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# Deficiency of vitamin D in most common complications of pregnancy and periodontal disease in pregnant women - a review

**Malgorzata Walentowicz-Sadlecka[1]*, Pawel Sadlecki[1] and Maria Teresa Arias Moliz[2]**

[1]Department of Obstetrics and Gynecology, L. Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, ul. Ujejskiego 75, Bydgoszcz 85-168, Poland

[2]Department of Microbiology, University of Granada, Avda. del Hospicio, 18071 Granada Spain

## Abstract

**Aim:** To provide a review of the role of deficiency of vitamin D in most common complications of pregnancy and periodontal disease in pregnant women.

**Materials & methods:** This review is based on systematic reviews (when available) and comparative human studies.

**Results:** Vitamin D deficiency is a common problem among pregnant women from many regions of the world. 1,25(OH)2D exerts an inhibitory effect on the hormones and inflammatory cytokines that play a role in the pathogenesis of preeclampsia and preterm labor. Periodontal disease is another factor associated with unfavorable pregnancy outcomes. Periodontal disease is a persistent source of bacterial infection that can induce systemic inflammation, which in turn, exacerbates the risk of adverse pregnancy outcomes. Although underlying mechanisms of these processes are not fully understood, a common element in their pathomechanisms may also be the deficiency of vitamin D.

**Conclusions:** Given the role of vitamin D in inflammatory response and maintaining the integrity of innate immune response, its supplementation might improve maternal oral health. Physicians who provide obstetric care should be aware of the possible link between poor dental health and unfavorable pregnancy outcomes. However, the relationship between maternal vitamin D status, periodontal disease and adverse pregnancy outcomes requires more research before definitive conclusions can be made. Available data imply that improvement of vitamin D status might be an intervention to improve oral health in a vulnerable group, such as pregnant women.

## Introduction

Nowadays, deficiency of vitamin D is postulated to be a widespread (pandemic) problem, which is associated with inadequate exposure to sunlight [1]. A study conducted in an European Caucasian population demonstrated that even persons in whom cutaneous synthesis of vitamin D during summer season was high (approximately 35% of body surface area exposed to sunlight for at least 90 min per day) required its supplementation in winter to maintain recommended serum levels of 25(OH)D (>30ng/ml). Adequate serum concentration of vitamin D is vitally important since, as shown in population-based and epidemiological studies, it is associated with lower risk of cardiovascular episodes, autoimmune disorders, some diseases complicating pregnancy, cancer and infectious diseases [2,3].

## Vitamin D metabolism

Since vitamin D has been identified as a dietary component preventing rickets in early 20th century, opinions about its role in maintaining homeostasis evolved considerably. Currently, vitamin D, and especially its most reactive metabolite, 1,25(OH)2D3 (calcitriol), is considered a hormone involved in complex endocrine systems and modulating growth and differentiation of cells from various lines. Based on the analysis of recently published papers it can be concluded that inadequate supply of vitamin D is not only a dietary issue but also an important endocrine problem [4]. Calcitriol belongs to the superfamily of hormones that directly modulate activity of many (approximately 500) genes. Binding to vitamin D receptor (VDR), vitamin D controls the activity of approximately 5% of human genome, which implies that it may exert multiorgan and pleotropic effects. Although synthesis of vitamin D is catalyzed primarily by 1-α-hydroxylase and takes place mainly in the lungs, pancreas, parathyroid glands and monocytes, to this date, VDR has been identified in another 36 sites of human body, including breasts, placenta, uterus and ovaries, to mention a few. Due to its antiproliferative properties, the active form of vitamin D is considered an important factor preventing infections and tumor growth. Vitamin D was shown to control the induction of apoptosis, angiogenesis and cell differentiation [5].

Vitamin D has important inflammatory and immune functions, and its deficiency has been associated with higher infection rates. Nowadays, a hot topic in the research of human innate immune system

***Correspondence to:*** Malgorzata Walentowicz-Sadlecka, Department of Obstetrics and Gynecology, L. Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, ul. Ujejskiego 75, Bydgoszcz 85-168, Poland, E-mail: walentowiczm@cm.umk.pl

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is the role of human cathelicidin, LL-37, in control of bacterial and viral infections. Synthesis of LL-37 is induced by 1,25-dihydroxyvitamin D (calcitriol) [6]. LL-37 was shown to exert strong antimicrobial and antiendotoxin effects [7]. Expression of cathelicidin can be triggered by a Toll-like receptor response to bacterial infection [8]. Toll-like receptor activation in human macrophages has in turn been shown to upregulate vitamin D receptor expression and vitamin D 1α-hydroxylase genes. This leads to induction of cathelicidin and killing of intracellular Mycobacterium tuberculosis [9]. PD is associated with presence of pathogens that stimulate inflammatory and immune responses as a part of host's defense, and Toll-like receptor-2 responses were shown to play an important role in the pathogenesis of PD [10]. A considerable fraction of those host's responses might be modulated by vitamin D.

### Vitamin D: deficiency and supplementation

Many epidemiological studies demonstrated that vitamin D deficiency is pandemic. According to the American Endocrine Society, deficiency or insufficiency of vitamin D can be diagnosed whenever serum concentrations of 25(OH)D are lower than 20 ng/ml or range between 20 and 30 ng/ml, respectively, whereas normal level of 25(OH) D corresponds to more than 30 ng/ml [11]. The same reference levels for serum concentrations of vitamin D are also stated in Polish recommendations. The authors of a study conducted in Poland found vitamin D concentrations <20 ng/mL (50 nmol/mL) in up to 70% of the population [12]. The dose of supplemented vitamin D should be adjusted for the severity of its deficiency and patient's age. The recommended loading dose of vitamin D can be calculated from van Groningen formula [13].

## Vitamin D in pregnancy

As demand for vitamin D in pregnancy is markedly higher, pregnant women should be adequately exposed to sunlight starting from the first trimester. Cutaneous synthesis of vitamin D depends on geographic latitude, time of the year and sunblock use [6]. In our geographic latitude, vitamin D can be synthesized in the skin between April and September, providing that at least 18% of body surface area (e.g. forearms and a part of legs) are exposed to sun for no less than 15 min between 10 am and 3 pm without application of a sunblock as the latter may decrease effectiveness of the process by even 90%. During winter, the cutaneous synthesis of vitamin D in our geographic region is virtually undetectable [14].

Deficiency of vitamin D is commonly observed among pregnant women from many regions of the world. 25(OH)D can cross placental barrier already in early gestation, and hence, adequate dietary provision of vitamin D to pregnant women is of utmost importance [8]. Deficiency of vitamin D may unfavorably affect metabolism of glucose in pregnancy. Moreover, 1,25(OH)2D exerts an inhibitory effect on the placental hormones and inflammatory cytokines that were implicated in the pathogenesis of preeclampsia and preterm labor [15].

Complications of pregnancy and labor are a common cause of morbidity in women of childbearing age, contributing to approximately 18% of health problems observed in this age group [16]. The most common causes of complications observed in pregnancy, labor and neonatal period are arterial hypertension, preeclampsia and gestational diabetes mellitus [17].

As a result of hydroxylation in the liver, vitamin D is converted to 25-hydroxy-vitamin D (25(OH)D). This moderately reactive compound is the primary form of vitamin D found in the blood. Serum concentration of 25(OH)D is the most accurate marker of vitamin D status. According to some authors, 25(OH)D may modulate function of various cells, regulating their proliferation, differentiation and apoptosis, and preventing angiogenesis [18].

During pregnancy, metabolism of vitamin D and calcium undergo substantial changes to provide the growing fetus with adequate amounts of the latter element. Early pregnancy is associated with an increase in the activity of renal 1α-hydroxylase, which is additionally supported by placental 1α-hydroxylase. The activity of these two enzymes contributes to enhanced synthesis of metabolically active vitamin D, calcitriol (1,25(OH)2D). As a result, in the third trimester, concentrations of 1,25(OH)2D in pregnant women with adequate supply of vitamin D are twice as high as before pregnancy. However, in pregnant women with deficiency of vitamin D, the only source of calcium for the growing fetus is maternal skeleton, which may result in demineralization and pregnancy-related osteoporosis [4,19].

In a study conducted among Polish women, normal concentrations of 25(OH)D (≥30 ng/ml) were found in only 10.87% of the participants [20]. Insufficiency of 25(OH)D (20–30 ng/ml) was detected in 43.48% of pregnant women participating in the study, and vitamin D deficiency (25(OH)D <20 ng/ml) in up to 45.65% [20]. Such evident deficits of vitamin D in pregnant women were likely associated with inadequate exposure to sunlight, inappropriate diet and too low supplementation of this vitamin. Adverse pregnancy outcomes are linked with maternal hypovitaminosis D, and low concentrations of 25(OH)D are considered a significant predictor of gestational hypertension and preeclampsia [21]. A systematic review and meta-analysis of 24 studies clearly demonstrated that pregnant women with vitamin D levels <20 ng/mL had a higher risk of preeclampsia [odds ratio, OR=2.09], pre-term birth [OR=1.58], small for gestational age [OR=1.52] and gestational diabetes mellitus [OR=1.38] [22].

## Vitamin D in periodontal disease

Periodontal disease (PD) is another factor that was shown to be associated with unfavorable pregnancy outcomes [23]. Periodontal disease is a chronic inflammatory condition of periodontium; in its advanced forms, the disease is associated with periodontal ligament loss and destruction of surrounding alveolar bone [24], if untreated, can lead to tooth loss, and may also affect systemic health. A classification scheme for periodontal and peri-implant diseases enables clinicians to correctly diagnose and appropriately treat patients with these conditions. Moreover, such scheme is useful for scientists who investigate the etiology, pathogenesis, natural history and treatment of diseases from this group.

The idea behind the recently introduced classification of periodontal diseases was to identify the well-defined clinical entities using clear-cut criteria that provide a link between diagnosis, prevention and treatment. The diagnostic criteria have been grouped into several categories: i) periodontal health; ii) gingivitis; iii) reduced but healthy periodontium (successfully treated periodontitis); iv) gingival inflammation in a periodontitis patient (treated periodontitis with persistent inflammation); v) periodontitis; vi) periodontitis as a manifestation of systemic diseases; and vii) necrotizing periodontal disease [25]. This concept constitutes a major change from the previous classification [26] that distinguished between various forms of periodontitis (chronic, aggressive, and as a manifestation of a systemic diseases). However, the analysis of published evidence carried out by the authors of the new classification system did not support the existence of different forms of periodontitis based on clear differences in pathobiology [25].

While a relationship between periodontal disease and vitamin D deficiency has been documented in several populations, the underlying mechanism of this association is yet to be identified [27-29]. Vitamin D exerts an effect on the innate immune activity of the gingival epithelium against periodontal pathogens to maintain microbial homeostasis and contributes to the inhibition of pro-inflammatory cytokines. The active form of vitamin D, 1,25(OH)2D3, induces the expression of the antimicrobial peptide LL-37 and innate immune mediators in cultured human gingival epithelial cells (GECs). Recently, Menzel *et al.* [30] demonstrated that the dietary restriction of vitamin D led to alveolar bone loss and exacerbated gingival inflammation in a mouse model. Treatment with 1,25(OH)2D3 inhibited intracellular growth of P. gingivalis in primary human gingival epithelial cells (GECs) and established human cell lines. Cultured GECs expressed two 25-hydroxylases (CYP27A1 and CYP2R1), as well as 1-α hydroxylase, which catalyzed conversion of vitamin D to both 25(OH) D3 and 1,25(OH)2D3. Based on those findings, the authors concluded that topical administration of vitamin D could lead to a localized inhibition of the inflammatory response in vivo. The results of this study not only support the hypothesis that at normal levels, vitamin D could maintain an anti-inflammatory state in the oral cavity, but also suggest that aside from enhancing the natural antimicrobial activity of the tissue, topical vitamin D might prevent or treat the inflammation associated with periodontal disease [30].

The authors of a recently published systematic review analyzed the association between vitamin D level and the risk of periodontal disease [Pinto]. Based on the analysis of 27 published studies, the authors concluded that available evidence in this matter is still inconclusive and suggested that the issue should be addressed in well-designed longitudinal studies using standardized definitions of periodontal disease and vitamin D deficiency [31].

Dietrich *et al.* [32] analyzed the data from the NHANES III (1988-94) and found that men and women older than 50 years, whose serum 25(OH)D concentrations were in the lowest quantile, presented with 0.39 mm and 0.26 mm greater periodontal attachment loss, respectively, than those in the highest 25(OH)D quantile. However, a similar association was not found among persons younger than 50 years, which is also consistent with the results of a Finish study [33].

Laky *et al.* [28] conducted a case-control-study to determine 25(OH)D status in periodontal disease. Aside from serum 25(OH)D levels, the authors analyzed periodontal probing depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), body mass index (BMI), as well as current smoking status and smoking history (pack-years). The study demonstrated a significant association between 25(OH)D deficiency and periodontal disease; these findings imply that monitoring of 25(OH)D levels in patients with periodontal disease is advisable, as vitamin D deficiency might be involved in the onset and progression of this condition [28].

As shown above, published data on the link between vitamin D status and periodontal disease are inconclusive. Most previous studies analyzing the problem in question had some major limitations that substantially limit causal inference; this justifies further research with appropriate methodological designs [31].

## Periodontitis and adverse pregnancy outcomes

A growing body of evidence supports the link between periodontal disease (PD) and adverse outcomes in pregnancy. Periodontitis might be associated with neonatal complications in the form of preterm labor, low birth weight and preeclampsia. PD is a persistent source of bacterial infection that can induce systemic inflammation, which in turn, exacerbates the risk of adverse pregnancy outcomes [34]. Offenbacher *et al.* [35] found that pregnant women with severe PD were 7.5 times more likely to experience preterm labor. While the relationship between PD and pregnancy outcome has been studied extensively, published evidence in this matter is still inconclusive. Among 25 studies included in one systematic review, 18 demonstrated that the risk of adverse pregnancy outcomes was associated with PD [OR 1.10-20.0], while no significant associations between these two factors were found in another seven studies [OR 0.73-2.50] [36].

The aim of the systematic review conducted by Corbella *et al.* [37] was to evaluate periodontal disease as an independent risk factor for adverse pregnancy outcomes. Out of 422 initially identified entries, 22 studies with a total of 17,053 subjects were eventually included in the review after application of inclusion and exclusion criteria. After correction for biased methodologies and heterogeneity of the source studies, RR for periodontitis was computed at 1.61 for preterm birth evaluated in 16 studies ($P < .001$), 1.65 for low birthweight evaluated in 10 studies ($P < .001$), and 3.44 for preterm low birthweight evaluated in four studies. These findings suggest that a weak albeit significant association might exist between periodontitis and adverse pregnancy outcomes [37].

Also, Konopka and Paradowska-Stolarz [38] conducted a meta-analysis to verify if periodontitis was an independent risk factor of preterm birth and/or low birth weight. The result of the meta-analysis was inconclusive, and the authors postulated that the problem should be verified in further well-designed cohort and intervention studies. Nevertheless, they emphasized the need for dental care in pregnant women as an integral component of prenatal care program [38].

In the study conducted by Gonzalez-Jaranay *et al.* [39], plaque index, gingival index and probing depth increased throughout pregnancy and then decreased postpartum. While the proportion of sites with probing depth >3 mm increased during pregnancy and decreased after birth, it was still significantly higher than at the baseline. The authors concluded that pregnancy is associated with a temporary deterioration of periodontal status [39].

Manrique-Corredor *et al.* [40] analyzed the relationship between maternal periodontitis and preterm birth in women of childbearing age. The authors reviewed case-control studies and prospective cohort studies that evaluated the problem in question in a total of 10 215 women. The analysis demonstrated that the risk of preterm birth in pregnant women with periodontitis was twice as high as in those without. In conclusion of their study, the authors highlighted the need for an international consensus regarding diagnostics of maternal periodontitis [40].

According to Russell *et al.* [23], the incidence of PD increased with parity. Diabetes mellitus, socioeconomic status, smoking, frequency of dental care visits and the time elapsed since the most recent live birth were identified as significant predictors of tooth loss [23].

Although the underlying mechanisms of the relationships mentioned above are not fully understood, a common factor in their pathomechanisms might also be deficiency of vitamin D [41].

As a result of hormonal changes and vasodilation, periodontal tissues of pregnant women are more susceptible to harmful effects of intrinsic and extrinsic factors; even a small amount of residual biofilm may cause irritation to the gums and contribute to their chronic inflammation [42]. Usually, gingivitis develops as a response to presence

of bacterial plaque. Hence, this condition is indirectly associated with local factors predisposing to biofilm retention, i.e. inadequate oral hygiene, deposition of dental plaque, presence of overhangs or poor-fitting dentures. The American Academy of Periodontology qualified gingivitis in pregnant women as a condition associated with bacterial plaque that can be modified by systemic factors [43]. An imbalance between the harmful effect of bacterial plaque and protective mechanisms of the body may result in gestational gingivitis. Maternal PD is found in ≤40% of pregnant women and is associated with adverse pregnancy outcomes. Deficiency of vitamin D may play a role in PD and tooth loss [44], and insufficient vitamin D status is a common problem among pregnant women [45,46]. Vitamin D status may play a role in the pathogenesis of PD in pregnant women, affecting immunity and bone metabolism. Boggess *et al.* [47] conducted a case-control study to analyze the relationship between vitamin D status and PD in pregnant women. The study showed that pregnant women with moderate to severe PD presented with lower serum levels of 25(OH)D and more often than women with good periodontal health had 25(OH) D concentrations <75 nmol/l. This association was also observed when the results were controlled for several potential confounders, such as race, which implies that insufficient maternal vitamin D status is a risk factor for moderate to severe PD during pregnancy. Furthermore, the study showed that adequate level of vitamin D was important to maintain good periodontal health and to attenuate the consequences of PD [47].

In the Third National Health and Nutrition Examination Survey, serum concentrations of 25-hydroxyvitamin D (calcidiol) turned out to be inversely associated with attachment loss among men and women aged 50 years or older. PD is caused by bacteria that form a biofilm on the tooth surface and leach calcium from the teeth and bones due to a decrease in pH; this eventually leads to tooth loss [48].

## Conclusion

Given the role of vitamin D in inflammatory response and maintaining the integrity of innate immune response, its supplementation might improve maternal oral health [49,50]. Physicians who provide obstetric care should be aware of the possible link between poor dental health and unfavorable pregnancy outcomes. However, the relationship between maternal vitamin D status, PD and adverse pregnancy outcomes requires more research before definitive conclusions can be made [51,52]. Available data imply that improvement of vitamin D status might be an intervention to improve oral health in a vulnerable group, such as pregnant women.

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## Competing interests

The authors declare that they have no competing interests.

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