

# The role of vitamin D in perinatology – what do we know at the beginning of 2018? An up-to-date review

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## Abstract

The role of vitamin D in perinatology is a subject of major interest in current medicine. There is growing evidence about the role of maternal vitamin D levels in pregnancy outcomes. The aim of this review is to summarize the current literature about the role of vitamin D in perinatology. Evidence from this review suggests associations between low levels of maternal vitamin D and higher risk of certain obstetrical complications. Vitamin D has been found to be related to preeclampsia, gestational diabetes mellitus, low birth weight, and preterm birth. The current literature supports vitamin D supplementation in pregnant women, but more high-quality data are necessary. The problem that remains is how to achieve an optimal 25-hydroxyvitamin D level. To determine the real benefits of vitamin D supplementation in pregnancy, we need high-quality trials in larger groups.

**Key words:** gestational diabetes mellitus, low birth weight, preeclampsia, preterm birth, vitamin D.

## Introduction

### Vitamin D – overview, sources, and metabolism

Vitamin D, also known as calciferol, is a fat-soluble steroid (a prohormone) playing an important role in various metabolic and physiological pathways [1–4]. Vitamin D is crucial in the regulation of calcium homeostasis, especially in bones, where it promotes mineralization [5–7]. Vitamin D receptors are present all over the human body, from bones and muscles to the central nervous system [8, 9]. The main source of vitamin D for the body is sunlight exposure, but it can also be extracted from diet or food supplements. Fish, fish oils, and dietary supplements enriched with vitamin D are valuable sources of this vitamin [10, 11]. Vitamin D may be found in two forms: ergocalciferol (vitamin D<sub>2</sub>) and cholecalciferol (vitamin D<sub>3</sub>) [12]. Vitamin D<sub>2</sub> is obtained from plants, whereas vitamin D<sub>3</sub>

is synthesized in the sunlight-exposed skin from 7-dehydrocholesterol under ultraviolet B radiation [2, 13–15]. Vitamin D bound to vitamin D binding protein is transported to the liver where it is hydroxylated to 25-hydroxyvitamin D (25(OH)D) [15, 16]. The next hydroxylation takes place in the kidneys, where 25(OH)D is converted into 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), the active form of vitamin D [14–16].

### Vitamin D – serum concentration values

According to available scientific data, the level of serum vitamin D concentration is best reflected by 25(OH)D, due to its long life and stability [3, 17]. The values defining vitamin D deficiency are the subject of a heated debate among experts, and probably no consensus will be reached in the near future. According to the Endocrine Society and its official guidelines, vitamin D deficiency is defined as a serum level of 25(OH)D lower than 20 ng/ml, whereas vitamin D insufficiency is a serum level of 25(OH)D from 21 to 29 ng/ml. The level of vitamin D which can be defined as sufficient is set at 30 ng/ml [4, 18]. It is believed that the calcium absorption is optimal at this level [3, 4, 18]. According to the latest review by Holick, the ultimate goal should be to keep the 25(OH)D serum level above 30 ng/ml, with the preferred range being 40–60 ng/ml [4] (Table 1).

### Vitamin D deficiency – a worldwide problem

Several studies have revealed that vitamin D deficiency is a worldwide problem in all people regardless of their age, sex, or social status [1, 19, 20]. What is already known is that the main causes of vitamin D deficiency in female populations are incorrect supplementation and insufficient exposure to sunlight (e.g. due to spending most of their time in closed rooms or living in northern lands) [3, 10, 11, 21, 22]. Factors influencing lower photon absorption (thus reducing the conversion of vitamin D to the skin) are older age, sunscreens, low sun exposure, geographical latitude, winter season, and increased skin pigmentation [23]. The latter factor is particularly important for African Americans, in which skin melanin content is much higher than that of other races [24, 25].

**Table 1.** Serum vitamin D concentration status in humans – classification

Condition	25(OH)D serum concentration [ng/ml]
Vitamin D deficiency	≤ 20
Vitamin D insufficiency	21–29
Vitamin D sufficiency	≥ 30
Optimal vitamin D status	40–60

According to studies performed by Palacios *et al.*, pregnant and lactating women showed a high incidence of vitamin D deficiency [26, 27]. The problem of reduced vitamin D level and its association with many childhood and adult diseases is well known and its importance has finally come to the consciousness of both physicians and patients [28]. In current medicine, awareness about the detection of vitamin D deficiency in pregnant women remains a problem [29, 30]. While vitamin D serum status examination and supplementation in newborns and in older children is a daily practice, it is often treated as a secondary problem in pregnant women.

### Vitamin D – role in pathophysiology

Vitamin D is an important link in inflammatory pathways [31]. It regulates immunological, circulatory and neurological processes [3, 32–36]. In adults (but also in the perinatal period) vitamin D regulates the immune system and is an anti-inflammatory agent that slows down the expression of pro-inflammatory cytokines and chemokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interferon  $\gamma$  (INF- $\gamma$ ), and interleukin 6 (IL-6) [31, 34, 37–39]. Steroid hormones (e.g., estrogens and progesterone) and human chorionic gonadotropin (HCG) are also connected with vitamin D pathways according to several available studies [38, 40].

The active metabolites of vitamin D have broad and diverse biological functions. According to older and recent reports, vitamin D deficiency is widely associated with many different conditions (e.g., type 1 diabetes mellitus, malignant neoplasms, cardiovascular diseases, etc.) [3, 33, 35, 41–43]. Other illnesses, which are not less important, are chronic kidney disease (kidney failure), gastrointestinal illnesses, and liver failure [41, 44].

### Vitamin D – role in uncomplicated pregnancy

Vitamin D plays a major role in human reproduction. The effect of vitamin D on pregnancy is a subject of major interest in current medicine. Vitamin D influences folliculogenesis, modulates endometrial receptivity, and regulates embryogenesis [45]. It plays an important role in trophoblast invasion [46]. There are plenty of studies that prove its effects on placental implantation, angiogenesis and endothelial function, immune function, inflammatory response during pregnancy, oxidative stress, and glucose homeostasis [47–53]. According to Hollis and Wagner, vitamin D plays an important role in embryo and fetal skeletal development [54]. The most important role of vitamin D during pregnancy is to elevate placental calcium transport [55]. Vitamin D status during pregnancy relies mostly on the mater-

nal stores [27]. During pregnancy, mobilization of maternal calcium increases to ensure adequate fetal bone mineralization [55]. 25(OH)D is a metabolite that crosses the placental barrier and is the main form of vitamin D used by the fetus [56–58]. Appropriate 25(OH)D serum concentrations are important to sustain the increased levels of 1,25(OH)<sub>2</sub>D during pregnancy [27, 59]. 1,25(OH)<sub>2</sub>D serum levels increase in early pregnancy and continue to grow until delivery [60]. Park *et al.* very recently reported that higher maternal vitamin D serum biomarker levels (maternal free 25(OH)D and 24,25(OH)<sub>2</sub>D) might be connected with attenuated bone resorption during the third trimester and proper calcium delivery to the fetus [61].

### Vitamin D and pathophysiology of pregnancy

There is growing interest in the effect of maternal vitamin D concentrations on pregnancy outcomes [62]. Maternal vitamin D status is proved to be associated with various obstetrical outcomes, such as early miscarriages, but also in the pathophysiology of other important obstetric complications [63–65]. The studies on vitamin D intake and its role in protection against adverse pregnancy outcomes differ, but there are still no large randomized control trials (RCTs) or clear guidelines regarding this problem [49, 55, 66]. One good available RCT, by Hollis *et al.*, included women with a singleton pregnancy at 12 to 16 weeks' gestation who received different daily doses of vitamin D until delivery [59]. There are still many contradictory opinions.

There are studies that suggest the increase of vitamin D deficiency in pregnant women and its connection with adverse pregnancy outcomes (maternal, fetal and in child) such as preeclampsia, gestational diabetes mellitus (GDM), preterm birth, low birth weight, impaired neurodevelopment, asthma development or future problems with body composition [49, 66–70]. As these four (preeclampsia, GDM, preterm birth and low birth weight) are the major problems in perinatology, and vitamin D deficiency during the perinatal period is one of the most common healthcare problems worldwide [27, 49, 71, 72], we decided to review available literature in this field.

The aim of this review is to summarize the current literature about the role of vitamin D in perinatology at the beginning of the year 2018. We have focused on preeclampsia, GDM, preterm birth, and low birth weight – the four major problems in current perinatology – and their relationship with vitamin D.

### Material and methods

This article presents an up-to-date review of publications about the current role of vitamin D

in perinatology. The main aim of our review was to critically review the influence of vitamin D in pregnancy and limited birth outcome (low birth weight). A literature search for this review was conducted in PubMed of the National Library of Medicine using the following keywords: “vitamin D”, “preeclampsia”, “gestational diabetes”, “preterm birth”, “intrauterine growth restriction”, and “low birth weight”. The above keywords were chosen to reflect the four major issues in current perinatology that influence both mother and fetus. The above problems are those that can be diagnosed during pregnancy and in the case of detection, a treatment attempt can be implemented. The other vitamin D related birth outcomes such as wheezing, asthma, autism, rickets, etc. were excluded due to the lack of possible diagnosis during pregnancy. During our search we combined the keywords into pairs, which resulted in: “vitamin D” and “preeclampsia” – 307 publications; “vitamin D” and “gestational diabetes” – 274 publications; “vitamin D” and “preterm birth” – 374 publications; “vitamin D” and “intrauterine growth restriction” – 41 publications; “vitamin D” and “low birth weight” – 368 publications. If the search was duplicated the papers were excluded. We selected papers that concerned the influence of vitamin D on selected pregnancy outcomes. The results of relevant original studies and reviews published in the English language up to May 2018 have been summarized and discussed in this consistent review. Additional different types of articles and reviews were considered when relevant.

There are many differences in methods to assess serum 25(OH)D and there might be some inconsistencies related to this when comparing different trials [73–75]. This is why some results should be interpreted with caution.

It might also be pointed out that according to recent findings vitamin D RCTs should be based on 25(OH)D concentrations, not vitamin D dose as proposed by Grant *et al.*, who proposed an observational approach to vitamin D RCTs' design, based on serum 25(OH)D concentration. That can prevent mistakes related to ultraviolet B (UVB) exposure and non-vitamin D molecular mechanisms [76].

## Discussion

### Preeclampsia

Preeclampsia is a pathological condition of pregnancy complicated by hypertension (high blood pressure), proteinuria, and coexisting dysfunction of selected organs (e.g., liver, blood, and kidneys) or other pregnancy complications (e.g., intrauterine growth restriction) [77, 78]. The incidence is estimated to be between 3% and 10% of all pregnancies [77, 79]. It is associated with

adverse perinatal outcomes and can cause long-term complications in both mother and fetus [78]. Even in the age of better perinatal care, it is still a leading cause of maternal death [79].

Abnormal maternal spiral artery remodeling during trophoblast invasion is believed to be the major cause of preeclampsia [77, 80]. There is still conflicting evidence whether vitamin D deficiency in pregnancy is associated with preeclampsia. The pathogenesis of preeclampsia involves a number of biological processes (e.g., inflammation, immunity, immune response, and angiogenesis) – all of them might be vitamin D-dependent [27]. According to the study by Chan *et al.*, vitamin D promotes extravillous trophoblast invasion [81]. Increased catabolism and abnormal placental uptake of 25(OH)D are believed to be associated with preeclampsia [82]. An interesting study from Australia revealed that the highest incidence of hypertensive disorders in pregnancy was associated with pregnancies giving birth in winter (low sun exposure) [83]. Vitamin D has been shown to be involved in gene regulation and expression signaling in early placental development [84]. Vitamin D plays a critical role in angiogenesis and oxidative stress control, which might be crucial in its relationship with preeclampsia [85–87]. Vitamin D has also been found to regulate angiogenesis with an influence on vascular endothelial growth factor genetic pathways. In the study by Schultz *et al.*, vitamin D was found to be associated with the expression of soluble fms-like tyrosine kinase-1 (sFlt-1) and vascular endothelial growth factor [88]. An interesting observation was that a maternal status of > 40 ng/ml can have an impact on related gene transcription and potentially decrease antiangiogenic factors that may result in better placentation [88]. According to Jia *et al.*, 1,25(OH)<sub>2</sub>D plays a major role in placental vasculature by relaxing smooth muscle cells [89]. In a study by Chinese scientists, 1,25(OH)<sub>2</sub>D was found to play a major role in reducing apoptosis in ischemic placentas. It was concluded that vitamin D might have potential anti-preeclampsia protection properties [90].

Robinson *et al.* investigated the association between low maternal vitamin D status and early, severe preeclampsia [91]. In their results, total 25(OH)D was decreased at the moment of diagnosis of early onset preeclampsia. A year later they published a study where they found lower 25(OH)D serum levels in patients with early onset preeclampsia with abnormal fetal growth in comparison to patients with preeclampsia and normal fetal weight [92]. One of the major facts that can be established from several studies is that an increased risk for preeclampsia is reported in women with vitamin D deficiency (serum levels under 20 ng/ml) [64, 65, 93, 94]. The findings

of other observational studies on vitamin D and preeclampsia are mixed. Some of them show an association between lower vitamin D serum levels and increased risk of preeclampsia [95–97], whereas others refute this association [98, 99]. The conflicting results are likely due to the differences in study design, different populations, geographic latitude, vitamin D measurement, and other factors [100]. In the PREvitD case-control study, low maternal 25(OH)D serum levels were associated with increased risk of preeclampsia, but after adjustment the authors concluded that there is a high probability that this is not a causal association [101]. According to the study by Bodnar *et al.*, vitamin D deficiency may be a risk factor for severe preeclampsia, but it is not associated with preeclampsia overall [96]. Palacios *et al.* reviewed several studies and (based on their data) confirmed that vitamin D deficiency is significantly associated with an increased risk of preeclampsia [27]. A very recent systematic review and meta-analysis by Akbari *et al.* found that women with vitamin D deficiency (serum levels lower than 20 ng/ml) are at higher risk of preeclampsia [102]. On the other hand, a meta-analysis of Spanish studies by Martinez-Dominguez *et al.* failed to confirm this dependence [103]. What about supplementation? A D-tect study from Denmark, which included more than 73 000 women (years 1983–1988), presented data indicating that fortified margarine (1.25 µg vitamin D/100 g margarine) did not influence the total risk of preeclampsia in any of the studied groups [104]. However, what is even more interesting, additional vitamin D supplementation in fetal life reduced the risk of preeclampsia later in life [105]. The study by Haugen *et al.* based on a group of more than 23 000 women found that proper vitamin D supplementation reduces the risk of preeclampsia by 27% [106]. According to Robinson *et al.*, an increase in maternal serum of 10 ng/ml of 25(OH)D reduces the possible risk of preeclampsia [92]. A recent study by Naghshineh also found a lower frequency of preeclampsia in pregnant women who received vitamin D supplementation in comparison to controls, but without statistical significance [87]. Additionally, a recent systematic review by Purswani *et al.* found that vitamin D supplementation did not have an independent effect on preeclampsia prevention [107]. In our opinion, these doubts should be resolved by future high-quality, well-designed studies on larger groups.

### Gestational diabetes mellitus

Gestational diabetes mellitus is a pathological condition in the pregnancy period in which a woman without diabetes develops hyperglycemia (high blood sugar levels) [108]. Pregnancy

confers a state of insulin resistance and hyperinsulinemia. The GDM is considered to share the same pathogenesis pathway as type 2 diabetes mellitus. The risk factors for GDM are being overweight, GDM in previous pregnancies, a positive family history of type 2 diabetes mellitus, and polycystic ovarian syndrome [108]. Vitamin D receptor and  $1\alpha$ -hydroxylase have been found in the placenta, suggesting that they play a role in its metabolism [81, 109]. How does vitamin D deficiency influence GDM occurrence? There are several pathways [53], but the most important are calcium pool dysregulation in the pancreas, an effect on insulin sensitivity and responsiveness, interactions of vitamin D with the insulin-like growth factor (IGF) system and inflammation generation [109].

Low serum levels of 25(OH)D have been related to the risk of developing type 2 diabetes in women [110]. Vitamin D deficiency is associated with impaired glucose tolerance and diabetes in the general population [111, 112]. The recent meta-analysis by Akbari *et al.* demonstrated that vitamin D supplementation might lead to an improvement in insulin resistance parameters (e.g., improvement in insulin resistance index and low-density lipoprotein cholesterol levels) [113]. Quite similar results were obtained in the recent study by Maktabi *et al.* where vitamin D supplementation had beneficial effects on glucose-related parameters in patients with polycystic ovarian syndrome [114].

There has been increasing evidence about the role of vitamin D in modifying the risk of GDM [109]. Maternal 25(OH)D serum levels have been found to be related to the risk of GDM in various studies [95, 115, 116]. Bener *et al.* in their study on 1873 women found that vitamin D deficiency was significantly associated with higher risk of GDM occurrence [95]. In the studies by Lacroix *et al.* and McManus *et al.*, the positive relationship between low 25(OH)D serum levels and GDM was also proven [117, 118]. Similar observations were made by Al-Ajlan *et al.* in Saudi Arabian women [119]. There are some well-performed systematic reviews and meta-analyses about the above-mentioned problem – in both of them lower vitamin D levels were found to be associated with the increased risk of developing GDM [65, 120–123]. According to the meta-analysis by Palacios *et al.*, vitamin D deficiency in early pregnancy was associated with elevated risk of developing GDM [27]. The meta-analysis by Zhang *et al.* found that low blood vitamin D level increases the risk of GDM, while vitamin D supplementation during pregnancy reduces the risk of GDM occurrence [123]. In a meta-analysis by Hu *et al.* 4,634 women diagnosed with GDM showed that maternal vitamin D insufficiency was associated with increased risk

of GDM by 39% [122]. The results obtained by Casey *et al.* from an Irish population found weak associations between 25(OH)D serum levels and markers of glucose and insulin metabolism [28]. A study by Hauta-Alus *et al.* found that a maternal vitamin D status specified as 25(OH)D serum level above 20 ng/ml may be sufficient for the physiological requirements of pregnancy [124]. On the other hand, negative dependence between vitamin D and GDM was found in the review of Spanish studies [103]. There are also several different studies in which vitamin D failed to prevent the development of GDM in pregnant women [72, 125, 126], such as the study by Makgoba *et al.*, which found no association between maternal first-trimester circulation of 25(OH)D and development of GDM [127].

In our opinion, the lack of repeatability of the results encourages further research in this field. Large prospective studies to finally evaluate the role of vitamin D in GDM are a must. It is important to select groups appropriately. Ethnicity, body mass index, and accompanying complaints can modify the results and lead to various conclusions. The moment of vitamin D level determination is crucial, which is why not all studies are comparable.

What about vitamin D supplementation in GDM? There have been various trials investigating vitamin D supplementation in the prevention or reduction of the risk of developing GDM. According to Robinson, vitamin D supplementation might be a low cost nutritional intervention to reduce GDM [128]. The study by Soheilykah *et al.* showed that supplementation with high doses of vitamin D in pregnant women significantly improved insulin resistance, which is why they concluded that low serum levels of 25(OH)D were related to insulin resistance during pregnancy [129]. Zhang *et al.* found that vitamin D supplementation during pregnancy reduces the risk of GDM occurrence [123]. In an interesting study by Yap *et al.*, two groups of vitamin D deficient women were supplemented with different doses of vitamin D – no differences in pregnancy outcomes were found [130]. There are also current meta-analyses that have presented the same incidence of GDM development in groups with and without vitamin D supplementation [13, 131]. In their review, Agarwal *et al.* concluded that vitamin D supplementation in the prevention of GDM is irrelevant [66].

### Low birth weight

Fetal growth restriction is a major problem in current perinatology. Intrauterine growth restriction, which may account for being small for gestational age (SGA) or low birth weight, greatly increases the risk of negative perinatal outcomes

and the probability of metabolic diseases later in life [132, 133]. Vitamin D, as a pleiotropic agent, regulates fetal growth and metabolism starting in early embryogenesis [54]. Vitamin D status during pregnancy plays a major role in musculoskeletal development, tooth enamel formation, fetal growth, and neurological development [134]. One of the most important clues may be the optimal fetal bone growth when maternal vitamin D serum levels are sufficient [135]. The study by Puthuraya *et al.* investigated whether vitamin D is associated with placental inflammation in very low birth weight fetuses, but found no correlation [136]. In a recent study by Workalemahu *et al.*, common placental genetic variations were investigated to identify associations between the influence of vitamin D and birthweight. Many associations in polymorphisms were found [137]. In our opinion, this is the starting point for larger studies that will provide some new information as to why some fetuses react to specific vitamin D levels, while others do not [137]. While in the above-mentioned pathologies, the results were very often contradictory, here the results were more similar. Bodnar *et al.* presented data indicating that maternal serum 25-hydroxyvitamin D levels were correlated with the birth of SGA neonates in white women [138]. In a study by Chen *et al.* enrolling almost 3700 pregnant Chinese women, maternal vitamin D deficiency during pregnancy was found to elevate the risk of low birth weight [133]. A multi-ethnic study by Leffelaar *et al.* concluded that women with low vitamin D levels had more than two times higher risk of finishing a pregnancy with an SGA neonate [139]. In the large study by Miliku *et al.* performed on almost 7100 pregnant women, low maternal 25(OH)D serum concentrations were associated with intrauterine growth restriction and increased risk of small size for gestational age at birth [140]. In a study by Gernand *et al.*, maternal vitamin D status was found to be related to the risk of SGA in white and non-obese women. This correlation was not confirmed in black and obese women [141]. According to data gained from several medical centers located in the USA, a maternal 25(OH)D serum level of at least 15 ng/ml during the first trimester of pregnancy was associated with a two times lower risk of giving birth to an SGA neonate [142]. In the study by Burris *et al.* second trimester 25(OH)D serum levels lower than 10 ng/ml were associated with higher odds of SGA in both black (higher risk) and white populations [143]. In an old, but very interesting, study by Marya *et al.*, the highest birthweights were obtained in mothers who received high vitamin D doses during the third trimester of pregnancy [144]. A systematic review and meta-analysis by Perez-Lopez *et al.* pointed out that vitamin D supplementation during pregnancy has been associated with higher

birthweight [131]. These data were also confirmed in a later meta-analysis of Spanish studies [103]. A very recent well-performed meta-analysis by Bi *et al.* based on 24 clinical trials found that vitamin D supplementation during pregnancy reduces the risk of an SGA neonate. The authors concluded that vitamin D supplementation with doses of 2000 IU/day (higher doses do not improve the outcomes) during pregnancy significantly reduces the risk of fetal or neonatal mortality [145]. Morley *et al.* reported that low vitamin D levels in late pregnancy were correlated with reduced fetal long bone growth [146]. On the other hand, Eggemoen *et al.* recently published their study in which they found no independent relationship between maternal vitamin D serum status and neonatal anthropometric measures [147].

In our opinion, the relationship between maternal vitamin D status at different gestational stages and the risk of low birth weight is backed by considerable evidence. In the above-mentioned literature we observed a positive relationship between maternal 25(OH)D serum levels during pregnancy and birth weight in their offspring. More research is still needed to determine the exact influences and groups of patients in whom the intervention would be necessary.

### Preterm birth

Preterm birth is a situation when a neonate is born before 37 weeks of pregnancy. The causes of preterm birth are still under investigation. The risk factors vary, from diabetes, hypertension, multiple pregnancies, obesity, underweight, or vaginal infections to alcoholism, smoking, and stress [148]. After preterm birth, infants are at higher risk for morbidities including cerebral palsy, bronchopulmonary dysplasia, and impairment of senses [149, 150]. The rapid rise of maternal corticotropin-releasing hormone (CRH) is believed to be a trigger for preterm birth [151, 152]. The exact functions of vitamin D in preterm birth are still unknown, but there are *in vitro* studies revealing it may have immunomodulatory and anti-inflammatory effects in preterm birth pathophysiology [150, 153]. Vitamin D is a factor that reduces the macrophage-mediated inflammatory processes. In the study by Mohamed *et al.*, women who experienced preterm birth showed high serum levels of maternal CRH and low vitamin D status [152]. This study has been described as preliminary, but further research might confirm that vitamin D regulates CRH through effects on inflammatory mechanisms [152]. The CRH is believed to be one of the main generators of parturition [152, 154]. Peripheral inflammation stimulates the central release of CRH. This stimulation ends with an increased level of glucocorticoids that will induce placental

CRH production [155]. Vitamin D might affect the occurrence and intensity of inflammation in several molecular pathways – in many opinions, this is a point where vitamin D status might be crucial [152, 156]. According to several studies, vitamin D plays an important role in immunomodulation and cytokine balancing. Vitamin D was shown to raise the production of anti-inflammatory cytokines (IL-4) with an additional effect on reducing the ones responsible for inflammation triggering (IL-2, IL-6, IL-10, TNF- $\alpha$ ) [157]. Vitamin D deficiency is one of the processes responsible for upregulation of monocyte toll-like receptors, which are known as pro-inflammatory cells [158]. Vitamin D inhibits cox-2 expression, due to the influence on the Akt/NF- $\kappa$ B signaling pathway [159]. According to Zhang *et al.* this vitamin inhibits macrophage pro-inflammatory cytokine production by the effect on mitogen-activated protein kinase phosphatase 1 [160]. A recent study by Javorski *et al.* found an interesting association between FokI and Cdx-2 single nucleotide polymorphisms within the vitamin D receptor gene, suggesting their involvement in the occurrence of spontaneous preterm birth. In groups with this symptom the T allele for rs2228570 and A allele for rs11568820 are more frequent [161].

The Canadian study about maternal vitamin D deficiency in early pregnancy revealed that it is associated with an increased risk of preterm birth in the future [162]. According to Baczyńska-Strzecha and Kalinka vitamin D serum levels lower than 10 ng/ml may be an important factor increasing the risk of preterm birth in the Polish population [163]. There are several other new studies about the relationship between vitamin D status and the risk of preterm birth. The results of these studies are very encouraging and suggest that optimal serum levels of vitamin D significantly reduce the risk of preterm birth in different populations [126, 164–168]. In a study by Wagner *et al.* 25(OH)D serum levels higher than 40 ng/ml in the third trimester were associated with almost 50% reduction in preterm birth numbers [167]. According to Bodnar *et al.*, the risk of preterm birth is highest when 25(OH)D serum levels are lower than 20 ng/ml, and it gets lower when serum levels are more than 35 ng/ml [169]. A very interesting study about twin pregnancies and the risk of preterm birth between women with sufficient and insufficient vitamin D status suggested an almost 60% reduction of risk in patients who had a 25(OH)D serum level of more than 30 ng/ml [170]. In a recent study by McDonnell *et al.*, patients were administered vitamin D supplements to achieve a 25(OH)D serum level of more than 40 ng/ml. The results were more than encouraging, as women with proper vitamin D levels had an almost 60% lower risk of preterm birth [63]. Maternal 25(OH)D

concentrations higher than 40 ng/ml were associated with a substantial reduction in preterm birth risk in a large, diverse population of women [63]. On the other hand, a meta-analysis of Spanish studies failed to prove the effect of higher 25(OH)D serum levels on pregnancy outcomes [103].

In our opinion, there is still a place for a RCTs regarding vitamin D status and supplementation in the reduction of preterm births because there are still no RCTs with preterm birth as a major outcome. The available data show that sufficient vitamin D status reduces the risk of preterm birth.

### Screening and supplementation

There are several questions about the role of vitamin D in perinatology at the beginning of the year 2018. What can be done to improve adverse perinatal outcomes using vitamin D? Do we need to screen for vitamin D deficiency? If yes, then who should be screened? What kind of supplementation should be chosen?

According to the above-mentioned data, some groups (e.g. overweight patients) are at increased risk for adverse perinatal outcomes due to vitamin D deficiency. In those groups, measurement of vitamin D status appears to be applicable with a good effect. There are still no good data that support routine screening for vitamin D deficiency in pregnancy. The testing is still expensive, in comparison with other blood examinations performed during pregnancy. The problem is the cost-effectiveness in universal application [171], but in 2013 a group of experts identified vitamin D as a critical intervention that might have a potential impact on reducing the risk of adverse perinatal outcomes worldwide [172]. Vitamin D supplementation in pregnancy remains a possible intervention that may improve pregnancy outcomes by preventing the occurrence of preeclampsia, GDM, low birth weight, and preterm birth [102, 173]. In an outstanding review from 2014, Wei supported this thesis [49]. A very recent study by Rostami *et al.*, who screened and supplemented vitamin D in pregnant women, found that this prenatal activity is an effective approach in detecting deficient women, improving vitamin D levels and decreasing adverse pregnancy outcomes (preeclampsia, GDM, and preterm delivery were decreased by 60%, 50% and 40% in selected populations). What is more, a monthly 50,000 IU injectable maintenance therapy contributed the most to achieving vitamin D sufficiency at delivery [174].

There are several guidelines about vitamin D supplementation in pregnancy [175–178]. As can be seen in the study by Ceccaldi *et al.*, some guideline-based supplementation doses may be insufficient, because they fail to obtain an optimal status in infants. As a result, some authors

suggest a new recommendation with higher vitamin D doses for all pregnant women [179]. Some researchers are using higher supplementation doses than proposed by guidelines, and are obtaining exceptionally good results [54, 57, 180]. Evidence supports optimal vitamin D serum levels and supplementation in improving fetal growth and neonatal outcomes [27, 49, 59, 145, 174, 181, 182]. As stated by Curtis *et al.*, evidence tends towards better vitamin D serum levels and supplementation being of overall benefit, but some of the data do not reach statistical significance [183].

The main clinical challenge is to find the optimal vitamin D status and the most cost-effective dose that would prevent adverse outcomes [178]. Top experts on vitamin D suggest that the optimal level of vitamin D should be higher than 30 ng/ml (preferred 40–60 ng/ml) [4, 177]. Very recent Polish guidelines by Rusińska *et al.* advise maintaining optimal concentrations within the range of 30–50 ng/ml when pregnancy is confirmed. The supplementation should be carried out under the control of 25(OH)D serum levels [178]. Based on cited data and our experience, we fully support this position, because at these levels we are obtaining the best obstetric outcomes. On the other hand, when summarizing the total costs and several inconveniences of vitamin D status population screening, why not just recommend higher doses of vitamin D (e.g. 4000 units/day) for all pregnant women? In the opinion of several experts, a quick review of risk factors and the recommendation proposed is simple and effective. High doses of vitamin D and 25(OH)D level examination after 4 to 8 weeks could be a convenient method due to the lag between supplementation start and the plateau of appropriate vitamin D serum levels [184, 185]. The supplementation strategy is also of high importance, as there are differences in low-dose daily doses and weekly or monthly loading dose effects in different groups [186].

Vitamin D is an inexpensive and safe drug with a low risk of toxicity. It can be safely supplemented in pregnancy, even in high doses. Due to these facts, vitamin D supplementation in pregnant women should be recommended to achieve appropriate serum levels and reduce the risk of adverse outcomes [30]. Especially this screening should be recommended in pregnant women with high risk of vitamin D deficiency [187]. Rather than using a universal supplementation dose of vitamin D, a better solution seems to be first trimester screening of vitamin D status using 25(OH)D [174] and individual dosage adjustment to compensate for potential deficits [178]. In our opinion, such a policy can bring surprisingly good results in a short time, but the problem is the overall cost of this procedure.

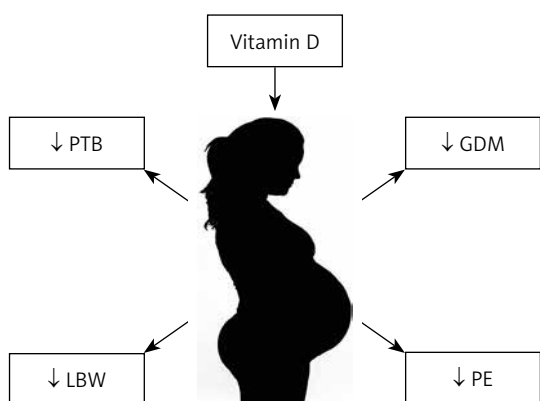
The emphasis should be placed on gynecologists and obstetricians to remember the role of vitamin D in pregnancy. At this point, the main role is played by national obstetrical societies that should keep up with current knowledge and make up-to-date guidelines about the role of vitamin D supplementation and its role in perinatology. It is also the role of experts and societies to collect opinions of other colleagues on optimal recommendations. In a study by Mohamed *et al.*, a large group of obstetricians was more likely to screen routinely. They also believed that vitamin D supplementation was beneficial for pregnant women [29]. A majority of those obstetricians indicated that vitamin D insufficiency in pregnant women was a problem in their practice [29].

We still should not forget about interactions between vitamin D, vitamin D receptors, genetics, and other factors [109, 161]. The effect of vitamin D on genomics has not been evaluated, and that is why we still need to be careful and do more research in this field to gain new knowledge [57].

## Conclusions

Vitamin D deficiency is an increasing problem worldwide. The evidence from this review suggests associations between low levels of maternal vitamin D and a higher risk of selected obstetrical complications. Vitamin D has been found to be related to various adverse perinatal outcomes, such as preeclampsia, GDM, low birth weight, and preterm birth (Figure 1).

A large body of mutually exclusive research has caused a huge problem in choosing the right course for this vitamin in pregnancy. The studies are ongoing and we will gain more data in the near future. To determine the real benefits of vitamin D supplementation in pregnancy, we need double-blind, high-quality RCTs on large or very large groups. This could show the real effect of vitamin D supplementation on adverse pregnancy



**Figure 1.** Vitamin D reduces the risk of four major severe pregnancy outcomes



outcomes and provide substantial information for public health. Available data are often inconclusive due to suboptimal clinical phenotyping, misleading characteristics and large heterogeneity [100].

In our opinion, vitamin D supplementation in pregnant women is considerable, but more high-quality data are still necessary. According to the systematic review by Roth *et al.*, current evidence seems insufficient to guide new clinical recommendations [188]. The problem that remains is how to achieve an optimal 25(OH)D level and a dose providing optimal supplementation. Perhaps the solution is routine screening and individual vitamin D dose selection. Only very high-quality randomized placebo-controlled trials will confirm the potential efficacy and safety of vitamin D supplementation in pregnancy [183].

### Conflict of interest

The authors declare no conflict of interest.

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