

## The Role of Personalized Preventive Medicine in Reproductive Risk Regulation

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### Abstract

Despite some success in the study of pre-eclampsia, it is still one of the main causes in the structure of maternal mortality. The tissues of the reproductive organs: ovaries, uterus, placenta, testis and pituitary have the receptors for vitamin D, and the association of vitamin D role with reproductive health is evident. The aim of the study was to study the effect of vitamin D deficiency on renin concentration among pregnant women from the groups of pre-eclampsia development risk. The pregnant women with pre-eclampsia and the patients with a high risk of pre-eclampsia development who are planning pregnancy were studied for vitamin D, endothelin and renin concentrations, since it is known from literature data that enzymes like renin are found in the uterus, placenta and in the walls of some large arteries. The material of the study was blood. The method of enzyme immunoassay and the sets of biomedicagruppe (Germany) were used to determine the availability of vitamin D, the enzyme immunoassay and Immuno Chem (USA) sets were used to determine the renin concentration. The patients with developed preeclampsia showed highly reliable correlations between low vitamin D values and high blood pressure ( $r = 0.68$ ,  $p < 0.01$ ), high endothelin level in blood ( $r = 0.56$ ,  $p < 0.01$ ), high renin concentration ( $r = 0.72$ ,  $p < 0.01$ ), an early onset of PE ( $r = 0.46$ ,  $p < 0.05$ ). The risk group of pre-eclampsia development among the women planning a pregnancy was composed of 30 women with hypertension, 31 - with kidney disease, 24 - with obesity (BMI > 34), 13 - with body weight deficit. The supply of vitamin D and the level of ionized Ca among these women were significantly lower ( $0.07 \pm 0.01$  mmol/l) than among the women not included in risk group ( $1.2 \pm 0.02$  mmol/l); the renin concentration exceeded the mean values among the women of the control group. The patients with hypertension and obesity had the renin concentration at the upper limit of physiological parameters ( $30.4 \pm 1.8$  and  $28.4 \pm 1.6$  pg/ml, respectively), and the level of vitamin D was lower than in other nosologies among the patients of high risk group ( $14.8 \pm 1.5$  and  $13.9 \pm 1.5$  ng/ml, respectively). At renal diseases and body mass deficiency, the renin concentration was  $16.6 \pm 0.7$  and  $12.4 \pm 0.8$  pg/ml, respectively, while the level of vitamin D was  $17.4 \pm 1.5$  and  $16.9 \pm 1.2$  ng/ml.

**Keywords:** Pre-eclampsia; Vitamin D; Renin; Reproductive risk; Prevention.

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### 1. Introduction

Preeclampsia is one of the most serious complications of pregnancy and is responsible for the death rate of almost 100,000 women in the world annually. The incomplete invasion of trophoblast is generally recognized as the key factor of preeclampsia pathogenesis. With the increase of pregnant women who have severe extragenital diseases in Russia, the frequency of preeclampsia increased from 16 to 20.6%. The tissues of the reproductive organs (ovaries, uterus, placenta and pituitary gland) had VDR and 1 $\alpha$ -hydroxylase, and the association of vitamin D role with the state of reproductive health is evident. Vitamin D, which has a steroid structure, penetrates a cell through the cytoplasmic membrane easily, then it binds to the receptor (VDR), which is the member of nuclear receptor superfamily. After the stimulation of ligand, VDR quickly enters the nucleus and is associated with the nuclear matrix, while interacting with transcription activators to target this regulatory complex on specific elements of gene promoter sequence. Thus, more than 3000 genes are regulated, many of which play a significant role in fetal development, including the inhibition of cell proliferation and the induction of terminal differentiation, angiogenesis and renin production, the stimulation of insulin production and the production of macrophages and the induction of apoptosis. Despite some success in the study of PE, the latter is still one of the main reasons in the structure of

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maternal mortality without a clear tendency to improve the situation. Perinatal mortality is 10-30 ‰, and the incidence of fetuses and newborns reaches 463-780 ‰. The aim of the study is to study the effect of vitamin D deficiency on renin concentration among pregnant women with the risk of pre-eclampsia development (Thorne-Lyman and Fawzi, 2012).

## 2. Methods

35 patients were examined at age of 19 - 41 years during 34-37 weeks of gestation with pre-eclampsia, the group of women with a high risk of pre-eclampsia development and planning pregnancy - 98 women and 30 patients (control group) with a physiological pregnancy. The material of the study was the venous blood of patients. To determine the availability of vitamin D, they used the method of enzyme immunoassay - the sets by biomedicagruppe (Germany), the level of ionized calcium in blood was determined via the automatic analyzer ABL 80. To determine the concentration of renin, they used enzyme immunoassay method and the ImmunoChem kit (USA). The statistical processing of the study results was carried out using Statistica for Windows software (version 6.1). They calculated the arithmetic mean and the standard error ( $M \pm m$ ). The differences between groups in terms of quantitative parameters were evaluated by the Student's criteria ( $p$ ), in the case of an incorrect distribution of the compared indicators or the number of observations in one of the groups less than 30, they used Mann-Whitney criterion ( $pm-u$ ). The differences between the groups by relative values were estimated by the chi-square test ( $p\chi^2$ ), if one of the values was less than 5, the exact Fisher method ( $pF$ ) was used. Differences were considered statistically acceptable with error probability ( $p$ ) less than 0.05 (Holick, 2007).

## 3. Results

The pregnant women with pre-eclampsia had a significantly reduced vitamin D content in serum. The mean value was  $10.7 \pm 0.6$  ng/ml, whereas the patients with a physiological pregnancy had the following mean value:  $19.82 \pm 1.5$  ng/ml ( $p < 0.01$ ). It should be noted that the level of vitamin D was equally low, both with moderate and severe preeclampsia (Kuznetsova *et al.*, 2015). The content of ionized calcium in blood was also significantly decreased. The decrease of vitamin D content was accompanied by the increase of the amount of endothelin in blood and the concentration of renin, depending on the severity of preeclampsia. There was a twofold increase of endothelin as compared with healthy women at moderate PE and a 20-fold increase at severe forms. At severe pre-eclampsia renin concentration in plasma was  $59.1 \pm 0.2$  pg/ml, which is 10 times higher than the concentration of renin among healthy pregnant women ( $5.3 \pm 0.2$  pg/ml). At a moderate preeclampsia renin concentration was  $38.9 \pm 0.7$  pg/ml. Reliable correlations between low vitamin D values and high blood pressure ( $r = 0.68$   $p < 0.01$ ), high endothelin level in blood ( $r = 0.56$   $p < 0.01$ ), high renin concentration ( $r = 0.72$   $p < 0.01$ ), the early onset of preeclampsia ( $r = 0.46$   $p < 0.05$ ), the threat of interruption during early pregnancy ( $r = 0.48$   $p < 0.05$ ), and the presence of retrochoric hematoma (Arriagada *et al.*, 2010).

We isolated and examined the patients planning pregnancy and belonging to the high-risk group of pre-eclampsia development - 98 women. 30 women with hypertension belonged to pre-eclampsia development risk group, 31 - with kidney disease 24 - obesity (BMI>34), 13 - body weight deficiency. The studies showed, that the provision of vitamin D and the level of ionized Ca among these women were significantly lower ( $0.07 \pm 0.01$  mmol/l) than among the women who do not belong to the risk group ( $1.2 \pm 0.02$  mmol/l). It should be noted that among all women with a high-risk of pre-eclampsia development, the renin concentration exceeded the mean values among the women of the control group. The patients with hypertension and obesity had the renin concentration at the upper limit of physiological parameters ( $30.4 \pm 1.8$  and  $28.4 \pm 1.6$  pg/ml, respectively), and the level of vitamin D was lower than among other nosology patients of the high risk group ( $14.8 \pm 1.5$  and  $13.9 \pm 1.5$  ng/ml, respectively). At renal diseases and body mass deficiency, the renin concentration was  $16.6 \pm 0.7$  and  $12.4 \pm 0.8$  pg/ml, respectively, while the level of vitamin D was  $17.4 \pm 1.5$  and  $16.9 \pm 1.2$  ng/ml. This is due to the fact that vitamin D is a potent endocrine suppressor of renin biosynthesis and is able to prevent hypertension through the suppression of renin-angiotensin system. Probably, its genomic actions are mediated by the inhibitory effect on the renin-angiotensin system, acting directly on the gene renin-promoter. Moreover, vitamin D reduces the expression of the angiotensin-2 receptor on the surface of endothelial cells, resulting in sequential reactions that are accompanied by the synthesis of such vasodilators as nitric oxide (Bodnar *et al.*, 2014).

The prescription of vitamin D and Ca drugs to the patients with high risk of PE development during pregnancy showed a significantly beneficial preventive effect on the course of pregnancy and childbirth. The obtained data determined the approaches to correction: vitamin D preparations and calcium preparations were prescribed to women for preventive purpose. The patients from high-risk group of pre-eclampsia development who were planning pregnancy had the prescription of vitamin D preparations at the dose of 4,000 units per day. Pregnancy occurred among 36 patients taking vitamin D during pregravid preparation and during pregnancy, the comparison group included 35 patients who did not take vitamin D during pregravid preparation and during pregnancy. The pregnant women with the pregnancy duration from 7 to 10 weeks, who underwent pregravid preparation within 3-4 months, experienced the study on the levels of vitamin D and Ca content. The level of vitamin D and Ca was determined among pregnant women with high risk of pre-eclampsia development who did not undergo pre-graduation training for a comparative evaluation of the results (Table 1) (Haugen *et al.*, 2009).

**Table-1.** The content of vitamin D, endothelin and the concentration of renin in blood among the patients with the pregnancy period of 7-10 weeks

Indicators	Healthy pregnant (n=30)	The patients of risk group who underwent pregravid preparation by Ca and vitamin D (n = 36)	The patients of risk group who did not undergo pregravid training (35)	Difference significance, p
Vit D (ng/ml)	19,82±1,5	27,4±1,3	15,41±1,6	$p\chi^2=0,027$
Ionized calcium mmol/l	1,2±0,02	1,1±0,05	1,0±0,06	$p\chi^2=0,003$
Endothelin 1-38 (pmol/l)	0,05±0,02	0,04±0,02	0,05±0,02	$p\chi^2=0,010$
Renin	5,3±0,2	7,4±0,4	24,5±1,1	$p\chi^2=0,007$

As was shown in Table 1, the level of vitamin D during the period of pregravid preparation increased and approached the physiological norm among the patients taking vitamin D preparations, the concentration of renin in blood decreased slightly. The patients continued to receive drugs prior to delivery in the same doses. This choice allowed to increase the vitamin content in blood, and also maintained it at optimal values during pregnancy. It should be noted that the vitamin D content reached the norm of  $31.4 \pm 1.4$  ng/ml and was maintained at this level.

The re-examination of vitamin D level, and D binding protein was carried out at the period of 20 weeks (Table 2) (Maltseva *et al.*, 2016).

**Table-2.** The content of vitamin D, endothelin and renin concentration in blood among the patients at a period of 20 weeks

Indicators	The patients with a physiological course of pregnancy (n=30)	The patients of risk group who underwent pregravid preparation by Ca and vitamin D (n = 36)	The patients of risk group who did not undergo pregravid training (35)	Difference significance, p
Vit D (ng/ml)	19,82±1,5	31,4±1,4	12,76±1,1	$p\chi^2=0,023$
Ionized calcium mmol/l	1,2±0,02	1,0±0,07	1,04±0,01	$p\chi^2=0,005$
Endothelin 1-38 (pmol/l)	0,05±0,02	0,05±0,10,02	0,07±0,02	$p\chi^2=0,011$
Renin 3,3-31,7 pg/ml	5,9±0,2	7,1±0,4	24,2±1,1	$p\chi^2=0,008$

The most optimal course of pregnancy was observed among the patients taking vitamin D and Ca from the period of pregravid preparation and during pregnancy, the complications of the pregnancy course were more often recorded among the women who had not undergone pregravid preparation. Among the patients who used vitamin D and Ca during pregravid preparation and during pregnancy, the premature detachment of the normally located placenta (PDNLP) was observed 3 times less frequently, the placental changes in the form of its volume decrease or increase were 3 times less often, the syndrome of fetus delayed development was 3.6 times less often (Table 3) (González and Villalobos-Antúnez, 2016; Parlak *et al.*, 2015).

**Table-3.** The frequency and the nature of pregnancy complications among the women with pre-eclampsia risk who underwent pregravid preparation and received vitamin D and who did not receive pregravid preparation and vitamin D during pregnancy (%)

Pregnancy complication type	The patients of risk group who underwent pregravid preparation by Ca and vitamin D (n = 36)	The patients of risk group who did not undergo pregravid training (35)
Threat of abortion	2 (5,6%)	6 (17,1%)
Preeclampsia - moderate - heavy	0	5 (14,3%) 3 (8,5%) 2 (5,7%)
Water excess, water retention	2 (8,3%)	5 (14,3%)
FPN	3 (6,9%)	8 (22%)
Hypo- and hyperplasia of the placenta	2 (8,3%)	6 (17,1%)
PDNLP	1 (2,8%)	3 (8,6%)
G syndrome	2 (5,6%)	7(20%)

According to observations, the pregnant women who underwent pregravid preparation and continued taking vitamin D and Ca during pregnancy, had an optimal course of pregnancy - no cases of pre-eclampsia were noted. The women who did not take vitamin D during pregnancy developed late moderate preeclampsia at 35-36 weeks - 3

(8.5%) patients and severe course was observed among 2 (5.7%) patients, and therefore women were hospitalized and were delivered after 37-38 weeks. But the patients taking vitamin D and the preparation Ca and the group of pregnant women who received vitamin D in several cases, had no increase of vitamin D level and the improvement of perinatal outcomes. This is probably related to the characteristics of woman genotype. The pregnant women who underwent pregravid preparation and received vitamin D during pregnancy on the admission to the obstetric ward for delivery had vitamin D content of  $34.6 \pm 1.6$  ng/ml and renin concentration was  $8.1 \pm 1.1$ . At the time of delivery, the content of 25(OH) D ionized calcium among those who did not receive vitamin D was  $16.22 \pm 1.1$  ng/ml and  $1.1 \pm 0.01$  mmol/l, respectively, the renin concentration was  $29.2 \pm 3.9$ .

#### 4. Discussion

According to our results, it can be argued that among the pregnant women with the risk of pre-eclampsia development, who received vitamin D and calcium preparations during pregravid preparation and during pregnancy, the vitamin D level increases, the concentration of renin decreases and persists until the birth in physiological concentrations, and in cases of refusal from the preventive doses of vitamin D it often leads to preeclampsia. These patients have an increased renin concentration, which reaches 59.4 pg/ml at severe preeclampsia. All pregnant women were delivered by 37-41 weeks, spontaneous deliveries among the patients, taking vitamin D and Ca during pregravid preparation and during pregnancy, proceeded with the least number of complications, 2 (5.6%) pregnant women were promptly delivered. Whereas risk group patients who did not undergo pregravid training and who did not receive vitamin D during pregnancy were delivered promptly 3 times more often. The indications for cesarean section were the preeclampsia of severe grade 3 (8.5%), a premature detachment of normally located placenta 2 (5.7%) and threatening fetal asphyxia. In addition, the weakness of labor was observed among 5 (14.3%) expectant mothers.

Thus, it can be concluded that the physiological level of vitamin D contributes to the physiological course of labor. As the results of our studies have shown, the existing recommendations for pregnant women with vitamin D administration at a daily dose of 600 IU (US Institute of Medicine) cannot prevent vitamin D deficiency among the women with high risk of pre-eclampsia development. Multivitamin complexes for pregnant and lactating women cannot do this, as they usually contain small doses of vitamin D (305 IU on average) and calcium (80 mg on average). The need for further research on the individualization and the optimization of the appointment time and the dosages of vitamin D preparations is obvious. Our experience has shown that low provision among the women from PE risk group requires at least 4000 IU of vitamin D and 1.5 g of calcium during pregnancy. This dose stably increases the vitamin D levels in blood (more than 30 ng/ml) and can reduce the incidence of obstetric and perinatal complications with a high risk of preeclampsia. According to existing ideas in order to prevent complications associated with vitamin D deficiency during pregnancy, it is necessary to maintain the level of 25(OH)D with more than 30 ng/ml.

According to our results, it can be argued that the administration of drugs with vitamin D and Ca preparation for pregnant women with the risk of pre-eclampsia is more appropriate since the period of pregravid preparation. In the group of pre-eclampsia risk development which did not receive vitamin D during pregravid preparation and pregnancy, the threat of pregnancy termination was noted 3 times more often, FPI was 3 times more common, G syndrome was 4 times more likely, preeclampsia developed in 14.3% of cases, pregnant women were delivered by Cesarean section 3 times more often (Kazakova and Klyoster, 2018).

#### 5. Conclusions

1. The pregnant women with moderate and severe preeclampsia had the decreased content of vitamin D and ionized calcium in serum.
2. The availability of vitamin D and the level of ionized Ca among the women at risk is significantly lower ( $0.07 \pm 0.01$  mmol/l) than among the women not included in it ( $1.2 \pm 0.02$  mmol/l), and the renin concentration exceeded the mean values among the women from the control group.
3. Pregravid preparation and the continuation of vitamin D and Ca intake during pregnancy helps to reduce the level of renin and promotes the optimal course of pregnancy, no cases of pre-eclampsia have been reported.
4. The women who did not take vitamin D during pregnancy developed late preeclampsia after 35-36 weeks.

#### 6. Summary

Thus, according to our research, the intake of vitamin D from the period of pregravid preparation of women with high risk of pre-eclampsia development and during pregnancy can be a reliable and an effective method of this serious complication prevention.

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