December 30, 2020

PharmacologyOnLine

Archives • 2020 • vol.3 • 270-278

ON THE EFFECTIVENESS OF A PERSONALIZED APPROACH IN THE PREVENTION OF CALCITRIOL-ASSOCIATED COMPLICATIONS OF PREGNANCY AND CHILDBIRTH

[1]Manasova, G.S.; [1]Shpak, I.V.; [1]Didenkul, N.V.; [1]Kuzmin, N.V.; [2]Badiuk, N.S.*
[1]Odessa National Medical University, Odesa, Ukraine
[2]State Enterprise "Ukrainian Scientific Research Institute of Transport Medicine of Health of Ukraine", Odesa, Ukraine

*badiuk_ns@ukr.net

Abstract

Aim: to assess vitamin D status (VDS) and frequency distribution of alleles and genotypes BsmI (A> G, rs1544410) polymorphism of the gene encoding VD receptors (VDR) in patients with placental dysfunction (PD) and physiological pregnancy, and to study the possibility of preventing calcitriol - associated complications of pregnancy and childbirth.

Methods. At the 1st stage of work made on the principle "case-control", 56 pregnant women with PD (group IA) and 40 women with physiological pregnancy (group IB) were examined. At the 2nd stage, 57 women with VD deficiency and the history of pregnancy complicated by PD were undere xamination; 27 of them were observed from the pre-gravid stage (group IIA) and 30 – starting from the 1st trimester of pregnancy (group IIB). The level of 25 (OH) D in the blood was determined by ELISA, and BsmI polymorphism of VDR gene - by PCR. Patients at the 2nd stage in addition to the vitamin-mineral complex received colecalciferol at a dose of 4000 IU per day, after optimization of VD level (3-4 months) it was prescribed at a dose of 2000 IU per day until the end of pregnancy.

Results. In pregnant women with PD, VD level was lower than in group IB (31.40 ± 8.6 and 43.54 ± 11.20) ng / ml, ($p \leq 0.05$). A heterozygous combination of A / G alleles was diagnosed in 67.8% and in 35% in groups IA and IB, (OR = 3.95; 95% CI 2.19-7.1; $\chi 2 = 20.88$, p <0, 01); genotype A / A - in 12.5% and 17.5%, (OR = 0.68; 95% CI 0.31-1.48; $\chi 2 = 1.013$, p <0.05); genotype G / G - in 19.6% and in 47.5%, (OR = 0.27; 95% CI 0.15-0.51; $\chi 2 = 16.71$, p <0.01). association of average strength between the frequency of AP and genotype A / G, (OR = 3.8; 95% CI 2.1-6.8; $\chi 2 = 20.88$; p <0.01), medium-strength feedback - with genotype G / G, (OR = 0.27; 95% CI 0.15-0.51; $\chi 2 = 16.71$; p <0.01) In groups IIA and IIB, VD level before treatment was 15.72 ± 2,59 ng / ml and 16.1 ± 1.99 ng / ml, (U = 883; p> 0.05); after 3 months increased by more than 2 times (38.31 ± 3.29 ng / ml and 36.13 ± 2.99 ng / ml; U = 900; p> 0.05). Women who received VDc subsidies at the pregravid preparation stage, had pregnancy accompanied by fewer complications. Early gestosis was diagnosed in 7.4% and 36.7%, (F = 0.00001; p <0.01), violation of fetoplacental perfusion - in 18.5% and 40%, (F = 0.0018; p <0.01); signs of amnionitis - in 18.5% and 33.3%, (F = 0.035; p <0.05); low placentation - in 3.7% and 20%, (F = 0.0008; p <0.01); hyper- or hypotrophy of the placenta - in 7.4% and 36.7% (F = 0.00001; p <0.01), preeclampsia - in 3.7% and 6.7% (F = 0.54; p <0.05). The frequency of cesarean section was significantly higher in group IIB (40% *vs* 14.8%, F = 0.0018; p <0.01).

Conclusion. Women with an aggravated obstetric history need to develop a personalized plan for pregnancy preparation and one of the directions of its management may be the assessment of vitamin D status and, possibly, the determination of BsmI of the VDR gene polymorphism associated with a

high risk of developing placental dysfunction. With a deficiency of VDc, its timely subsidy from the stage of gravidar preparation is a pathogenetically determined and promising approach to pre-gravidar, preclinical prevention of perinatal and intrapartum complications.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

Key words: pregnancy, vitamin D, placental dysfunction, pregravid preparation.

The effect of the VD / VDR system on reproductive function is due to the presence of VD receptors in endometrial cells, myometrium, ovarian tissue, vascular endothelium, trophoblast cells and in the placenta [1, 2, 3]. One of the conditions for the normal functioning of the ovaries, steroid and folliculogenesis, ovulation and full-fledged

luteal phase, as well as endometrium functional state adequate for conception is the optimal level of VD in the blood [4].

Chronization of inflammatory changes in the endometrium, impaired receptivity, "defective implantation window", various types of hyperplasia or "thin" endometrium are processes, accompanied by pathological invasion of the trophoblast and the formation of primary placental insufficiency and associated with VD deficiency [1, 5].

According to recent studies, the implementation of the pleiotropic effects of calcitriol can be genotypically determined due to the polymorphism of genes encoding VD receptors, and phenotypically change under the influence of environmental factors: the endocrine system in the form of a VD / VDR complex controls more than 2000 genes and can specifically respond to the level of calcitriol in 38 organs and tissues of the body [2, 6, 7].

There is information about the significance of TaqI-polymorphism of VDR genes in menstrual dysfunction [8], about the association of FokI-polymorphism of the VDR gene with the state and quality of embryos obtained as a result of assisted reproductive technologies [9], association of FokI-polymorphism of the VDR gene and functional state some immunocompetent cells, in particular, T-lymphocytes [10].

Expression of the nuclear vitamin D receptor directly in the placenta is genetically determined, and in the presence of genes polymorphism, encoding and regulating the functional activity of the VDR, placental dysfunction can form and the risk of preterm birth significantly increases [2, 6, 11, 12, 13].

The modern concept of the development of personalized and predictive clinical medicine provides, in addition to the patient's direct informed participation in the prevention and treatment of diseases (participativity), personalization and risk prediction, in particular, by studying the genetic determinant or the human genetic passport [14, 15].

To study the possibility of timely preclinical prevention of gestational process complications by preliminary personalization of risks is seen as a promising direction of modern obstetrics.

Objective to evaluate vitamin D status and frequency distribution of alleles and genotypes BsmI (A> G, rs1544410) polymorphism of the gene encoding VDR in patients with placental dysfunction (PD) and physiological pregnancy, as well as to study the possibility of preventing calcitriol-associated complications of pregnancy and childbirth.

Methods

The study was carried out on the basis of Maternity hospital № 5 and Maternity hospital № 1 (Odessa, Ukraine) in accordance with the principles of the Declaration of Helsinki and approval of the research protocol by the local ethical committee (LEC) of Odessa National Medical University.

From September 2017 to September 2019, 96 pregnant women were examined according to the "case-control" principle after obtaining informed consent (the 1st stage of work). The main group (I A) consisted of 56 pregnant women with a high infectious risk (HIR) and the established diagnosis of "placental dysfunction" (PD), the control group (I B) included 40 women with physiological pregnancy without HIR.

All patients underwent standard general clinical examinations, as well as HIR and PD verification in accordance with the requirements of regulatory documents.

HIR was supported by the presence of various foci of chronic infection or infectious agents (bacterial vaginosis, colpitis of mixed etiology, acute or exacerbation of chronic TORCH infection, ARVI, chronic inflammatory diseases of the kidneys, nasopharynx), as well as ultrasound signs of placenta, amnion and fetus contamination (oligo-, hydroamnion, hypertrophy, calcification, placenta's premature maturation, fetal ventriculomegaly, intestinal hyperechogenicity). Ultrasound examination of pregnant women was carried out on the device "Samsung Medison UGEO WS80A" (Samsung Medison CO, LTD, Korea; 2014).

To assess the state of the fetal-placental complex and the intrauterine fetus, ultrasound, Doppler-assessment of blood flow, cardiotocography,

assessment of the biophysical profile of the fetus were used; placenta's hormonal function was investigated (the level of human chorionic gonadotropin (HCG) and estriol). Their levels were determined by ELISA on Cobas Integra 400 Plus (Roch-Diagnostics, Switzerland).

At the second stage of the work, 57 multiparous women were examined, 27 of which (group II A) applied to the hospital at the stage of pregnancy planning, and 30 (group II B) - in the first trimester of pregnancy. The inclusion criteria for the study were the presence of vitamin D deficiency (below 20 ng / ml) at the time of treatment and indications of PD presence in a previous pregnancy, which ended in the birth of a live child.

The exclusion criteria from the study at both stages were age less than 18 or more than 40 y.o., the presence of severe extragenital pathology (diabetes mellitus, chronic kidney and liver disease with failure), impaired fat metabolism, skin and autoimmune diseases, diseases of thyroid and parathyroid glands.

Group II A patients at the pregravid stage, in addition to the vitamin-mineral complex (VMC) containing 500 IU of colecalciferol and 800 μg of folic acid, additionally received colecalciferol in a daily dose of 4000 IU. After reaching the target VD level (at least 30 ng / ml), pregnancy was recommended. On average it happened in 3 ± 1.2 months. Throughout pregnancy, these patients received a maintenance dose of VD (2000 IU of colecalciferol).

From the moment of diagnosis group II B women were also prescribed 4000 IU of cholecalciferol in addition to VMC and after reaching the target values of 25 (OH) D in the blood, they continued to receive VD 2000 IU.

25-hydroxycalciferol (25 (OH) D) concentration was determined by ELISA – test on a Cobas Integra 400 Plus analyzer (Roche Diagnostics, Switzerland). Blood sampling for the study was carried out on an empty stomach, after 8 hours of fasting; level of the body provision by VD was determined in accordance with "Methodological recommendations for the treatment and prevention of vitamin D deficiency for the population of Central Europe", [17]. VD level in blood serum less than 20 ng / ml indicates its deficiency, and 20 -30 ng / ml - about VD insufficiency.

Peripheral blood was used for genetic research. Real-time PCR study of VDR gene site for the presence of the mutant Bsml (rs 1544410) polymorphism was performed. DNA was isolated by the express method (Proba-Rapid-Genetics reagent, DNA-Technology); forward and reverse primers were used for amplification to study the VDR gene site (detecting amplifier DT-96 ("NPO DNA-Technology" LLC, Russia).

Statistical analysis was performed using Statistica 6.0 software from Install Shield Software Corporation (USA). To calculate the reliability of the quantitative indicators of the results obtained, Student's test for data with a normal distribution and nonparametric Mann-Whitney test for data with an abnormal distribution were used. After determining these variations series distribution normality the Shapiro-Wilk test was used. The reliability of the results obtained for qualitative indicators was determined using the Fisher test.

To assess the statistical significance of the frequency indicators of the distribution of various alleles and genotypes in groups, we used the calculation of the odds ratio (OR using a 95% confidence interval (CI).

Results

According to the age and anthropometric data the groups were homogeneous at the first and second stages of the survey. At the first stage of the study, the mean age of women in group I A was 29.21 ± 4.3 years, and in women with physiological pregnancy in group I B it was 30.35 ± 3.12 years ($p > 0.05$). Body mass index (BMI), respectively, for groups I B and I A were (22.8 ± 1.93) and (22.2 ± 1.7) c.u, ($p > 0.05$).

40 women out of 56 (71.43%) in group I A and 22 out of 40 (55.00%) in group I B were primiparous ($F = 0.028$; $p < 0.05$); multiparous, respectively were 16 (28.57%) and 18 (45%; $F = 0.028$; $p < 0.05$).

Vitamin D status in PD pregnant women was characterized by a significantly lower level (25 (OH) D compared to the control group (31.40 ± 8.6 and 43.54 ± 11.20) ng / ml, ($p \leq 0.05$). In accordance with the recommendation of some medical communities, the recommended lower threshold value for VD in the blood of pregnant women is 40 ng / ml [16]. The proportion of patients with vitamin D levels below 30 ng / ml (suboptimal level) was 76.78% and 15%,

respectively, I A and I B groups, (F = 0.0258; p <0.01); of these, 38.39% of I A group women were diagnosed VDD status, in group I B VDD was not detected in anyone (F = 0.0001; p <0.01) The data obtained indicate that the course of pregnancy against the background of suboptimal calcitriol level is significantly more often complicated by PD, which can be explained by the pleiotropic effects of colecalciferol.

Based on the results of molecular genetic testing of pregnant women, it was found that the patients of the groups under examination have certain differences in the genotypes and alleles of the BsmI polymorphism (rs1544410) of the gene encoding vitamin D receptors.

In 19.6% (11 persons) of pregnant women with PD, homozygous carriage for the G allele (G / G) was revealed, which is 2.4 times less than in group I B 47.5% (19 persons), (OR = 0.27; 95% CI 0.15-0.51; $\chi 2$ = 16.71, p <0.01), (Fig. 1).

A heterozygous combination of A / G alleles was diagnosed in 67.8% (38 persons) of pregnant women with PD, while in the group of healthy pregnant women, only 35% (14) women were carriers of this genotype, (OR = 3.95; 95% CI 2, 19-7.1; $\chi 2$ = 20.88, p <0.01).

With a high degree of probability, it can be assumed that the heterozygous A / G variant of the Bsml-polymorphism allele of the VDR gene, which is detected in more than 2/3 of women with VDD and a HIR, is an additional risk factor for complications of the gestational process with placental insufficiency, while carriers of a homozygous combination of the G allele, (47.5% of healthy pregnant women) have a lower risk of developing PD.

12.5% (7 women) in group IA and 17.5% (7 women) in group IB had A / A genotype, (OR = 0.68; 95% CI 0.31-1.48; $\chi 2$ = 1.013, p <0.05), this variant of the genotype is probably not associated with the formation of PD in pregnant women.

According to the correlation analysis and risk calculations, it was established that there is a direct associative relationship of average strength between the presence of PD and A / G genotype of single nucleotide BsmI polymorphism of the gene encoding VDR (OR = 3.8; 95% CI 2.1-6.8; $\chi 2$ = 20.88; p <0.01), (Table 1.).

An inverse correlation of medium strength was found between the frequency of G / G genotype and the frequency of PD (OR = 0.27; 95% CI 0.15-0.51; $\chi 2$ = 16.71; p <0.01). Women with this variant of genotype have a significantly lower risk of PD developing, which is confirmed by the fact that in 47.5% of women with G / G genotype the course of pregnancy was physiological, while in PD group, carriers of this genotype were only 19.7%.

Pearson's criterion (G / G - $\chi 2$ = 16.71; A / G - $\chi 2$ = 20.88) confirms the presence of significant differences between the distribution of genotypes A / G and G / G in the compared groups and the association of the incidence of PD with single nucleotide BsmI -polymorphism of the VDR gene: the risk of a possible complication of pregnancy by PD in pregnant women with A / G allelic VDR genes is 4 times higher than in patients with other variants of genotypes.

Genotype A / G was diagnosed in 87.5% of pregnant women with clinical manifestations of PD and VDD; among women with physiological pregnancy and suboptimal VD levels, there were no carriers of this genotype (F = 0.00001; p <0.01). In 83.3% of women with physiological course of pregnancy and suboptimal VD level, G / G genotype was revealed, among women with PD and a low VD level, there were no carriers of this genotype (F = 0.00001; p <0.01). A / A genotype was identified in both groups in less than 20% (12.5% in group IA and 16.7% in group IB, (F = 0.553; p <0.05).

The average age of women examined at the 2nd stage of work was 32.9 ± 3.9 and 32.53 ± 3.8 years, respectively, in groups IIA (pregravid stage) and IIB (1st trimester of pregnancy). Height-weight indicators of women in the groups under examination did not deviate from population norms. The average body weight was 61.37 ± 5.1 and 62.7 ± 4.22, respectively, and BMI in both groups was less than 25 (22.13 ± 1, 55 and 23.03 ± 1.28, respectively, for groups IIA and IIB). The general somatic status of the patients also had no significant differences.

The course of the previous pregnancy in both groups was accompanied by various complications, which together formed PD; these were various placentation disorders, early gestosis, threatened abortion syndrome and childbirth before term, poly-, oligohydramnios, anemia, preeclamspia and others - no significant differences were found between the groups in the frequency of nosoforms.

The level of 25 (OH) D in the blood at the initial treatment in both groups corresponded to VDD state (15.72 ± 2.59 ng / ml and 16.1 ± 1.99 ng / ml, respectively, for groups IIA and IIB; U = 883; p > 0.05), (Fig. 2.).

After 3 months of colecalciferol donation at a dose of 4,000 U, the 25 (OH) D level in both groups rose to the optimal one (38.31 ± 3.29 ng / ml and 36.13 ± 2.99 ng / ml, respectively, for groups IIA and IIB, U = 900; p> 0.05), (Fig. 2). In women from group IIA, pregnancy occurred within 1 - 3 months.

Discussion

Thus, in the group that underwent pregravid training with an additional subsidy of colecalciferol, pregnancy occurred under conditions of 25 (OH) D concentration correspondence to the "optimum" level (39.82 ± 3.06 ng / ml). Under these conditions, the processes of implantation, placentation and the first wave of trophoblast invasion important from the point of view of the uterine-placental-fetal circle of blood circulation formation, took place.

In women included in the study in the 1st trimester of pregnancy, the formation of the mother-placenta-fetus system took place in conditions of VD deficiency (16.1 ± 1.99 ng / ml (U = 558.5; p <0.05).

The course of pregnancy in women who did not undergo VD deficiency correction at the pre-gravid stage was characterized by a significantly higher frequency of complications (Table 2).

Thus, the frequency of early gestosis in group IIA was 7.4% versus 36.7% in group IIB, which is 5 times less (F = 0.00001; p <0.01). Placentation disorders in the form of its low attachment were diagnosed in 20% (n = 6) of women from group IIB and in 3.7% (n =1) - from group IIA, (F = 0.0008; p <0.01); marginal attachment was noted only in 16.7% (n =5) in group IIB. Placental hypertrophy or hypotrophy was observed 5 times more often in women from group IIB (36.7% *vs* 7.4%; F = 0.00001; p <0.01). Pathological changes in Doppler parameters (disorders of fetal-placental, uteroplacetal, fetal circulation) were significantly less frequently detected in group IIA women (18.5% *vs* 40%; F = 0.0018; p <0.01). Signs of inflammatory changes in the amniotic membrane were diagnosed in 18.5% and 33.3% of women in groups IIA and IIB, respectively (F = 0.035; p <0.05). Pregnancy was complicated by the formation of intrauterine growth retardation syndrome in 1 patient (3.7%) from group IIA and in 3 women (10%) from the comparison group, (F = 0.16; p> 0.05); with preeclampsia - in 3.7% and in 6.7% of women, (F = 0.54; p <0.05). In addition, in 3.3% of pregnant women in group IIB, premature detachment of a normally located placenta was diagnosed.

Pregnancy in all women in both groups ended in term delivery; the frequency of delivery by caesarean section in the comparison group was 42.8% *vs* 14.8% in the group that underwent pregravid preparation with colecalciferol subsidy (F = 0.034; p <0.05). Reliably more often in childbirth in group IIB, various obstetric aids were used: vacuum extraction of the fetus - in 3.3%, manual separation and isolation of the placenta - in 6.7%.

Thus, according to the results of the research carried out, some conclusions can be drawn.

Women whose reproductive history is complicated by an indication of placental insufficiency are at risk with the re-formation of this obstetric syndrome and need to develop a personalized preparation plan for pregnancy, provided they are consciously involved in this process.

More than in 2/3 pregnant women with PD, the level of vitamin D in the blood corresponds to an insufficient or deficient status, while in the physiological course of pregnancy, the suboptimal VD level is detected only in 15% (76.8% VS 15%, F =0.0258; p <0.01).

The study of single-nucleotide Bsml polymorphism of the gene encoding VDR showed that heterozygous carriers of genotype A / G in conditions of insufficient or vitamin D deficient status have a risk of pregnancy complications with placental insufficiency 4 times higher than in women with other allelic variants (A / A and G / G).

In conditions of vitamin D deficiency, the risk of developing certain complications of pregnancy, including preeclampsia, placental dysfunction and others, as well as the frequency of delivery by the abdominal route is 2 to 4 times higher.

It seems expedient to introduce into the program of pre-admission training of women with a burdened obstetric history, determination of vitamin D status and, possibly, genetic testing, followed by a donation of colecalciferol in case of its

insufficiency, which is a pathogenetically determined and promising approach to the prevention of perinatal and intranatal complications.

Conflict of interest

The authors declsre that there are no conflicts of interest.

References

Barrera D, Avila E, Hernández G, Méndez I, González L, Halhali A, Larrea F, Morales A, Díaz L. Calcitriol affects hCG gene transcription in cultured human syncytiotrophoblasts // Reprod Biol Endocrinol. – 2008. –Vol. 6:3.

2. Javorskia I. N. Vitamin D receptor (VDR) polymorphisms are associated to spontaneous preterm birth and maternal aspects / I. N.Javorskiab et al. //Gene Volume. – 2017. – Vol. 642. – P. 58 – 63
3. Knabl J, Vattai A, Ye Y, Jueckstock J, Hutter S, Kainer F, Mahner S, Jeschke U. Role of placental VDR expression and function in common late pregnancy disorders. Int J Mol Sci. 2017 Nov 6; 18 (11):2340.
4. Merhi Z et al. (2014). Vitamin D alters genes involved in follicular development and steroidogenesis in human cumulus granulosa cells. J Clin Endocrinol Metab. 99 (6): 1137–1145
5. Gil A, Plaza-Diaz J, Mesa M.D. Vitamin D: classic and novel actions. Ann Nutr Metab 2018; 72: 87-95.
6. Manzon L. Vitamin D receptor polymorphism fokL is associated with spontaneous idiopathic preterm birth in an Israeli population. / L. Manzon et al. // Eur. J. Obstet. Gynecol. – 2014. – Vol. 177. – P. 84–88
7. DeLuca H.F. Overview of general physiologic features and functions of vitamin D //Am J Clin Nutr December. – 2004. – Vol. 80, № 6. – P. 1689-1696.
8. Gerasimova L.I. Genetic aspects of the physiological metabolism of vitamin D in the functioning of the reproductive system. / L.I. Gerasimova, M.S.Denisov, T.G. Denisova // Bulletin of Health and Education in the XXI century. - 2016. - No. 9. - P.1-5. (in Russian)
9. Naimi Z.M.S. Association of vitamin D receptor gene polymorphism with embryological parameters and efficiency of in vitro fertilization programs. / Z.M.S. Naimi, E.A. Kalinin, A.E. Donnikov, A.Kh. Dudarova // Obstetrics and gynecology. - 2017. - No. 2. - S. 51 – 57. (in Russian)
10. Etten E. The vitamin D receptor gene FokI polymorphism: Functional impact on the immune system. E. Etten // European Journal of Immunology. – 2007. – Vol. 37, № 2. – P. 395–405
11. Aghajafari F. Association between maternal serum 25-hydroxyvitaminD level and pregnancy and neonataloutcomes: systematicreview and meta-analysis of observational studies. / Aghajafari F., Nagulesapillai T., Ronksley P.E. // BMJ. - 2013. – Vol. 346
12. Chan S.Y. Vitamin D promotes human extravillous trophoblast invasion in vitro / S.Y. Chan, R. Susarla // Placenta. — 2015. — Vol. 36, № 4. — P. 403-409.
13. Shahrokhi S. Z.Role of vitamin D in female reproduction. / S.Z. Shahrokhi,F.Ghaffari, F. Kazerouni. // Clin.Chim.Acta. – 2016. – Vol. 455. – P. 33 – 38.
14. Hood L., Auffray C. Participatory medicine: a driving force for revolutionizing healthcare Genome Med, 5 (12) (2013), p. 110.
15. Flores M., Glusman G, Brogaard K., Price N.D., Hood L. P4 medicine: how systems medicine will transform the healthcare sector and society Per Med., 10 (6) (2013), pp. 565-576.
16. Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults.
17. Practical guidelines for supplementation of vitamin D and treatment of deficits in Central Europe: recommended vitamin D Intakes in general population and groups being at risk of vitamin D deficiency / P. Pludowski, E. Karczmarewicz, M. Bayer [et al.] // Endokrynologia Pol. — 2013. — 64, № 4. — P. 120-127.

Figure 1. Distribution of allelic variants of the VDR gene (BsmI-polymorphism) in patients with placental dysfunction (group I A) and in pregnant women with physiological pregnancy (group I B).

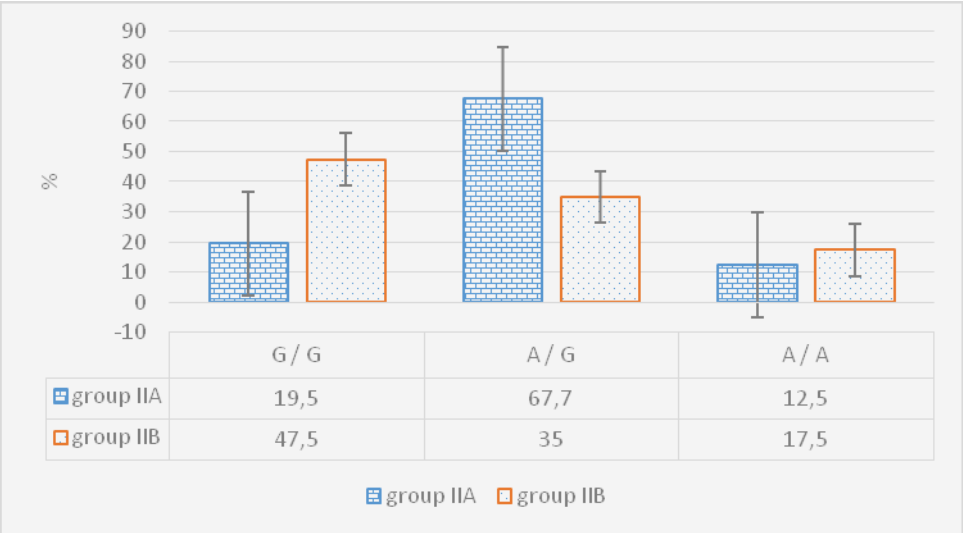

Table 1. Distribution of genotypes of BsmI polymorphism of the gene encoding vitamin D receptors in pregnant women with placental dysfunction and HIR and in pregnant women with physiological pregnancy

genotypes	Group IA, n=56		Group IB, n=40		OR	χ2	P
G/G	11	19.67%	19	47.5%	0.27;95% CI 0.15-0.51	16.71	P <0.01
A/G	38	67.86%	14	35%	3.95; 95% CI 2.19-7.1	20.88	P<0.01
A/A	7	12.5%	7	17.5%	0.68; 95% CI 0.31-1.48	1.013	P>0.05

Figure 2. Dynamics of the VD level in the blood of women at different stages of the examination:
group IIA: 1 - stage of pregravid preparation, 2- 3 months after donation of colecalciferol before conception;
group IIB: 1 - 1st trimester of pregnancy, 2 - after 3 months of colecalciferol donation.
* - Differences are significant at P <0.05.

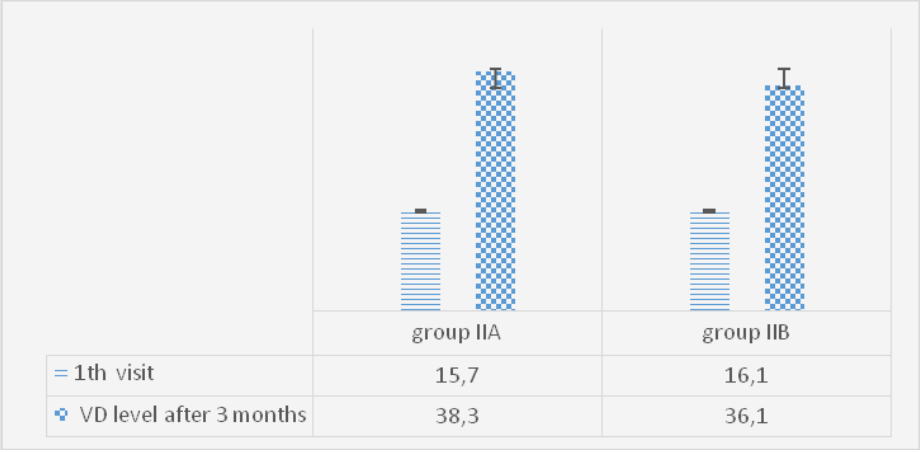

Table 2. Features of the course of pregnancy and childbirth in women with 25 (OH) D deficiency who received colecalciferol subsidies from the pre-gravid stage (group IIA) and from the first trimester of pregnancy (group IIB)

Complications of birth and labours	Group IIA, n=27		Group IIB, n=30		Reliability
	Abs. number	%	Abs. number	%	
Early gestosis	2	7.4	11	36.7	F=0.00001;p<0.01
IUGR	1	3.7	3	10	F=0.16; p>0.05
Violation of fetoplacental perfusion	5	18.5	12	40	F=0.0018; p<0.01
Signs of amnion inflammatory changes	5	18.5	10	33.3	F=0.035;p>0.05
Placenta hypo-, hypertrophy	2	7.4	11	36.7	F=0.00001; p<0.01
Low placentation	1	3.7	6	20	F=0.0008; p<0.01
Marginal placenta presentation	0	-	5	16.7	-
Detachment of the normally located placenta	0	-	1	3.3	-
Premature maturation of the placenta	1	3.7	3	10	F=0.16; p>0.05
Preeclampsia	1	3.7	2	6.7	F=0.0295; p<0.05
The threat of termination of pregnancy	6	22.2	11	36.7	F=0.238;p>0.05
Pre-labor rupture of membranes	2	7.4	4	13.3	F=0.238; p>0.05
Fetus vacuum extraction	-	-	1	3.3	-
Manual separation and extraction of afterbirth	-	-	2	6.7	-
Caesarean section	4	14.8	12	40	F=0.0018; p<0.01