% (3)	8.33% (1)	$\chi^2 = 1.658$	$p_{1-2} = .198$
Number ofabrasionin anamnesis (%)	50% (7)	35.4% (22)	16.67% (2)	$\chi^2 = 3.172$	$p_{1-3} = .075$
Polyp of endometrium in anamnesis (%)	28.57% (4)	19.4% (12)	8.33% (1)	$\chi^2 = 1.704$	$p_{1-3} = .192$
Chronic endometritis in anamnesis (%)	14.28% (2)	4.8% (3)	25% (3)	$\chi^2 = 5.485$	$p_{2-3} = .020$
Endometriosis in anamnesis (%)	21.42% (3)	11.3% (7)	25% (3)	$\chi^2 = 1.617$	$p_{1-2} = .204$
Autoimmune thyroiditis in anamnesis (%)	35.7% (5)	19.4% (12)	8.3% (1)	$\chi^2 = 5.306$	$p_{1-3} = .022$
Hypothyroidism (%)	14.28% (2)	8.1% (5)	0%	$\chi^2 = 1.857$	$p_{1-3} = .173$
I trimester of pregnancy progress					
Threat of miscarriage (%)	85.7% (12)	69.3% (43)	33.3% (4)	$\chi^2 = 7.490$	$p_{1-3} = .007$
Vomitus gravidarum (%)	21.42% (3)	11.3% (7)	16.67% (2)	$\chi^2 = 1.856$	$p_{1-3} = 0.8$
Mildpregnancyanemia (%)	7.14% (1)	8.1% (5)	25% (3)	$\chi^2 = 1.181$	$p_{1-3} = .8$
APS (%)	0%	0%	8.33% (1)	$\chi^2 = 1.058$	$p_{1-3} = .7$
Asymptomaticbacteriuria (%)	14.28% (2)	17.7% (11)	0%	$\chi^2 = 2.501$	$p_{1-3} = .114$
ARVI symptoms (%)	21.42% (3)	11.3% (7)	8.33% (1)	$\chi^2 = 0.851$	$p_{1-3} = .357$
Biochemical parameters of blood					
Homocysteine level (SD)	5.2 ± 1.7	5.9 ± 1.6	5.8 ± 1.1	t-st = 1.56	$p_{1-3} = .225$
Baseline Vitamin D level (нг/мл)	7.6 ± 2.1	19.9 ± 5.3	43.6 ± 8.5	$\chi^2 = 1.772$	$p_{1-3} < .001$
Hemoglobin level in the blood (SD)	118.3 ± 10.2	123.9 ± 9.6	119.2 ± 10.1	t-st = 1.43	$p_{1-3} = .85$
Ferritin(SD)	40.2 ± 21.7	51.6 ± 35.6	26.6 ± 17.9	t-st = 2.58	$p_{2-3} = .012$
Plateletcount, $\times 10^9$ (SD)	261.9 ± 46.9	248.9 ± 47.4	271.3 ± 51.5	t-st = 1.50	$p_{2-3} = .8$
D-dimer(SD)	0.4 ± 0.2	0.4 ± 0.3	0.3 ± 0.1	t-st = 1.33	$p_{1-3} = .85$
Fibrinogen (SD)	3.6 ± 1.1	3.3 ± 0.7	3.9 ± 1.1	t-st = 1.68	$p_{2-3} = .87$
Quick prothrombinindex, % (SD)	103.4 ± 20.7	100.4 ± 12.8	117.2 ± 8.3	t-st = 1.87	$p_{2-3} = .75$
INR (SD)	1.1 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	t-st = 1.08	$p_{1-3} = .89$
APTT (s) (SD)	31.4 ± 4.8	27.8 ± 8.7	27.2 ± 2.3	t-st = 1.45	$p_{1-3} = .76$

Note: SD –standard deviation.

(recurrent pregnancy loss, RPL) 3 times more often in the anamnesis compared with group 2 (14.3% and 4.8%, respectively).

Thyroid dysfunction (subclinical hypothyroidism/hypothyroidism and/or autoimmune thyroiditis) occurred in every second woman in the group with vitamin D deficiency, which significantly differed from group 3 (50% and 0%, $\chi^2 = 8.211$, $p_{1-3} = .005$). All indicators of blood and hemostasis in the first trimester did not differ among all groups (Table 2).

In the first trimester of pregnancy among the complications in the group with vitamin D deficiency in the first place in 86% there was revealed the threat of miscarriage, which had statistically significant differences from group 3 with normal levels of vitamin D (85.7% and 33.3%, $\chi^2 = 7.490$, $p = .007$). Other complications of the first trimester (vomiting of pregnant women, mild anemia of pregnant women, antiphospholipid syndrome, asymptomatic bacteriuria, and SARS) were observed in isolated cases.

When analyzing the course of threatened miscarriage among patients with different levels of vitamin D, specific features were revealed. In patients with threatened miscarriage and 25(OH)D deficiency, ultrasound examination showed myometrial tone in 67.4%, whereas, in group 3, only every 4 patients noted this symptom (67.4%, 25%, $\chi^2 = 2.855$, $p = .092$) (Table 3). Retrochorial hematoma occurred 3.5 times more often in group 1 compared with pregnant women from the group with normal vitamin D levels (57.1% and 16.67%, respectively, $\chi^2 = 4.473$, $p = .035$). Thus, the volume of retrochorial hematoma of more than 30% in group 1 was found in 28.6% of patients, while in the group with a normal level of vitamin D not a single case of chorionic detachment was diagnosed ($\chi^2 = 1.778$, $p = .183$).

The number of women with early termination of pregnancy (missed abortion and premature birth) from group 1 turned out to be statistically significant, which amounted to 33.5%, compared with group 3, where this complication was not detected in any pregnant woman (33.5% and 0%, $\chi^2 = 4.052$, $p = .045$). Preeclampsia, placental insufficiency, and fetal growth retardation developed in isolated cases.

There were no statistically different differences in the 3 groups: term of delivery, height-weight parameters, and the state of the newborn according to the Apgar scale. In the group with a pronounced deficiency of 25(OH)D in the blood, pregnant women were 2 times more likely to develop indications for emergency delivery by cesarean section compared with group 3 (16.7% and 35.7%, respectively) (Table 4).

Discussion and conclusion

As a result of our study, among 88 pregnant women in the North-West region of the Russian Federation in the 1st trimester of gestation, vitamin D deficiency was diagnosed in 86.4%, while a pronounced deficiency (<10 ng/ml) was found in 15.9% of women, which confirms the generally accepted world health organization (WHO, 2016) information on the globalization of this deficiency state in the world population [16]. So, vitamin D hypovitaminosis is considered a common condition/disease (ICD E55: Vitamin D deficiency) among pregnant women, reaching

Table 3. Characteristics of patients in the study groups with threatened miscarriage.

	1 group ($n = 12$) 25(OH)$D \leq 10$ ng/ml	2 group ($n = 43$) 25(OH)D 10–30 ng/ml	3 group ($n = 4$) 25(OH)$D \geq 30$ ng/ml	Significant	
Pregnant women with uterine hypertonus (%)	58.3% (7)	67.4% (29)	25% (1)	$\chi^2_{2-3} = 2.855$	$p_{2-3} = .092$
Pregnant women with uterine hypertonus (%)	65.5% (36)		25% (1)	$\chi^2_{1+2/3} = 2.610$	$p_{1+2/3} = .107$
Pregnant women with retrochorial hematoma (% of the total number)	**57.1% (8)**	41.9% (26)	**16.67% (2)**	$\boldsymbol{\chi^2 = 5.600}$	$\boldsymbol{p_{1-3} = .018}$
The hematoma's volume is more than 30% (%)	28.57%(4)	6.9% (3)	0%	$\chi^2_{1-3} = 1.778$	$p_{1-3} = .183$
AIT andhypothyroidism (%)	**58.3%% (7)**	30.2% (13)	**25% (1)**	$\boldsymbol{\chi^2 = 5.306}$	$\boldsymbol{p_{1-3} = .022}$
Carrier of high-risk hereditary thrombophilia genes (%)	16.67% (2)	13.95% (6)	0%	$\chi^2 = 0.762$	$p_{1-3} = .383$
Homocysteine level (SD)	4.6 ± 1.1	5.9 ± 1.6	5.8 ± 1.1	t-$st = 1.56$	$p_{1-3} = .225$
Baseline Vitamin D level (ng/ml)	$\mathbf{7.2 \pm 1.9}$	$\mathbf{19.2 \pm 5.5}$	$\mathbf{47.4 \pm 9.2}$	**t-$st_{1-3} = 3.5$**	$\boldsymbol{p_{1-3} = .008}$
				t-$st_{2-3} = 4.56$	$\boldsymbol{p_{2-3} = .001}$
				t-$st_{1-2} = 5.48$	$\boldsymbol{p_{1-2} < .001}$

Note: SD: standard deviation.

Table 4. Maternal and neonatal pregnancy outcomes.

	1 group ($n = 14$) 25(OH)$D \leq 10$ ng/ml		2 group ($n = 62$) 25(OH)D 10–30 ng/ml		3 group ($n = 12$) 25(OH)$D \geq 30$ ng/ml		Significant
Criteria	Threat of miscarriage ($n = 12$)	Normal ($n = 2$)	Threat of miscarriage ($n = 43$)	Normal ($n = 19$)	Threat of miscarriage ($n = 4$)	Normal ($n = 8$)	p-value
Preeclampsia (%)	0%	0%	9.3% (4)	15.8% (3)	0%	25% (2)	$p = .78$
Placental insufficiency (%)	8.3% (1)	0%	2.3% (1)	0%	0%	0%	$p = .86$
Fetal growth retardation (%)	0%	0%	2.3% (1)	0%	0%	0%	$p = .77$
Missed abortion (%)	8.3% (1)	0%	11.6% (5)	0%	0%	0%	$p = .216$
Preterm birth on 32–37 weeks of gestation (%)	25% (3)	0%	9.3% (4)	5.3% (1)	0%	0%	$p_{1-3} = .268$
Premature termination of pregnancy (%)	**33.5% (4)**		16.1% (10)		**0%**		$\boldsymbol{p_{1-3} = .045}$
Deliveryatterm (%)	58.3% (7)	100% (2)	62.8% (27)	94.7%(18)	100% (4)	75%(6)	$p_{1-3} = .120$
Naturalbirth (%)	41.7% (5)	50% (1)	45.2% (28)	68.4% (13)	75%(9)	75% (6)	$p_{1-3} = .099$
Emergency C-section (%)	33.3% (4)	50%(1)	19.4% (12)	21.1%(4)	16.67%(2)	25% (2)	$p = .276$
Apgar scale (SD)	7.6 ± 0.5	7.5 ± 0.5	7.6 ± 0.7	7.8 ± 0.8	6.6 ± 2.5	7.1 ± 0.6	$p = .76$
Birth weight (g) (SD)	3010.6 ± 576.7	3202.7 ± 640.5	3523.2 ± 515.5	3460 ± 465.7	3062.5 ± 806.9	3350.8 ± 565.5	$p = .79$
Newborngrowth (cm) (SD)	50.1 ± 3.4	51.2 ± 3.2	50.4 ± 6.9	51.2 ± 5.4	49.4 ± 5.6	52.1 ± 6.2	$p = .81$

Note: SD: standard deviation.

100% in some populations, and therefore, additional intake of vitamin D during the entire gestational period is justified as preventive protection of the pregnant woman and the fetus.

It is known that vitamin D performs pleiotropic functions that regulate the processes of implantation, growth, and development of the fetus, as discussed above [17]. The favorable background created in this way ensures the adequate work of many internal processes of the body, which contributes to the growth and proper development of the embryo in the uterus throughout the entire period of gestation, and the normal course of pregnancy in the first trimester is the key to well-being at all subsequent stages, including its outcomes, prognosis, and development. for a newborn [18].

It has been demonstrated that vitamin D deficiency causes unfavorable complications of pregnancy: secondary hypertension and preeclampsia [19], an increase in the frequency of cesarean section and spontaneous preterm birth [20,21], the development of bacterial vaginosis in early pregnancy [22], gestational diabetes mellitus [23]. In our study in the first trimester among pregnant women with vitamin D deficiency, early and late threatened miscarriage and premature birth were the most frequent among the complications. At the same time, the frequency and severity of symptoms directly correlate with the level of vitamin D. Thus, in the group with a pronounced deficiency of vitamin $D < 10$ ng/ml, the risk of miscarriage is 2 times higher than the population indicator, which is 15–20%, which demonstrates the importance of determining the level 25(OH)D in the blood of patients both at the pregravid stage and in the control of the first trimester of gestation. At the same time, the appointment of doses of cholecalciferol can be personalized, both preventive and therapeutic in nature, which is recommended by the WHO, the Russian Association of Endocrinologists, the European Society of Endocrinology (ESE), the American Association of Clinical Endocrinologists (American Association of Clinical Endocrinologists – AACE), while improving the course and outcomes of pregnancy. Vitamin D levels are one of the indicators of women's reproductive health.

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