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

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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.

Key words: periodontal disease, vitamin D deficiency, pregnancy pathology

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

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Received: April 09, 2019; Accepted: April 22, 2019; Published: April 25, 2019
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 health 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 Finnish 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-Jarayani 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 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.

Funding statement

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that they have no competing interests.

References

1. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, et al. (2012) Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab 97: 1153-1158. [Crossref]
2. Płudowski P, Karczmarewicz E, Bayer M, Carter G, Chlebna-Sokół D, et al. (2013) Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe - recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol 64: 319-327. [Crossref]
3. Walentowicz-Sadlecka M, Grabiec M, Sadlecki P, Gotoswka M, Walentowicz P, et al. (2012) 25(OH)D3 in patients with ovarian cancer and its correlation with survival. Clin Biochem 45: 1568-1572. [Crossref]
4. Doroszko A, Niedzielska E, Gronowicz E (2008) Wpływ witaminy D na płodność i zdrowie potomstwa – przegląd literatury. Ginekol Pol 79:198-202.
5. Muscelin S (2011) Vitamin D and cancer: Deciphering the truth. Biochim Biophys Acta 1816: 172-178. [Crossref]
6. Gombart AF, Borregaard N, Koeffler HP (2005) Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. FASEB J 19: 1067-1077. [Crossref]
7. Gombart AF, Luong QT, Koeffler HP (2006) Vitamin D compounds: activity against microbes and cancer. Anticancer Res 26: 2531-2542.
8. Mookherjeer N, Rehaume LM, Hancock RE (2007) Cathelicidins and functional analogues as antimicrobials. Expert Opin Ther Targets 11: 993-1004. [Crossref]
9. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, et al. (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 311: 1770-1773. [Crossref]
10. Burns E, Bachrach G, Shapira L, Nussbaum G (2006) Curbing edge: TLR2 is required for the innate immune response to Porphyromonas gingivalis: activation leads to bacterial persistance and TLR2 deficiency attenuates induced alveolar bone resorption. J Immuol 177: 8296-8300. [Crossref]
11. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, et al. (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96: 1911-1930. [Crossref]
12. Płudowski P, Karczmarewicz E, Chlebna-Sokół D (2013) Vitamin D supplementation in healthy population and risk groups of vitamin D deficiency – practice guidelines for Central Europe 2013 [in Polish]. Stand Med Pediatr 10: 573-578.
13. van Groningen L, Opendersdft S, van Sorge A, Teuling D, Giessen A, et al. (2010) Cholecalciferol loading dose guideline for vitamin D-deficient adults. Eur J Endocrinol 162: 855-861. [Crossref]
14. Brzozowska M, Karowicz-Bilińska A (2013) Rola niedoboru witaminy D w patofizjologii zaburzeń występujących w zespole pozytycznych jajników. Ginekol Pol 84: 456-460.
15. Węgienia K, Kaur H, Sanghra R, Cassidy-Bushrow AE (2016) Maternal-cord blood vitamin D correlations vary by maternal levels. J Pregnancy 2016: 7474192. [Crossref]
16. Bener A, Al-Hamaq AO, Saleh NM (2013) Association between vitamin D insufficiency and adverse pregnancy outcome: global comparisons. Int J Womens Health 5: 523-531. [Crossref]
17. Zawiejska A, Wender-Orgzezowska E, Bogacz A, kricek R, Mikołajczak P, et al. (2018) An observational study of the risk of neonatal macrosomia, and early gestational diabetes associated with selected candidate genes for type 2 diabetes mellitus polymorphisms in women with gestational diabetes mellitus. Ginekol Pol 89: 705-710. [Crossref]
18. Pike JW, Meyer MB, Lee SM, Onal M, Benkusky NA (2017) The vitamin D receptor: contemporary genomic approaches reveal new basic and translational insights. J Clin Invest 127: 1146-1154. [Crossref]
19. Pilz S, Zittermann A, Obed R, Hahn A, Płudowski P, Trummer C, et al. (2018) The role of vitamin d in fertility and during pregnancy and lactation: a review of clinical data. Int J Environ Res Public Health [Crossref]
20. Domaracki P, Sadlecki P, Odrowoz-Szymciewa G, Dzikowska E, Walentowicz P, et al. (2016) Serum 25(OH) Vitamin D Levels in Polish Women during Pregnancies Complicated by Hypertensive Disorders and Gestational Diabetes. Int J Mol Sci. [Crossref]
21. Tatabaiaei N, Auger N, Herba CM, Wei S, Alland C, et al. (2017) Maternal vitamin d insufficiency early in pregnancy is associated with increased risk of preterm birth in ethnic minority women in canada. J Nutr 147: 1145-1151. [Crossref]
22. Wei SQ, Qi HP, Lao ZC, Fraser WD (2013) Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 26: 889-899. [Crossref]
23. Russel SL, Ickovics JR, Yuffee RA (2008) Exploring potential pathways between parity and tooth loss among American women. Am J Public Health 98: 1263-1270. [Crossref]
24. de Pablo P, Chapple II, Buckley CD, Dietrich T (2009) Periodontitis in systemic rheumatic diseases. Nat Rev Rheumatol 5: 218-224. [Crossref]
Walentowicz-Sadlecka M (2019) Deficiency of vitamin D in most common complications of pregnancy and periodontal disease in pregnant women - a review

25. Caton JG, Armitage G, Berglundh T, Chapelle IL, Jepsen S, et al. (2018) A new classification scheme for periodontal and peri-implant diseases and conditions - Introduction and key changes from the 1999 classification. J Periodontol 89 Suppl 1: S1-S8. [Crossref]

26. Armitage GC (1999) Development of a classification system for periodontal diseases and conditions. Ann Periodontol 4: 1-6. [Crossref]

27. Antonoglu GN, Knuttila M, Niemelä O, Raunio T, Karttunen R, et al. (2015) Low serum level of 1,25(OH)2D is associated with chronic periodontitis. J Periodontal Res 50: 274-280. [Crossref]

28. Laky M, Bertl K, Haririan H, Andrukhov O, Seemann R, et al. (2017) Serum levels of 25-hydroxyvitamin D are associated with periodontal disease. Clin Oral Investig 21: 1533-1558. [Crossref]

29. Lee HJ, Je DI, Won SJ, Paik DI, Bae KH (2015) Association between vitamin D deficiency and periodontal status in current smokers. Community Dent Oral Epidemiol 43: 471-478. [Crossref]

30. Menzel LP, Ruddick W, Chowdhury MH, Brice DC, Clance R, et al. (2019) Activation of vitamin D in the gingival epithelium and its role in gingival inflammation and alveolar bone loss. J Periodontal Res. [Crossref]

31. Pinto JPNS, Goergen J, Muniz FWMG, Haas AN (2018) Vitamin D levels and risk for periodontal disease: A systematic review. J Periodontal Res 53: 298-305. [Crossref]

32. Dietrich T, Josphira KJ, Dawson-Hughes B, Bischoff-Ferrari HA (2004) Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. Am J Clin Nutr 80: 108-113. [Crossref]

33. Antonoglu GN, Suominen AL, Knuttila M, Ylöstalo P, Ojala M, et al. (2015) Associations between serum 25-hydroxyvitamin d and periodontal pocketing and gingival bleeding: results of a study in a non-smoking population in Finland. J Periodontol 86: 755-765. [Crossref]

34. Offenbacher S, Beck JD, Jared HL, Mauriello SM, Mendoza LC, et al. (2009) Maternal oral therapy to reduce obstetric risk (MOTOR) investigators. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. Obstet Gynecol 114: 551-559.

35. Offenbacher S, Lin D, Strauss R, McKaig R, Irving J, et al. (2006) Effects of periodontal therapy during pregnancy on periodontal status, biologic parameters, and pregnancy outcomes: a pilot study. J Periodontol 77: 2011-2024. [Crossref]

36. Xiong X, Buekens P, Fraser WD, Beck J, Offenbacher S (2006) Periodontal disease and adverse pregnancy outcomes: A systematic review. BJOG 113: 135-143. [Crossref]

37. Corbella S, Taschieri S, Del Fabbro M, Francetti L, Weinstein R, et al. (2016) Adverse pregnancy outcomes and periodontitis: A systematic review and meta-analysis exploring potential association. Quintessence Int 47: 193-204. [Crossref]

38. Konopka T, Paradowska-Stolarz A (2012) Periodontitis and risk of preterm birth and low birthweight—a meta-analysis. Ginekol Pol 83: 446-453.

39. González-Jaramay M, Téllez L, Roa-López A, Gómez-Moreno G, Moreu G (2017) Periodontal status during pregnancy and postpartum. PLoS One 12: e0178234. [Crossref]

40. Manrique-Corredor EZ, Orozco-Beltran D, Lopez-Pineda A, Quesada JA, Gil-Guillen VF, et al. (2019) Maternal periodontitis and preterm birth: Systematic review and meta-analysis. Community Dent Oral Epidemiol. [Crossref]

41. Madianos PN, Bobetzi YA, Offenbacher S (2013) Adverse pregnancy outcomes (APOs) and periodontal disease: pathogenic mechanisms. J Periodontol 84(4 Suppl): S170-80. [Crossref]

42. Bilinska M, Sokalski J (2016) Pregnancy gingivitis and tumor gravidarum. Ginekol Pol 87: 310-313. [Crossref]

43. Jepsen S, Caton JG, Albandar JM, Bissada NF, Bouchard P, et al. (2018) Periodontal manifestations of systemic diseases and developmental and acquired conditions: Consensus report of workshop 3 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol 89 Suppl 1: S237-S248. [Crossref]

44. Zhan Y, Sanietz S, Holtfreter B, Hannemann A, Meisel P, et al. (2014) Prospective Study of Serum 25-hydroxy Vitamin D and Tooth Loss. J Dent Res 93: 639-644. [Crossref]

45. Khammissa RAG, Ballyrasm, Radwat Y, Fourie J, Lemmer J, et al. (2018) Vitamin D deficiency as it relates to oral immunity and chronic periodontitis. Int J Dent.

46. Genuis SJ (2015) Maternal and Pediatric Health Outcomes in relation to Gestational Vitamin D Sufficiency. Obstet Gynecol Int.

47. Boggess KA, Espinola JA, Moss K, Beck J, Offenbacher S, et al. (2011) Vitamin D status and periodontal disease among pregnant women. J Periodontol 82: 195-200. [Crossref]

48. Grant WB (2008) High vitamin D and calcium requirements during pregnancy and tooth loss. Am J Public Health 98: 1931-1932. [Crossref]

49. Iheozor-Ejiofor Z, Middleton P, Esposito M, Glenny AM (2017) Treating periodontal disease for preventing adverse birth outcomes in pregnant women. Cochrane Database Syst Rev 6: CD005297. [Crossref]

50. Boggess KA, Espinola JA, Moss K, Beck J, Offenbacher S, et al. (2011) Vitamin D status and periodontal disease among pregnant women. J Periodontol 82: 195-200. [Crossref]

51. Bjorn Jensen C, Thorne-Lyman AL, Vadgård Hansen L, Strøm M, Odgaard Nielsen N, et al. (2013) Development and validation of a vitamin D status prediction model in Danish pregnant women: a study of the Danish National Birth Cohort. PLoS One 8: e53659. [Crossref]

52. M Krawiec, M Dominiak. The role of vitamin D in the human body. Dental and Medical Problems 2018, vol. 55, nr 4, October-December, p. 419–424 doi: 10.17219/ dmp/99051 Activation of vitamin D in the gingival epithelium and its role in gingival inflammation and alveolar bone loss.