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SUPPLEMENTATION OF VITAMIN D IN PREGNANT WOMEN WITH 25(OH) D DEFICIENCY AND RISK OF PREECLAMPSIA DEVELOPMENT IMPROVES PERINATAL OUTCOMES

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Abstract

Hypertensive disorders in women during pregnancy account for about 14% of maternal deaths while preeclampsia / eclampsia can be avoided through preventive measures and the provision of timely and effective care for women with these complications.

The aim. To determine the possibility of preventing preeclampsia by VD supplementation in a group of women with its insuffiency / deficiency and a high risk of developing this complication of pregnancy.

Materials and methods. Randomized controlled clinical trial was carried out in 2017-2020, the annual number of deliveries is 2200-2400. All the subjects (n=54) gave informed consent to participate in the examination and processing of their personal data. Selection criteria: 1st trimester, presence of 25 (OH) D3 deficiency and risk factors for PE. In the 1st group (n = 25) women received a multivitamin-mineral complex (MVMC) (including colecalciferol 500 IU), in the 2nd (n = 29) colecalciferol was additionally prescribed at a dose of 4000 IU until the completion of structural formation placenta (16 weeks of pregnancy), then 2.000 units until the end of pregnancy. The level (25 (OH) D) in the blood was determined by ELISA.

Results. The groups were homogeneous in terms of age, anthropometric data, birth parity, general somatic and reproductive history. VD supplementation led to its significant increase by the 3rd trimester in the 2nd group (28.7 ± 5.9 ng / ml and 38.3 ± 7.1 ng / ml; Uemp = 146; p <0.01), in contrast to the 1st (26.08 ± 7.5 ng / ml and 28.9 ± 6.9 ng / ml; Uemp = 284; p> 0.05). In the 1st group (24% VS 6.9%) PE developed 3.5 times more often (F = 0.0014; p <0.01; OR = 3.27; 95% CI 1.018 - 10.524); preterm birth was observed 2 times more often (36% VS 17.2%; F = 0.0037; p <0.01; OR = 2.74; 95% CI 1.416 - 5.327), cesarean section - 1.7 times (48% VS 27.6%; F = 0.0055; p <0.05; OR = 2.374; 95% CI 1.320 - 4.369) and intrauterine growth retardation - 4.5 times more often (16% VS 3.5%; OR = 4.571; 95 % CI 1.471 - 14.210).

Conclusions. Supplementation of colecalciferol to the vitamin and mineral complex throughout pregnancy is accompanied by a significant improvement in perinatal outcomes, including a lower incidence of preeclampsia, premature birth, fetal growth retardation and cesarean sections. Further research is needed to obtain convincing data with a reliable

evidence base and substantiate the need to assess and correct vitamin D status in women at the stage of preconception preparation.

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.

Keywords: *pregnancy hypertensive disorders, mother-placenta-fetus system, vitamin D insufficiency/ deficiency.*

Introduction

Hypertensive disorders in women during pregnancy remain one of the most common causes of maternal and neonatal morbidity and mortality. The share of hypertensive disorders worldwide accounts for about 14% of maternal deaths and preeclampsia / eclampsia are the main cause of these problems. A feature of hypertensive disorders is that most of the negative consequences and deaths due to preeclampsia and eclampsia can be avoided through preventive measures and the provision of timely and effective care for women with these complications [1, 25].

At present, attention is paid to certain mechanisms of the development of preeclampsia, such as immune maladjustment, hereditary component, pathological apoptosis and necrosis of trophoblasts and the development of an inflammatory response syndrome in the body of a pregnant woman, metabolic disorders of lipid metabolism associated with the toxic effects of very low density lipoproteins, as well as chronic uterine - placental ischemia [2].

There are also studies that highlight the role of an imbalance of angiogenic factors in the pathogenesis of preeclampsia [3].

Also, studies of recent decades have significantly supplemented the understanding of the biological role of the hormonal system vitamin D / vitamin D receptors (VD / VDR) in the human body [3]. In particular, this is information on the synthesis by vascular smooth muscle cells, cardiomyocytes and endothelial cells of the enzyme 1-α-hydroxylase, the main catalyst for the conversion of 25 (OH) D to 1.25 (OH) 2D, which is VDR natural ligand. Thanks to this mechanism, the synthesis of the active form of VD can be carried out directly in the vascular bed, which takes part in the regulation of the renin-angiotensin system, in the processes of angiogenesis, and regulation of the coagulation potential of blood. The possible effect of VD on the cardiovascular system can also be mediated by its immunogenic effect, participation in the regulation of calcium-phosphorus homeostasis and carbohydrate metabolism. The combination of these effects of VD suggests its pathogenetic significance in the development of cardiovascular disorders [4].

The effect of VD / VDR on the processes of trophoblast invasion and the formation of the microvasculature of the mother-placenta-fetus system, the participation of calcitriol in the activation of NO synthetase and the formation of endothelial dysfunction, as well as the participation of VD in the formation of a systemic inflammatory response suggest that calcitriol can play one of the key roles in the pathogenetic mechanisms of preeclampsia development [5, 6, 7].

Vitamin D deficiency among the population is from 18% to 84% and depends on the country of residence, ethnicity and many other factors. Taking into account the above **the aim** of the study was to determine the possibility of preventing preeclampsia by supplementation of VD in a group of women with its insuffiency / deficiency and a high risk of developing this complication of pregnancy.

Materials and methods

Randomized controlled clinical trial was carried out in the municipal maternity hospital No. 5 (Odessa, Ukraine), which is the clinical base of the Odessa National Medical University during 2017-2020 This maternity hospital specialization is the management of women with miscarriage and premature birth. The annual number of deliveries in the ihospital is 2200-2400.

The primary examination of women was carried out in the 1st trimester of pregnancy within 10-12 weeks. All the subjects gave informed consent to participate in the examination and processing of their personal data (Order of the Ministry of Health of Ukraine dated January 21, 2016 N 29), as well as in compliance with moral and ethical principles in accordance with the main provisions of the World Medical Association Declaration of Helsinki (1994, 2000, 2008) and the positive decision of the Commission on Bioethics of the Odessa National Medical University.

Further, the course of pregnancy, its outcome and childbirth for the mother and child were assessed.

The inclusion criteria for the study were the presence of VD insufficiency / deficiency, as well as the presence of the following risk factors for the development of preeclampsia (according to the recommendations of ACOG 2020 - [8] the forthcoming first birth, multiple pregnancy,

preeclampsia (PE) in a previous pregnancy, chronic hypertension, pre-existing or gestational diabetes, thrombophilia, systemic lupus erythematosus, body mass index over 30 kg / m^2, antiphospholipid syndrome, maternal age 35 years old or more, kidney disease, use of assisted reproductive technologies, or indication of obstructive sleep apnea.

Besides, women who at the time of selection had already taken a multivitamin-mineral complex that contains at least 500 IU of cholecalciferol were included into the study, too.

By the beginning of our study in Ukraine there were no registered and recommended for pregnant women multivitamin - mineral preparations containing a greater amount of cholecalciferol.

To determine the vitamin D status, we used the recommendations of Polish colleagues (2019) according to which VD deficiency was stated at a blood level of 25 (OH) D less than 30 ng / ml [9].

The level of the circulating metabolite of vitamin D, total for chole- and ergocalciferol, (25 (OH) D) was determined by the enzyme-linked immunosorbent assay on a Cobas Integra 400 Plus analyzer (Roche Diagnostics, Switzerland) at the initial examination and before childbirth. Blood samples for the study were taken from a vein on an empty stomach after a night's sleep (6-8 hours without food).

After selection, 54 pregnant women were included into study. They were divided into 1 (n = 25) and 2 groups (n = 29); the first group continued to take the multivitamin-mineral complex (colecalciferol 500 IU), and women from group 2 were recommended to take additional colecalciferol at a dose of 4000 IU (replacement, loading dose) until the completion of the structural formation of the placenta (16 weeks of pregnancy), then switched to a dose of 2000 IU, which was taken until the end of pregnancy.

The criterion for the diagnosis of PE was considered the level of systolic blood pressure (SBP) 140 mm Hg or more or diastolic blood pressure (DBP) 90 mm Hg or more with 2-fold measurement within 4 hours after 20 weeks of pregnancy in women with previous normal blood pressure; with a systolic blood pressure of 160 mm Hg or more, or a systolic blood pressure of 110 mm Hg or more, a single blood pressure measurement was sufficient for the timely initiation of antihypertensive therapy. The diagnosis of PE was confirmed by proteinuria in the middle portion of urine collected twice with an interval of 4 hours or more at a protein content of 0.3 g / L or daily protein excretion of 0.3 g. dysfunction and other criteria for PE.

Statistical analysis was performed using MS Excel and www.socscistatistics.com. To calculate the reliability of the results obtained of quantitative indicators, Student's t- test for the data with a normal distribution or Mann-Whitney's test for the data with an abnormal distribution was used. This was done after determining the normal distribution using Shapiro-Wilk's criterion. The reliability of the results obtained for qualitative indicators was determined using Fisher's criterion.

Results

The groups under examination were homogeneous in age (27.4 ± 4.4 y.o. and 28.2 ± 4.6 y.o.; Uemp = 218; p> 0.05) and anthropometric data (weight - 85.8 ± 10.5 kg and 82.8 ± 11.7 kg; Uemp = 325; p> 0.05; height - 166.3 ± 3.4 cm and 165.2 ± 4.2 cm; Uemp = 315; p> 0.05). There were also no differences in BMIs in groups 1 and 2 (30.31 ± 3.68 kg / m^2; 29.42 ± 4.50 kg / m^2; Uemp = 278; p> 0.05).

When analyzing the parity of childbirth, statistical homogeneity of groups was also established (primiparous - 64.2% and 65.5%, respectively, to groups F = 0.82; p> 0.05; multiparous - 36.3% and 34.5%; F = 1; p> 0.05); there were 3 (or more) deliveries 12.3% and 3.5% (F = 0.066; p> 0.05).

The characteristics of the reproductive and general somatic history are presented in Table 1.

In general, there were no significant differences in the groups either in reproductive history or in the frequency of this or that extragenital pathology. Assisted reproductive technologies (ART) were used more often in the 2nd group (4% and 24.1%; F = 0.0001; p <0.01); 8% (2 patients) and 3.5% (1 patient) indicated a complication of a previous pregnancy with PE, respectively, but this difference is not statistically significant, (F = 0.2134; p> 0.05; OR = 2, 08; 95% CI 0.608 - 7.167).

When assessing the primary vitamin D status of the patients, there was no significant difference in indicators between the groups (26.08 ± 7.5 ng / ml in the 1st and 22.9 ± 6.9 ng / ml in the 2nd groups; Uemp = 284; p>0.05).

In dynamics before childbirth, the level of 25 (OH) D3 was significantly higher in the group where additional to the vitamin-mineral complex (VMC) cholecalciferol supplement took place (28.7 ± 5.9 ng / ml and 38.3 ± 7.1 ng / ml; Uemp = 146; p < 0.01) (Fig. 1).

Analysis of perinatal outcomes in the groups showed that pregnant women with an initial 25 (OH) D3 deficiency in the blood without supplementing the VMC by colecalciferol preparations (in 6 women out of 25–24%) significantly more often developed a clinical picture of PE than in the group that received VD in addition to the VMC (2 women out of 29 - 6.9%; F = 0.0014; p <0.01; OR = 3.27; 95% CI 1.018 - 10.524). In addition, in the 1st group preterm birth was significantly more frequent (9 out of 25 - 36% versus 5 out of 29 - 17.2%; F = 0.0037; p <0.01; OR = 2.74; 95% CI 1.416 - 5.327), delivery by abdominal route (12 people out of 25 - 48% and 8 out of 29 - 27.6%; F = 0.0055; p <0.05; OR = 2.374; 95% CI 1.320 - 4.369), (Table 2).

It also draws attention to The reliably (F = 0.0081; p <0.01) more frequent complication of pregnancy by the formation of intrauterine fetal growth retardation syndrome (FGRS) also cannot but draw attention - in the 1 group patients (4 out of 25 people - 16% and in 1 out of 29 people. - 3.5%; OR = 4.571; 95% CI 1.471 - 14.210).

There were no significant differences in blood pressure indices in the groups at the initial examination in 1 trimeter; by the time of delivery there was a significant increase in blood pressure in the group of pregnant women who did not receive additional VD (Table 3). The changes concerned indicators of both diastolic and systolic pressure. So, if in the 1st trimester of pregnancy, diastolic blood pressure (DBP) figures up to 90 mm Hg were in 14 patients (56%) in the 1st group and in 20 people. (68.9%) in the 2nd group (F = 0.0793; p> 0.05), then in the 3rd trimester these figures were, respectively, 8 (32%) and 14 (48.2%) persons (F = 0.0301; p <0.05).

In both groups the number of women with DBP ranged 90-109 mm Hg increased (in the 1st group from 11 patients or 44% to 17 patients - 68%; in the 2nd group from 9 patients - 31.03 % up to 15 patients - 51.7%). In the 1st trimester the differences between the groups were statistically insignificant (F = 0.0793; p> 0.05), in the 3rd trimester they became significant (F = 0.0301; p < 0.05). Similar changes both in the level of systolic blood pressure (SBP) and in the ratio of the number of patients depending on the mean values of SBP were found in the groups under examination.

Discussion

The homogeneity of the groups (by age, the existing risk factors for the development of PE, the anthropometric characteristics) allows to make a comparative analysis of the results of additional supplement of cholecalciferol to the VMC in one of 2 groups of pregnant women with diagnosed deficiency of 25 (OH) D3.

Clinical studies show that VD deficiency is associated with many adverse pregnancy outcomes and is very common in pregnant and lactating women [10], and may also have a negative impact on fertility and ART success [11]. We found that in the groups of pregnant women under examination every 10th woman (12% and 10.3%, respectively, in the 1st and 2nd groups) had infertility and, accordingly, ART were applied. Probably, taking into account this fact, we can say that these women had combined risk factors for the development of PE, since it is known about the independent role of vitamin D deficiency (VDD) in the development of PE [12, 13]. It should be noted that every 10th patient from both groups also indicated gestational hypertension in a previous pregnancy without further observation and clarification of its genesis outside of pregnancy. Previously these women were not examined for VD status. Taking into account the information on the correlation of VDD with higher systolic blood pressure and a higher incidence of hypertension and cardiovascular disease [14], it can be assumed that these women had a long-term uncorrected VD insufficiency.

Women in both groups had extragenital pathology (hypertension, impaired fat metabolism, bronchial asthma, chronic kidney and gastrointestinal tract diseases), which can be both a consequence of an insufficient level of 25 (OH) D3, and play a role in violation of the metabolism stages and synthesis of VD active metabolite [15, 16].

The analysis of perinatal outcomes showed a significantly higher (2 times) frequency of preterm births in the group of women without additional VD supplement (OR = 2.74; 95% CI 1.416 - 5.327), which is

consistent with literature data indicating an increase in the risk of childbirth before term in pregnant women with circulating 25-OHD deficiency [17]. Also, in 1 group patients childbirth was performed by caesarean section 1.7 times more often (OR = 2.374; 95% CI 1.320 - 4.369); newborns in this group had FGRS 4.5 times more often (OR = 4.571; 95% CI 1.471 - 14.210) and Apgar score was significantly lower (OR = 3.255; 95% CI 1.686 – 6.282).

One of the possible reasons for insufficient fetal growth may be a violation of the expression of vitamin D receptors directly in the endo- and myometrium in the zone of implantation and subsequent placentation [18, 19, 20]. The supposed explanation for the significantly higher incidence of PE in the group of pregnant women who did not receive colecalciferol supplement (OR = 3.27; 95% CI 1.018 - 10.524) may be certain physiological and pathological reactions in with VD involved. Thus, there is evidence that under the conditions of VD insufficiency, an imbalance between pro- and anti-angiogenic factors directly in the area of placenta formation can lead to the development of PE [21]. According to Aliashrafi S. et al. (2016), the effect of VD on angiogenesis may be ambiguous: in cells with excessive angiogenesis, the addition of VD leads to inhibition of angiogenesis due to a decreased activity, proliferation, migration, and germination of endothelial cells, while under the conditions of intact vascular endothelium, VD increases hypoxia-inducible factor 1-α - HIF1-α) and promotes the expression of Stromal Cell – Derived Factor 1 - SDF1, which later on mediates cell proliferation and vascular regeneration, and in embryonic development SDF-1 controls migration of different types of cells and has an important role in the formation of organs [22, 23].

Pregnancy is accompanied by significant changes in VD metabolism, which is explained by the activation of the enzyme 1α-hydroxylase (CYP27B1 - a catalyst for the synthesis of 1.25 (OH) 2D), as well as the expression of vitamin D receptors (VDR) in the kidneys, decidua, trophoblast and placental tissue. The immunomodulatory role of VD also plays a certain role, which is important under the conditions of activation of nonspecific immunity and suppression of specific immunity during pregnancy. Ganguly A, Tamblyn JA, Finn-Sell S. et al. (2018) in a review of literature data emphasize the potential role of 1.25 (OH) 2D in the regulation of trophoblast invasion in early pregnancy, which can lead to the formation of primary placental dysfunction and negative perinatal outcomes, and PE may be one of them [24].

Thus, our study and literature data on the pleiotropic effects of VD, as well as the search for possible ways to prevent PE in women at risk, allows us to draw a number of conclusions.

Conclusions

In women with anamnestic, general somatic and objective risk factors for the development of preeclampsia there is an uncorrected vitamin D deficiency against which the laying, formation and morpho-functional formation of the uteroplacental-fetal complex is carried out. Supplement of colecalciferol to the vitamin and mineral complex throughout pregnancy is accompanied by a significant improvement in perinatal outcomes, including a lower incidence of preeclampsia, premature birth, fetal growth retardation and cesarean sections.

Further research is needed to obtain convincing data with a reliable evidence base and substantiate the need to assess and correct vitamin D status in women at the stage of preconception preparation.

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The authors declsre that there are no conflicts of interest.

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Table 1. Reproductive and somatic history of pregnant women from risk groups for the development of preeclampsia

Indicator	Abs. number	%	Abs. number	%	significance
Reproductive History					
ART use	1	4	7	24.1	F=0.0001; p< 0.01
Frozen pregnancy	7	28	4	13.8	F=0.023; p < 0.05
Medical abortions	6	24	2	6.9	F=0.0014; p < 0.01
Infertility	3	12	3	10.3	F=0.8217; p > 0.05
Caesarean section	3	12	2	6.9	F=0,335; p>0,05
History of placental abruption	1	4	0	0	F=0.1212; p> 0.05
History of preeclampsia	2	8	1	3.5	F=0.2134; p> 0.05
Gestational hypertension at the previous pregnancy	3	12	3	10.3	F=0.8217; p > 0.05
Extragenital pathology					
Hypertension	2	8	1	3.45	F=0,2134; p>0,05
Vegeto-vascular dystonia	5	20	4	13.79	F=0,3467; p>0,05
Autoimmune thyroiditis, hypothyroidism	2	8	1	3.5	F=0.2134; p> 0.05
Fat metabolism disorders	4	16	6	20.7	F=0.4667; p> 0.05
Bronchial asthma	1	4	0	0	F=0.1212; p> 0.05
Varicose veins of the lower extremities	3	12	4	13.8	F=0.8339; p> 0.05
Mitral valve prolapse	1	4	1	3.5	F=1; p> 0.05
Chr. pyelonephritis	2	8	1	3.5	F=0.3727; p> 0.05
Chr. gastrointestinal diseases	3	12	4	13.8	F=0.8339; p> 0.05
Diabetes mellitus type 2	0	0	1	3.5	F=0.1212; p> 0.05

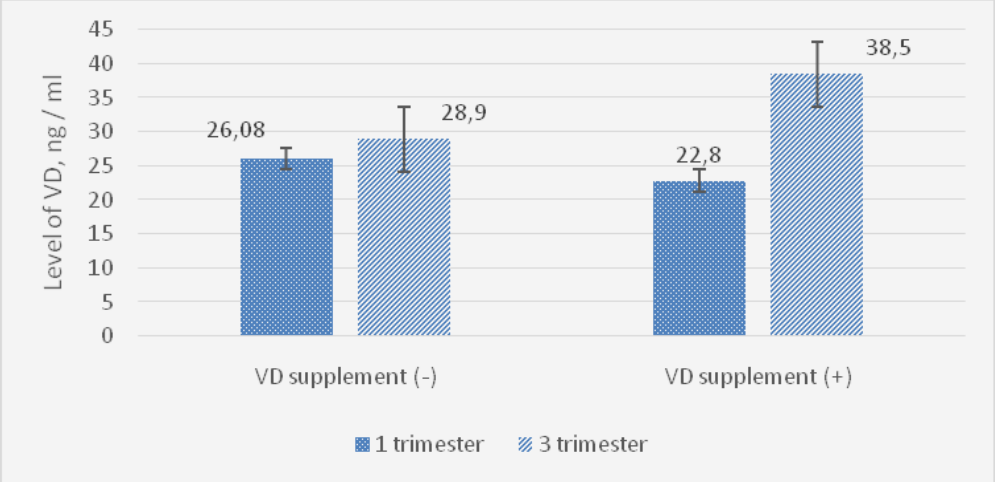

Figure. 1. The level of 25 (OH) D3 in the blood of pregnant women in the 1st and 3rd trimesters of pregnancy (before childbirth)

Table 2. Comparative perinatal outcomes in groups of pregnant women depending on the colecalciferol supplement

indicator	1st group, without VD suppl., n=25		2nd group, with VD suppl., n=29		significance
	n	%	n	%	
Childbirth before term	9	36	5	17.2	F = 0.0037; p< 0.01
Delivery on time	16	36	24	82.8	F= 0.0037; p< 0.01
Childbirth per vias naturalis	13	64	21	72.41	F=0,0055; p < 0,05
Caesarean section	12	52	8	27.57	F=0,0055; p < 0,05
Premature rupture of membranes	4	48	2	6.9	F = 0.0744; p > 0.05
Fetal distress	1	4	1	3.5	F=1; p > 0.05
FGRS	4	16	1	3.45	**F=0.0081; p< 0.01**
PE	6	24	2	6.90	F=0.0014; p < 0.01
Apgar score-7b	7	28	5	17.24	F=0.0296; p < 0,05
Apgar score-8b	15	60	24	82.76	F=0.001; p < 0.01
Apgar score-6b	2	8	0	0	F=0.0068; p < 0.01
Surfactant administration to newborns	2	8	0	0	F=0.0068; p < 0.01
CPAP therapy	2	8	0	0	F=0.0068; p <0.01
Blood loss in childbirth more than 0.5% of body weight	10	40	11	37.9	F=0.8848; p > 0.05

Table 3. Blood pressure indicators in dynamics in groups of pregnant women, depending on the donation of cholecalciferol

Blood Pressure Indicator , mm Hg	1st group, without VD supplement, n=25		2nd group, with VD supplemet, n=25		significance
	n	%	n	%	
Blood pressure indicators in the 1st trimester					
DBP up to 90	14	56	20	68.97	F=0.0793; p>0.05
DBP ≥ 90 -109	11	44	9	31.03	F=0.0793; p>0.05
DBP ≥110	0	0	0	0	
SBP up to 140	20	80	24	82.76	F=0.8572; p>0.05
SBP 141-159	4	16	5	17.24	F=1; p>0.05
SBP≥160	1	4	0	0.00	F=0.1212; p>0.05
Blood pressure indicators in the 2nd trimester					
DBP up to 90	8	32	14	48.28	F=0.0301; p<0.05
DBP ≥ 90 -109	17	68	15	51.72	F=0.0301; p<0.05
DBP ≥110	0	0	0	0	
SBP up to 140	17	68	23	79.3	F=0.0332; p<0.05
SBP 141-159	6	24	6	20.7	F=0.2933; p>0.05
SBP≥160	2	8	0	0	F=0.0068; p<0.01