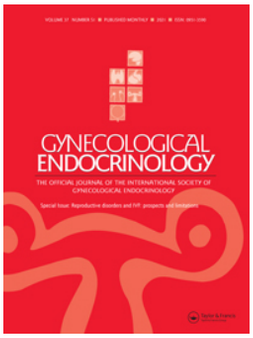

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Vitamin D insufficiency as a risk factor for reproductive losses in miscarriage

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ABSTRACT

Objective: To study the relationship between vitamin D deficiency, VDR gene polymorphism rs10735810 (A > G), and a missed abortion in the first trimester of gestation; to determine the predictors of its risk.

Research methods: 178 women aged between 18 and 41 were surveyed. The main group consisted of patients with miscarriage ($n = 101$), verified at the hospital stage (O02.0; O02.1), which were stratified by I group ($n = 58$, patients with the first miscarriage) and II groups ($n = 43$, patients with repeated miscarriage). The control group ($n = 77$) consisted of women with a successful pregnancy (Z34.0), which subsequently ended in delivery at term with a live fetus. Patients were surveyed and data was extracted from primary medical records. The level of 25(OH)D in the blood serum was investigated by mass spectrometry ($n = 99$). Genotyping for the vitamin D receptor gene polymorphism rs10735810 (VDR A > G) was performed for 177 patients. Statistical data analysis was performed *via* Statistica 10 and SAS JMP 11 application packages, using single-factor prediction for quantitative and binary factors, ROC analysis, and CHAID decision tree construction.

Results of the study: WE found that patients with miscarriage in the first trimester of gestation ($n = 60$) more frequently than those in the control group ($n = 39$) had vitamin D insufficiency (93.3% versus 76.9%, $p = .0183$) including its deficiency, occurring at 25(OH)D of blood <20 ng/ml (71.7% versus 51.3%, $p = .0392$). This pattern was found in patients with the first miscarriage, where significant differences in the frequency of vitamin D deficiency were also detected in comparison with the control group (80.0% versus 51.3%, $p = .0026$). No direct correlation was found between the frequency of miscarriages in the first trimester and the variant of the polymorphism of the vitamin D receptor gene (VDR A > G [rs10735810]); the GG genotype in patients with repeated miscarriages was even less frequent compared to the control group (14.0% versus 23.7%, $p = .3344$). However, the decision tree has identified four risk classes and has determined that the highest risk of missed abortion in the cohort studied is formed by three predicates: smoking, serum level 25(OH)$D < 6.5$ ng/ml and VDR AA and GG genotypes.

Conclusion: The data obtained show that vitamin D insufficiency plays a pathogenetically significant role in early reproductive losses associated with miscarriages, both first and recurrent.

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Vitamin D deficiency; VDRgene; miscarriage; early pregnancy loss; missed abortion

Introduction

Missed abortion(MA) is a topical problem of modern obstetrics and gynecology. The MA is defined as a pathological symptom complex that includes the non-viability of the embryo, pathological inertia of myometrium, and/or dysfunction in the hemostasis system [1], which, according to ICD-10, is encoded as O02.0 or O02.1. According to various authors, the proportion of miscarriages in the cohort of early pregnancy loss patients ranges from 10 to 88.6% [2,3]. At the same time, about 80% of reproductive losses occur in the 1st trimester [2,4]. Miscarriage in the first trimester is a special problem, as the factors that determine it stop the gestation program at the beginning. These include genetic and chromosomal abnormalities of the embryo, genital anatomy, endometrium pathology, hereditary thrombophilia, antiphospholipid syndrome and others [5]. Most of these factors are difficult to correct, but there are also controllable ones whose negative effects can be completely mitigated before conception. These include nutritional deficits, including vitamin D insufficiency (E 55.9) [6,7].

Vitamin D plays an important role in supporting women's reproductive health through its metabolism of 1.25(OH)D (calcitriol, «hormone D»). Its receptors (VDR) are found in the endometrium, placenta, deciduous cells, ovarian granule cells, uterine tube epithelium, pituitary gland, and hypothalamus [8]. The placenta was described as one of the first extrarenal tissues capable of synthesizing calcitriol with CYP27B1 activity in decidual tissue and trophoblast cells [9]. It expresses enzymes and proteins that are necessary for metabolism and cholecalciferol regulation, such as VDR, VDBP, CYP2R1, CYP27B1, CYP24A1 [10]. It is important to emphasize that vitamin D is an endometrial expression regulator of the HOXA-10 gene, which in turn is a transcription regulator. It plays an important role in the functional differentiation of the endometrium, which correlates with the quality of implantation processes at the early stages of pregnancy [11].

Objective

To study the relationship between vitamin D deficiency, VDR gene polymorphism rs10735810 (A > G), and a missed abortion

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in the first trimester of gestation; to determine the predictors of its risk.

Material and research methods

The present prospective cohort study was carried out in 2017–2020. At the clinical sites of the Department of Obstetrics and Gynaecology and perinatology of the Medical Institute of the Russian Peoples' Friendship University. The study included 178 eligible women. The main group consisted of patients ($n = 101$) with confirmed PL (U/S, HCG) at the hospital stage, who were admitted to the urgent gynaecological hospital with diagnoses Missed abortion O02.0 and O02.1. They were stratified into group I ($n = 58$, patients with the first miscarriage) and group II ($n = 43$, patients with repeated miscarriage, two or more). The criteria for inclusion in the core group are reproductive age; verified pregnancy loss (O02.0, O02.1), confirmed at the hospital stage (U/S, HCG), Russian nationality, voluntary informed consent of the patient. Exclusion criteria: severe and moderate somatic diseases during decompensation, genetic, anatomical, endocrine, immunological, infectious causes of pregnancy loss, oncological diseases, refusal to carry out necessary diagnostic and therapeutic measures, taking medications or supplements of native vitamin D during the last three months, pregnancy with the use of assisted reproductive technologies, abortions in history.

The control group was formed at the outpatient stage from pregnant women during the gestation period of 5–12 weeks ($n = 77$), who, when registering for pregnancy, met the inclusion criteria (Z34.0): reproductive age, blood intake for 25 OH-vitamin D in 5–12 weeks, Emergency delivery of a live fetus with an Apgar score not lower than 8–9, Russian nationality, voluntary informed consent of the patient to participate in the study. Exclusion criteria: severe and moderate somatic diseases during decompensation, oncological diseases, taking medications or supplements of native vitamin D during the last three months.

The patients were interviewed and the data was extracted from the medical records. The level of 25(OH)D in the blood serum ($n = 99$) was determined by the method of mass spectrometry adapted to clinical practice according to international standards (DEQAS, NIST) by the approved method according to the Government Standards (ГОСТР) 8.563-2009 [12]. The research was carried out in the laboratory of LLC «Clinic of new medical technologies ArchiMed» (the head of the laboratory – Candidate of Sciences, Biology, Nizhnik A.N). The blood serum level of $25(OH)D < 10$ ng/ml was considered to be a severe deficiency, <20 ng/ml was considered to be a deficiency, the range of 20–29 ng/ml was considered to be an insufficiency of vitamin D, and levels of 25(OH)D of 30 to 100 ng/ml were considered as the norm [13,14]. Genotyping for VDR rs10735810 gene polymorphism was performed using a commercially available kit for Real time-PCR (Syntol, Russia).

The statistical analysis of the data set was performed using Statistica 10 and SAS JMP 11 software packages. The comparison of the two numerical groups was based on the Mann-Whitney nonparametric criterion. Comparisons of three or more groups on numerical scales were made using the nonparametric Kruskal-Wallis method. The average value and the standard deviation of «M ± S» were used to describe the quantitative scales. The difference was considered significant at $p < .05$. ROC analysis was used to assess prognostic values of features. One-factor miscarriage risk prediction was performed for quantitative and binary factors. The statistical significance of the factors' influence on the binary target variable was calculated using the criteria χ^2 and Pearson. The relative risk was calculated. The CHAID decision tree method was used to distinguish risk classes. To assess the predictive quality of the built CHAID decision tree, AUC, sensitivity, and specificity were used.

Results of the study

The analysis (Table 1) showed that pregnancy loss patients in both groups were older than women in the control group ($p_{1-3} < .01$, $p_{2-3} < .05$ respectively) and comparable in anthropometric data. However, patients with the first miscarriage had a lower body weight than patients in the control group ($p_{1-3} < .01$). In the main group, the proportion of patients over 35 years of age was 26.7%, in the control group 15.5% ($p = .08$). Among women with pregnancy loss, there were 8.7 times more smokers (34.6% versus 3.9% in the control group, $p < .001$).

The results of the analysis (Table 1) show significant differences between groups II and III in terms of pregnancy parity ($p = .0001$) and birth parity between all groups compared ($p = .0001$). Interestingly, the main group of patients was more likely to have excessive and frequent menstruation with regular cycle and/or irregular menstruation (21.8% versus 3.9% in the control group, $p = .0001$) and primary dysmenorrhea (respectively 10.9% versus 3.9%, $p = .003$).

It has been found (Figure 1) that vitamin D insufficiency (93.3% versus 76.9%, $p = 0183$) is significantly more frequent in patients with miscarriage in the first trimester of gestation ($n = 60$) than in the control group ($n = 39$), including 25(OH)D level below 20 ng/ml (71.7% versus 51.3%, $p = .0392$). This pattern was more common in patients with the first miscarriage, where differences were also found (Table 2) in the frequency of vitamin D deficiency in comparison with the control group (80.0% versus 51.3%, $p = .0026$). No direct relation was found between the pregnancy loss frequency in the first trimester and the variant of the vitamin D receptor gene polymorphism (VDR A > G [rs10735810]) – as can be seen from Table 3, the genotype of GG VDR in patients with repeated miscarriage was even less frequent compared to the control group (14.0% and 23.7% respectively $p = .3344$).

Based on the data obtained (Table 4), it can be concluded that 6 factors have a significant impact on the risk of pregnancy loss, with a risk increase range of 37.8% to 56.9%. These factors increase the probability of miscarriage in the first trimester of gestation from 23.7% to 45.0%. The leading are smoking, menstrual disorders, and serum level $25(OH)D < 6.5$ ng/ml. Ultimately, the CHAID decision tree (Figure 2) identified four risk classes and determined that the highest risk of pregnancy loss in the cohort under study forms the integral influence of a combination of three predictors: smoking, serum level $25(OH)D < 6.5$ ng/ml and AAor GG genotypes for VDR rs10735810. The absolute risk of reproductive loss associated with pregnancy loss in the first trimester is found in women who smoke and have the VDR AA or GG genotype. At $25(OH)D < 6.5$ ng/Ml, the risk of reproductive loss increases to 91% even in the absence of such a trigger as smoking.

Discussion of the obtained results

To date, numerous studies have been published confirming the role of vitamin D in the development of obstetric complications such as miscarriage and recurrent loss of pregnancy, premature birth, preeclampsia, gestational diabetes mellitus and many

Table 1. Clinical and social characteristics of pregnant women cohort studied.

Parameter	One miscarriage ($n = 58$)		Repeated miscarriage ($n = 43$)		Control group ($n = 77$)		p
Age	31.4 ± 4.8*		30.9 ± 4.4*		29.1 ± 4.5*		p_{1-3}=.0152* p_{2-3}=.1625
Height, cm	166.0 ± 4.6		165.7 ± 5.6		166.6 ± 5.7		p_{1-3}=.7419 p_{2-3}=.6378
Weight, kg	61.50 ± 8.2*		63.77 ± 10.8		65.6 ± 9.0*		p_{1-3}=.7402 p_{2-3}=.08368
Registered marriage	54 (93.1%)*		38(88.4%)*		77 (100.0%) *		p_{1-3}=.0193* p_{2-3}=.0022*
Smoking	18 (31.0%)*		17(39.5%)*		3 (3.9%)		p_{1-3}=.0001 p_{2-3}=.0001*
Intellectual worker	29 (50.0%)		16 (37.2%)		51 (66.2%)		.0077
Housewife	23 (39.7%)		25 (58.1%)		19 (24.7%)		
Physical worker	6 (10.3%)		2 (4.7%)		7 (9.1%)		
Onset of sexual activity, years	17.9 ± 1.9		18.2 ± 1.8		17.8 ± 1.9		p_{1-3}=.7440 p_{2-3}=.0800
Ageofmenarche, years	13.0 ± 1.1		12.8 ± 1.3		13.1 ± 1.1		p_{1-3}= .7440 p_{2-3}=.0800
Average menstrual cycle length	29.1 ± 5.1		28.8 ± 2.5		29.0 ± 4.3		p_{1-3}= .9759 p_{2-3}=.8665
Average menstrual period length	5.0 ± 0.8		5.0 ± 0.9		5.2 ± 1.1		p_{1-3}= .8584 p_{2-3}=.8598
Pregnancy in history	1.9 ± 1.0		3.1 ± 1.2*		1.6 ± 0.7*		p_{1-3}= .2102 p_{2-3}=.0001
Birth	0.6 ± 0.7*		0.7 ± 1.0*		1.6 ± 0.7*		p_{1-3}= .0001 p_{2-3}= .0001
	abs.	%	abs.	%	abs.	%	
Chronic salpingo-oophoritisN70.1	6	10.3*	4	9.3*	0	0*	p_{1-3}=.0039 p_{2-3}= .0065
Ectropion of cervix uteriN86	17	29.3	6	13.9	14	18.2	.1290
N92.0 Excessive and frequent menstruation with regular cycle, N 92.6 Irregular menstruation,unspecified	14	24.1*	8	18.6*	3	3.9*	p_{1-3}= .0004 p_{2-3}= .0074
N94.4 Primary dysmenorrhea	5	8.6*	6	13.9*	3	3.9*	p_{1-3}= .2498 p_{2-3}= .00449

Note: *differences between groups are significant ($p < .05$).

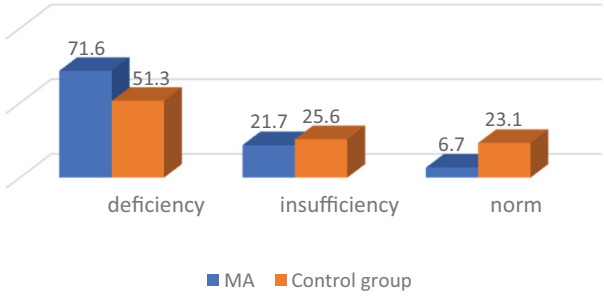

Figure 1. Results of vitamin D insufficiency testing of patients in comparable groups.

Table 2. Serum 25(OH)D (ng/ml) concentration in patients examined.

Vitamin D level	One miscarriage ($n = 30$)		Repeated miscarriage ($n = 30$)		Control group ($n = 39$)		p
	abs.	%	abs.	%	abs.	%	
Optimal level	2	6.7*	2	6.7*	9	23.1*	p_{1-3}=.0654 p_{2-3}=.0654
Insufficiency	4	13.3	9	30.0	10	25.6	p_{1-3}=.1368 p_{2-3}=.8702
Deficiency	14	46.7	12	40.0	12	30.8	p_{1-3}=.1775 p_{2-3}=.4264
Severe deficiency	10	33.3	7	23.3	8	20.5	p_{1-3}=.2299 p_{2-3}=.7798

Note: *differences between groups are significant ($p < .05$).

others [15–21]. However, work on the role of vitamin D in pregnancy loss pathogenesis is very limited [22]. The literature mainly discusses the role of vitamin D insufficiency in the pathogenesis of spontaneous miscarriage, and the results of these studies are highly controversial [23]. At the same time, Andersen and others [24] demonstrated that vitamin D insufficiency increases the risk of miscarriage more than twofold. Our findings indicate that vitamin D insufficiency is found in patients with pregnancy loss in the first trimester (5–12 weeks) and vitamin $D < 6.5$ is a predictor of reproductive loss.

It has been established that smoking is the absolute predictor of an unfavorable outcome. Among women with pregnancy loss, there were 8.7 times more smokers (34.6% versus 3.9% in the control group, $p < .001$). This is consistent with Ghimire et al. [25] who showed that smoking women have a higher risk of miscarriage than nonsmokers (OR = 1.27; 95% of MDIs: 1.07, 1.50).

To date, it is very relevant to assess the influence of polymorphisms of the VDR gene on reproductive loss. There are several studies of this kind that have shown contradictory results [26,27]. In turn, we have not found a correlation between the miscarriage frequency and the polymorphism variants of the vitamin D receptor gene. However, when constructing a decision tree, it has been shown that VDR polymorphisms may potentiate the effects of such a predictor as smoking.

The results of the research show that vitamin D deficiency plays a pathogenetically significant role in early reproductive losses associated with miscarriage, both first and repeated. Women with severe deficits form a high-risk group at 25(OH)$D < 6.5$ ng/ml. The absolute predictor of an unfavorable

Table 3. Occurrence of genotypes and alleles of polymorphism VDR A > G [rs10735810] in patients examined.

Gene	Genotypes and alleles	I group, ($n = 58$) abs.	%	II group, ($n = 43$) abs.	%	Control group ($n = 76$) abs.	%	p	OR (CI 95 %)
VDR A-G	AG	30	51.7	21	48.8	37	48.7	.1472	2.29 (0.738–7.075)
	AA	16	27.6	16	37.2	21	27.6		
	GG	12	20.7	6	14.0	18	23.7		
	A	62	53.4	53	61.6	79	52.0	.150	1.48 (0.866–2.543)
	G	54	46.6	33	38.4	73	48.0		

Note: *differences between groups are not significant ($p > .05$).

Table 4. Key risk factors of pregnancy loss.

Risk factor	Factor – no abs.	%	Factor – yes abs.	%	Risk change (95% CI)	Relative risk (95% CI)	p
Smoking	66	47.1	35	92.1	45.0 (33.1; 56.9) %	1.95 (1.60; 2.38)	<.0001
Menstrual disorder: N92.0 Excessive and frequent menstruation with a regular cycle, N 92.6 Irregular menstruation, unspecified, N94.4 Primary dysmenorrhea	68	48.9	33	84.6	35.7 (21.6; 49.7)%	1.73 (1.39; 2.15)	<.0001
Age, years ≥ 33.0	54	47.8	47	72.3	24.5 (10.3; 38.8) %	1.51 (1.18; 1.93)	.0015
Ageofmenarche, years < 13.0	50	47.2	51	70.8	23.7 (9.5; 37.8) %	1.5 (1.17; 1.93)	.0018
Occupacy (Housewife)	53	47.7	48	71.6	23.9 (9.7; 38.1) %	1.5 (1.17; 1.92)	.0018
25 OH-Vitamin D < 6.5ng/ml	49	56.3	11	91.7	35.3 (16.6; 54.1) %	1.63 (1.27; 2.09)	.0188

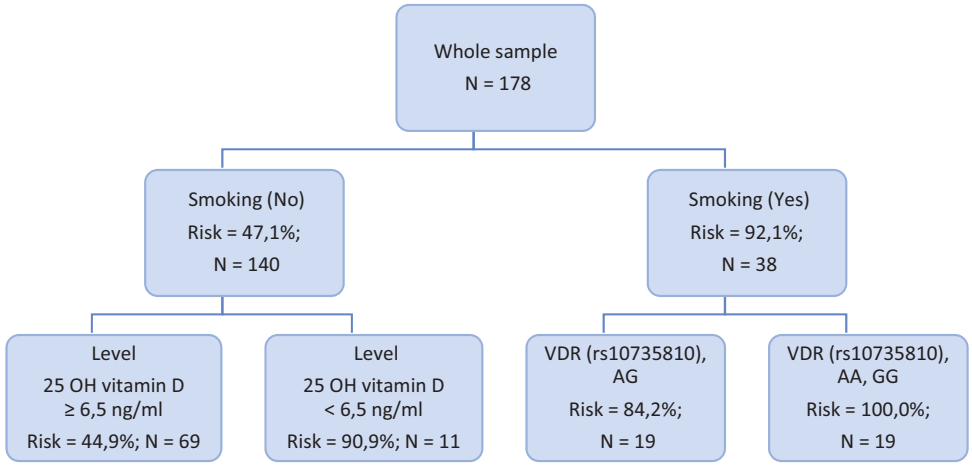

Figure 2. Integral influence of pregnancy loss risk predictors.

outcome is smoking. Its effects may be potentiated byAA and GG genotypes for the VDR gene polymorphism rs10735810. Further research is needed to confirm this hypothesis.

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