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Review

Review: Influence of Vitamin D blood concentration and supplementation during pregnancy on preeclampsia development and neonatal outcomes.

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Abstract: Vitamin D plays an essential role in embryogenesis and the course of intra- and postnatal periods and is crucially involved in the functioning of the mother-placenta-fetus system. Low quantity of Vitamin D during pregnancy can lead to the elevated risk for preeclampsia occurence. Despite the numerous studies on the association of Vitamin D deficiency and preeclampsia development, the current research on this theme is contradictory. In this review we summarize and analyze study data on the effects of vitamin D deficiency and supplementation on pregnancy, labor, fetal and neonatal outcomes.

Keywords: preeclampsia; neonatal outcome; vitamin D; 25(OH)D, 1,25(OH)2D; diabetes; pregnancy complication; vitamin D deficiency; vitamin D supplementation.

1. Preeclampsia and vitamin D insufficiency/deficiency

Preeclampsia is a multisystem pathological condition that occurs after the 20th week of pregnancy and is characterized by arterial hypertension combined with proteinuria (≥0.3 g/l in daily urine), edema and manifestations of multiple organ dysfunction [1-3]. Preeclampsia occurs in 3-8% of pregnant women and is one of the top five causes of maternal morbidity and mortality [4-8].

The etiology and pathogenesis of preeclampsia are not fully understood. There are potential epigenetic, biochemical and biophysical biomarkers for predicting the development of this pathology. Numerous studies have confirmed the contribution of vitamin D concentrations to the development of preeclampsia [9-25].

Studies show the correlation between vitamin D concentration level and preeclampsia severity until 22 week of gestation [11, 27-28]. However, it is not clear whether the level of vitamin D is depleted due to the preeclampsia development or the low level of the vitamin D causes the preeclampsia to progress. It's also essential to determine whether the vitamin B level has a role in early-onset preeclampsia development or can act as a marker of it. In this review, we will analyze and discuss all the significant studies connected with the role of Vitamin D deficiency in preeclampsia development.

Early scientific evidence on the relationship between preeclampsia and Vitamin D was contradictory - a decrease in preeclampsia progression was associated with vitamin D administration, while the supplementation addition (such as calcium or halibut oil) was not linked with treatment and prevention of the disease. Recent studies have shown that low 25(OH)D concentrations are an independent risk factor for early and late onset [29-34]. For example, Ullah et al. found an up to 5-fold increase in the risk of developing preeclampsia and eclampsia in women with vitamin D deficiency [35].

For preeclampsia research, most of the measurements of vitamin D concentrations are collected from the blood of pregnant women. Halhali et al. (2007) refreshed and

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simplified this approach by showing that total urinary calcium excretion positively correlated with blood 1,25-dihydroxyvitamin D (1,25(OH)2D) concentration in both normotensive and preeclamptic women [36]. On the other hand, Hyppönen et al. investigated the relationship between vitamin D intake at an early age and the subsequent development of preeclampsia during pregnancy and found that the risk of preeclampsia was halved in women who received regular vitamin D supplements during the first year of life [37]. Bener et al. also noted a significant relationship between maternal vitamin D deficiency during pregnancy with an increased risk of not only preeclampsia, but gestational diabetes mellitus (GDM) and anemia [38]. So Scholl et al. found that some women with vitamin D (25-Hydroxycalciferol, 25(OH)D) deficiency developed secondary hyperparathyroidism, which was associated with an increased risk of preeclampsia [39].

Recent studies investigated the role of vitamin D concentration in gestational hypertension or preeclampsia [40-41]. In the context of preeclampsia, it is important to consider concentrations of the active form of vitamin D, 1,25(OH)2D. The enzyme 25-hydroxyvitamin D-1 alpha-hydroxylase (1 alpha-OHase) converts 25(OH)D to 1,25(OH)2D. In the preeclamptic placenta, this enzyme is significantly reduced, which can lead to insufficient concentrations of the active form of vitamin D [42]. According to available data, low concentrations of 25(OH)D do not necessarily lead to low concentrations of 1,25(OH)2D [34]. However, in a study by Abbasalizadeh et al. a mediated effect of vitamin D deficiency on the risk of developing preeclampsia through hypocalcemia was found, which increases the risk by 8.5 times [41].

These data support the existence of a threshold level of vitamin D after which the risk of preeclampsia may increase, both directly through regulation of gene expression and indirectly through changes in calcium metabolism.

2. Vitamin D concentrations in the first trimester of pregnancy (<14) complicated by preeclampsia

For early prediction and diagnosis of preeclampsia a number of researchers have sampled and analyzed whether vitamin D concentrations can affect the development of pathology in the first trimester of pregnancy. Results have shown that low blood 25(OH)D concentrations in the first trimester of pregnancy are not associated with adverse pregnancy outcomes and do not predict any complications [39, 43-47]. Although vitamin D concentrations were not associated with preeclampsia, Benachi et al. showed that women with vitamin D concentrations within the normal range in the 1st and 3rd trimesters of pregnancy had a significantly lower risk of developing preeclampsia. It emphasizes the hypothesis that there is a threshold effect of vitamin D concentration on the risk of developing preeclampsia: the risk of preeclampsia increases with vitamin D concentration <30 ng / ml [47]. This hypothesis is also supported by the results of Achkar et al. 2015, where vitamin D deficiency early in pregnancy (before 14 weeks), defined as 25(OH)D < 30 nmol/L, was an independent risk factor for the development of preeclampsia [48].

Overall, the data demonstrate that solely vitamin D concentrations cannot be used to forecast preeclampsia. However, women with a 25(OH)D deficiency <30 ng/mL are at increased risk and need to be prescribed supplements to normalize blood vitamin D concentrations.

The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance. The current state of the research field should be carefully reviewed and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the principal conclusions. As far as possible, please keep the introduction comprehensible to scientists outside your particular field of research. References should be numbered in order of appearance and indicated by a numeral or numerals in square brackets—e.g., [1] or [2,3], or [4–6]. See the end of the document for further details on references.

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3. Vitamin D concentrations in the second trimester of pregnancy (14-26) complicated by preeclampsia

Although there is no direct relationship between vitamin D concentrations and preeclampsia during the second trimester, a decreased maternal blood 25(OH)D concentration was found to be associated with an increased risk of preeclampsia [49-53] . However, some researchers have found no correlation [54-55].

4. Vitamin D concentrations in the third trimester of pregnancy (>26 weeks) complicated by preeclampsia

During the 3rd trimester total free and bioavailable maternal 25(OH)D3 correlated with placental 25(OH)D3 in the 3rd trimester, but this trend did not persist in preeclampsia [56-57]. Tamblyn, J A et al. showed that women with preeclampsia had significantly lower concentrations of 1,25(OH)2D3 and albumin than women with a normal pregnancy. However, concentrations of 25(OH)D3 were not significantly different. In contrast, women with preeclampsia had the highest blood concentrations of 3-epi-25(OH)D3 and 24,25(OH)2D3. The levels of 25(OH)D3 and 3-epi-25(OH)D3 in the placenta of women with preeclampsia were lower than in physiologic pregnancy, while 24,25(OH)2D3 concentrations were the highest in the preeclamptic placenta. In conclusion, preeclampsia is associated with decreased activation, increased catabolism, and impaired placental 25(OH)D uptake [57].

While comparing the results of measuring the concentration of vitamin D throughout pregnancy by different researchers, it was discovered that the concentration of vitamin D < 30 ng/ml in women with preeclampsia (Table 1). These results indicate the need to maintain an optimal level of 25(OH)D throughout the entire gestation period.

Table 1. 25(OH)D concentrations during normal and complicated by preeclampsia pregnancy.

Week of gestation	25(OH)D concentrations during normal pregnancy, mean ± SD (ng/ml)	25(OH)D concentrations during pregnancy complicated by preeclampsia, mean ± SD (ng/ml)	References
First trimester of gestation (< 14)			
12	19.44 ± 8.2	20.88 ± 8.2	[44]
14	18.88 ± 7.08	20.92 ± 6.88	[48]
First-second trimester of gestation			
12-18	20.1 ± 9.3	22.3 ± 11.1	[47]
12-18	19.33 ± 4.75	pre-eclampsia 12.29 ± 2.79 severe pre-eclampsia 9.56 ± 2.68	[52]
Second trimester of gestation (15-26)			
15-20	39.2 (27.2 - 45.2)[1]	30 (18.8-42.8)[1]	[31]
15-21	28.6 ± 12.6	27.4 ± 14.4	[54]
16	18.84-23.96 (21.24)[1]	18.16 (15.44-21.36)[1]	[11]
24-26	22.8 ± 7.64	19.56 ± 6.72	[49]

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Second - third trimester of gestation			
20-32	19.76 ± 9.04	16.92 ± 6.92	[57]
25-35	15.73 ± 5.85	10.09 ± 6.66	[27]
25-38	22.76 (17.56–28.32)*	All preeclampsia 21.84 (18.2–27.84)[1] Early-onset preeclampsia 21.4(16.96–24.68)[1]	[43]
25-39	14.9 ± 12.0	Severe pre-eclampsia 5.8 ± 4.5 Non-severe pre-eclampsia 11.8 ± 7.3	[53]
Third trimester of gestation (> 26)			
26-31	32 (20–44)[1]	18 (13–31)[1]	[30]
26-37	13.41 ± 8.05	6.88 ± 9.46	[20]
30	10.09 ± 6.6	15.73 ± 5.85	[15]
30-40	23.7 ± 5.93	19.3 ± 4.31	[14]
30-40	19.5 ± 6.5	14.8 ± 5.4	[22]
30-40	31.4 ± 1.7	11.0 ± 7.1	[28]
30–36	22.57 ± 4.33	pre-eclampsia 18.68 ± 3.50 severe pre-eclampsia 9.48 ± 2.98	[52]
32-38	30.8 ± 11.0	27.7 ± 12.2	[47]
35-40	24.86 ± 1.02	23.96 ± 1.31	[35]
35-41	23.84±6.93	15.27±3.52	[19]

[1] mean (min - max) 25(OH)D

5. Effect of Vitamin D Concentrations on Hypertensive Disorders in Pregnancy

According to several studies, low concentrations of 25(OH)D and 1,25(OH)2D correlate with high systolic and diastolic blood pressure (BP) during pregnancy [58-63] and only a few papers have demonstrated opposite results [64]. Because vitamin D is an approved supplement during pregnancy, Nassar, Seham Zakaria, and Noha Mohamed Badae tested the hypothesis of lowering systolic BP by vitamin D supplementation and found that its administration reduced systolic BP, proteinuria [65]. Thus, there is strong evidence for the need to measure vitamin D concentrations among pregnant women with any form of hypertension to prescribe optimal doses of vitamin D, thereby possibly providing a reduction in elevated systolic and diastolic blood pressure, reducing the risk of additional complications for the mother and fetus.

6. Impact of proteinuria on vitamin D concentrations during pregnancy complicated by preeclampsia

One of the key symptoms of preeclampsia is proteinuria-vitamin D binding protein (DBP) loss in the urine. For this reason, women with preeclampsia form a vulnerable vitamin D3 deficiency group, reabsorption of which occurs in the proximal renal tubules after endocytosis together with the vitamin D binding protein, because proteinuria contributes to damage and tubular dysfunction. Albejante et al. suggested that the

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proteinuria seen in preeclampsia may contribute to the loss of reabsorption of vitamin D along with other proteins in the urine. As a result, the authors were able to prove an association between preeclampsia and vitamin D3 deficiency, because proteinuria causes the loss of proteins responsible for reabsorption of vitamin D3 by renal tubules. In combination with other factors, proteinuria can accelerate vitamin D3 deficiency in preeclampsia [66]. Therefore, both the symptoms of preeclampsia, arterial hypertension and proteinuria are both associated with vitamin D deficiency. In addition, the optimal vitamin D concentrations before pregnancy can have a small impact on immunity and embryogenesis, while with an initial deficiency, additional loss of vitamin D can cause serious consequences, especially for fetal development.

7. Effect of Vitamin D Concentrations on the Risk of Preeclampsia in Diabetes Mellitus

Vitamin D metabolism changes rapidly during pregnancy. When it results in deficiency it starts associating with a number of adverse complications, including gestational diabetes and preeclampsia [67-70]. Pregestational diabetes type 1 or type 2 is a risk factor for preeclampsia. Preeclampsia is known to be diagnosed in 15-20% of pregnancies in women with type 1 diabetes and in 10-14% of pregnancies in women with type 2 diabetes and the incidence of preeclampsia in gestational diabetes mellitus (7.3%) is higher than in the general population (4.5%) [70].

The results of studies of the relationship between vitamin D status in a pregnant woman with type 1 diabetes and preeclampsia show that lower vitamin D concentrations were observed in women with preeclampsia due to type 1 diabetes compared with women with type 1 diabetes alone [71-74]. Several studies support an association between low blood 25(OH)D levels and an increased risk of GDM and preeclampsia [68-69]. In contrast, a recent case-control study found no evidence of an association between 25(OH)D levels in either the former or and in the second half of pregnancy and further development of GDM [75].

Despite the high prevalence of type 2 diabetes in pregnant women, the association with changes in vitamin D levels in pregnant women with type 2 diabetes and preeclampsia has not yet been studied [76]. Given the increasing prevalence of pregestational diabetes and GDM in pregnant women, future studies should continue to investigate the impact of vitamin D deficiency on the risk of developing preeclampsia in these pathologies.

8. Maternal vitamin D concentrations after delivery

While the conversion of vitamin D to 25(OH)D remains unchanged during pregnancy, the conversion of 25(OH)D to 1,25(OH)2 D during pregnancy is unique. Recent research data indicate that starting early in pregnancy, serum 1,25(OH)2 D concentrations increase and reach a 3-fold increase in the third trimester. Moreover, 1,25(OH)2 D levels may be influenced by the placenta, which contains the enzyme CYP27B1 (25-hydroxyvitamin D3 1-alpha-hydroxylase) and produces 1,25(OH)2 D [77-78].

9. The influence of maternal vitamin D concentrations on the health of newborns and young children

The vitamin D and the optimal amount of its metabolites contribute to the development of the fetus and minimize the risk of adverse pregnancy outcomes. The depleted levels of vitamin D in the body of a pregnant woman contributes to an increase in the incidence of health complications not only in the mother, but also in newborns [11, 79-80], including from pre-eclamptic mothers [50, 79-92]. Study shows more than half of the children born prematurely have vitamin D deficiency (less than 20 ng/ml) [93]. The protective effect of vitamin D has been demonstrated in a study by Vasilyeva et al., 2017 showing a reduction in adverse neonatal outcomes such as fetal growth retardation,

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hypoxia, fetal cerebral injury, and vitamin D deficiency with vitamin D supplementation at a concentration of 4000 IU/day [94].

The insufficient amount of vitamin D is associated with many adverse neonatal outcomes: vitamin D deficiency in newborns [11, 79–80], births premature and small for gestational age children [50, 87-95], low birth weight [92], limitation of head growth, length and weight of the fetus in the third trimester [92], Apgar score at 1 and 5 minutes < 7 points [96], respiratory syncytial infection in children at 1 year of age [97], deterioration of respiratory status [98], BPD in preterm infants [99] (Table 2).

Table 2. Vitamin D threshold concentrations associated with adverse neonatal and postnatal outcomes.

Adverse Neonatal and Postnatal Outcomes	Vitamin D Threshold Concentrations in ng/ml	Reference
Neonatal Outcomes		
Vitamin D Deficiency in Newborns	<12	[79]
Low Body Mass at Birth	<30	[50]
Birth of Premature Babies	<20	[93]
	<30	[95]
Apgar score at 1 and 5 minutes < 7 points	<30	[96]
Deterioration of Respiratory Status	<12	[98]
BPD in Premature Infants	<20[1]	[99]
Postnatal Outcomes		
Respiratory Syncytial Infection in Children at First Year of Life	<20	[97]

[1]Vitamin D deficiency at 1 month of age.

Nevertheless, not all researchers have found an association between vitamin D deficiency and neonatal outcomes [103-104]. The following researchers Velkavrh M, Wierzejska R, Levkovitz O did not confirm the relationship between maternal vitamin D concentration with weight, body length, and head circumference of the newborn [104-106]. Cooper et al. (2016) showed that whole body bone mineral content in infants born to mothers administered cholecalciferol 1000 IU/day was not significantly different from that in infants born to mothers administered placebo [107].

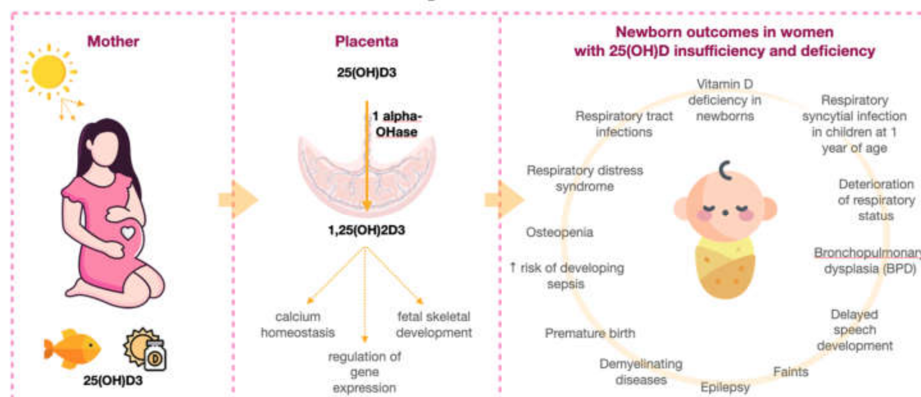

Figure 1. Neonatal outcomes in conditions of maternal vitamin D insufficiency and deficiency.

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Vitamin D deficiency during pregnancy impairs fetal skeletal formation and leads to reduced fetal bone mass, but also has a certain effect on the child's susceptibility to diseases immediately after birth, since vitamin D affects the synthesis of surfactant and one of its properties is the ability to stimulate the formation of peptides (β2-defensins and cathelicidins) with pronounced bactericidal activity [108-116]. In addition, vitamin D can regulate both adaptive and innate immune responses at the fetal-maternal interface [113-114]. Vitamin D is a neurosteroid that is essential for the division, growth and differentiation of neurons and has a neuroprotective and neurotrophic effect. For these reasons, insufficient intake of vitamin D in the fetus causes a decrease in the levels of neurotrophic factors in the brain of newborns (NGF, p75NTR, GDNF]) and may lead to a delay in the formation of fetal brain structures [116-117].

The vitamin D deficiency in pregnant women adversely affects the postnatal development of children, especially when the level of vitamin D in the mother's blood serum is less than 50 nmol/l (<20 ng/ml) [50, 82, 114]. Furthermore, 25(OH)2D deficiency in the early postnatal period may result in delayed speech development, fainting, epilepsy, and a number of demyelinating diseases [118-120]. In addition, it has been shown that preschool children with attention deficit hyperactivity disorder at birth had low levels of 25(OH)D3 in the cord blood compared to newborns without this pathology [121-122]. Vitamin D deficiency at birth can cause bronchial asthma in children of the first 10 years of life [99-100]. A study by Thiele et al. (2017) showed a linear dependence of the dynamics of the physical development of children at the age of 18 months on the level of vitamin D in the umbilical cord blood [81].

The level of 25(OH)D3 in the cord blood of a child is 50–80% of its level in the mother's blood serum, regardless of the gestational age [111]. Since 25(OH)D3 deficiency is widespread among pregnant women, this explains the large number of newborns with vitamin D deficiency by the appointment of vitamin D supplements during pregnancy. At the same time, it was noted that the most important factor that allows the concentration of 25(OH)D3 in the blood serum of pregnant women and, as a result, newborns, is the appointment of vitamin D supplements during pregnancy [123-125].

10. Safety of vitamin D supplements prescription during pregnancy

The period of pregnancy is a high-risk state for both mother and fetus. It is important to conduct qualitative and quantitative research to prescribe any supplement, especially for hormone-like vitamin D. As some preclinical animal studies show that there is a potential dose-dependent toxicity of vitamin D to the fetus - growth failure, skeletal malformations, and cardiovascular anomalies. However, Roth (2011) found no data on the teratogenic effects of vitamin D on women during pregnancy and their newborns [126]. (Roth 2011) Magielda-Stola et al. stated that vitamin D supplementation is a safe treatment option with no risk of side effects or toxicity. Vitamin D supplementation should be given at the planning stage of pregnancy in order to get the most beneficial effect, with serum vitamin D levels in excess of 30 ng/mL [127].

11. Effect of vitamin D supplementation on pregnancy complicated by preeclampsia

Medical community suggests that vitamin D supplementation can help prevent preeclampsia and increase vitamin D levels to optimal levels, including in newborns [123-125]. Vitamin D supplementation was used as early as 1942. Taking 1200 IU/day of vitamin D with calcium (375 mg/day) for 8–10 weeks by a pregnant woman reduced blood pressure in women susceptible to preeclampsia, thereby reducing the incidence of pathology [128]. Numerous studies have demonstrated that vitamin D supplementation reduces the risk of preeclampsia [129-135].

The effect of vitamin D supplementation may vary depending on the initial maternal serum concentrations of the vitamin, the dosage administered, and the frequency of administration. In a study by Zatollah et al. showed that multimineral supplementation of vitamin D (800 mg calcium, 200 mg magnesium, 8 mg zinc and 400 IU vitamin D3) for

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9 weeks in pregnant women at risk of preeclampsia led to an increase in circulating levels of calcium, magnesium, zinc and vitamin D in maternal serum and a decrease in both systolic and diastolic blood pressure [136]. According to Maryam et al. after supplementation without prior assessment of vitamin D levels, only 2% of women achieved sufficient vitamin D levels (>20 ng/mL) compared with 53% of women who participated in screening. Adverse pregnancy outcomes, including preeclampsia, gestational diabetes mellitus, and preterm birth, were reduced by 60%, 50%, and 40%, respectively, at the screening site. An additional injection of D3 at a dosage of 50,000 IU in addition to monthly maintenance therapy most contributed to the achievement of sufficient vitamin D concentration during labor [137]. These data suggest that optimal vitamin D concentrations, which can be achieved with supplementation, reduce the risk of disease. Moreover, in a study by Skowrońska-Jóźwiak et al. (2014), half of the subjects who reported taking vitamin D failed to reach the optimal serum 25(OH)D concentration [138].

The vitamin D supplementation can improve insulin sensitivity and glucose tolerance, which are the main pathophysiological disorders in diabetes (DM1, T2DM, GDM) - a risk factor for preeclampsia [139–142]. Samimi et al. noted that high-concentration vitamin D supplementation along with calcium (50,000 IU vitamin D3 every 2 weeks and 1,000 mg calcium daily) for 12 weeks beneficially affected glycemic status, HDL-cholesterol, GDM incidence, and blood pressure among susceptible women. risk of preeclampsia [143]. In another study, administration of 50,000 IU 25(OH)D every 2 weeks from 20 to 32 weeks of gestation resulted in a significant increase in antioxidant system proteins and had a beneficial effect on lipid and insulin metabolism [144]. In a clinical trial where pregnant women at 12-16 weeks of gestation with a serum 25(OH)D concentration of less than 30 ng/mL received vitamin D supplements (50,000 IU) every 2 weeks, Mahdieh et al. 2015 noted a decrease in the incidence of GDM, but no difference was observed between neonatal outcomes [145].

Vitamin D supplementation during pregnancy also has a positive effect on neonatal outcomes. When taking low doses (≤2000 IU/day) of vitamin D, there is a significant reduction in the risk of intrauterine or neonatal mortality, as well as the formation of a small fetus by gestational age [146]. Zatollah et al. (2015) found a multimineral vitamin D supplement during pregnancy with the risk for preeclampsia resulted in an increase in neonatal body length [147]. Higher doses of vitamin D (1000-4000 IU/day) have been used by Faustino et al. and found that these doses may be convenient to achieve better outcomes for improving maternal, fetal, and subsequent offspring health [148]. In a study by Nausheen et al. (2019) also found that vitamin D supplementation 4,000 IU per day was more effective in reducing vitamin D deficiency among pregnant women and in improving serum 25(OH)D levels in mothers and their newborns compared to 2,000 IU per day and 400 IU per day [149]. In a study by Vasilyeva et al. (2017), a comparative assessment of the condition of newborns from women at high risk of preeclampsia with preconception preparation with vitamin D at a dose of 4000 IU/day in comparison with no supplementation received group[94]. Women who received 4000 IU/day of vitamin D, the level of 25(OH)D3 was 2.2 times higher (28.3±1.5 ng/ml versus 12.4±1.1 ng/ml). ml, respectively, $p<0.05$) had newborns with the decreased frequency of clinical syndromes (fetal growth retardation, hypoxia and cerebral lesions of the fetus) compared to the control group. However, not all researchers found a similar effect. Mirzakhani et al. showed that vitamin D levels of 30 ng/ml or higher at the beginning and at the end of pregnancy were associated with a lower risk of preeclampsia development, while vitamin D 4400 IU started between 10 and 18 weeks of gestation did not reduce the incidence of preeclampsia [150].

In conclusion, the administration of vitamin D - 50,000 IU of vitamin D3 once every two weeks appears to be protective against recurrent preeclampsia. Moreover, vitamin D therapy during pregnancy may help reduce the incidence of gestational hypertension [151].

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12. Recommendations for the prevention of pregnancy complications with vitamin D supplements.

The currently existing national and international clinical recommendations for the intake of vitamin D during pregnancy differ significantly from each other. Various investigators have noted the need for vitamin D supplementation, but have considered different dosages: 200 IU [152], 400 IU [153–154], 600 IU [155], 50,000 IU [144–145]. Grant (2010) concluded that blood levels of 25(OH)D should be 80 nmol/L for optimal health. However, they found that 1000 IU of vitamin D per day increased serum 25(OH)D levels by about 10 ng/mL [156]. However, a meta-analysis of studies on the effect of vitamin D supplementation on the occurrence of pregnancy complications in the Cochrane database, considered the current "gold standard" of evidence-based medicine, did not answer the question of whether vitamin D supplementation should be used as a standard preparation for pregnancy planning [130]. The European Food Safety Authority (EFSA) states that the adequate intake of vitamin D for pregnant women remains the same as for non-pregnant women, at 600 IU per day [157]. These recommendations assume good nutrition and minimum effective exposure to the sun.

Recommendations for vitamin D supplementation to prevent pregnancy complications vary greatly from country to country. The International Endocrinological Society (clinical recommendations from 2011) recommends taking 1500-2000 IU per day. while the US Institute of Medicine (IOM) does not recommend >600 IU per day for pregnant women due to safety concerns. However, experts suggest that in the case of suboptimal 25(OH)D concentrations, it may be necessary to increase the daily dose to 1500-2000 IU with a maximum allowable dose of 4000 IU [158]. The Argentine Federation of Endocrinological Societies suggests 800-1200 IU per day. The new IOM and American Academy of Pediatrics proposal for children from birth to one year of age is 400 IU per day, and between 1 and 18 years of age 600 IU per day [159]. According to Russian clinical guidelines, pregnant and lactating women need to take at least 800-1000 IU of vitamin D per day. When vitamin D deficiency is detected, adequate correction of levels at a dose of 1500-4000 IU per day is necessary [160].

Although there is no consensus on the optimal dose of vitamin D during pregnancy, it is recommended to maintain optimal levels of vitamin D in the blood of pregnant women. The administration of the supplemental dosage should be calculated depending on the region of residence, lifestyle and nutrition [38]. Recent scientific evidence suggests the relevance of using high doses (50,000 IU) of vitamin D every 2 weeks instead of weekly low doses of vitamin D (200-400 IU), but there is still a question about the duration of supplementation [137, 144-145].

13. Conclusions

The results of numerous studies suggest that blood vitamin D concentrations alone cannot be used to predict preeclampsia. However, women with 25(OH)D deficiency <30 ng/mL are at increased risk and require supplementation to normalize blood vitamin D concentrations. The amount of severe neonatal outcomes and negative long-term consequences in children increases with maternal vitamin D concentrations <20 ng/ml. Moreover, low concentrations of 25(OH)D and 1,25(OH)2D correlate with high blood pressure and proteinuria during pregnancy.

Vitamin D insufficiency and deficiency in pregnant women can be compensated by supplementation containing 25(OH)D, with every 1000 IU of vitamin D/day increasing serum 25(OH)D concentration by 10 ng/ml, and the use of large doses of vitamin D (50,000 IU) every 2 weeks reduces the risk of developing both preeclampsia and other pregnancy complications along with negative neonatal outcomes.

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