International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn23303

Vitamin D deficiency and preterm birth: a comprehensive review

Cristiane Fadel Bearzi[1]*, Danilo Chiaradia Finamor[2], Giovana Marim[1], Fausto Rohnelt Durante[3]

[1] Fadel Bearzi Clinic, São Paulo, Brazil.
[2] Finamor Clinic, São Paulo, Brazil.
[3] Dr. Fausto Durante Clinic, Curitiba, Paraná, Brazil.

*Corresponding Author: Cristiane Fadel Bearzi.
Fadel Bearzi Clinic. Street: Júlio de Castilhos 1049,
Zip Code: 03059-005, São Paulo, Brazil.
E-mail: cfbearzi@gmail.com
DOI: https://doi.org/10.54448/ijn23303
Received: 06-02-2023; Revised: 08-03-2023; Accepted: 08-09-2023; Published: 08-10-2023; IJN-id: e23303

Abstract

Introduction: Pregnancy and its prognosis are highly influenced by maternal nutritional status before and during pregnancy. We know the importance of adequate macronutrient intake and micronutrient supplementation in the preconception period, during pregnancy and in the puerperium. **Objective:** This literature review aimed to study the relationship between preterm birth and hypovitaminosis D. **Methods**: Literature review carried out in the Google Scholar, Virtual Health Library (VHL), SciELO and PubMed databases in period of last 5 year- 2017-2022 (june). **Results and Conclusion**: recent evidence supports that vitamin D deficiency during pregnancy is associated with an increased risk of preterm birth. It is known that hypovitaminosis D during pregnancy can be a risk factor for preterm birth and all its complications for the newborn. But its isolated supplementation during pregnancy is still not a preventive action with statistically significant benefits in preterm birth. Researchers and physicians should be made aware of this issue to improve prenatal care. Strategies adopted to prevent preterm birth are scarce, and it is hoped that in the posterity the evidence mentioned in this article on the role of vitamin D may help to reduce its incidence and, consequently, mortality and, as such, improve the health of women pregnant women and their respective descendants.

Keywords: Vitamin D deficiency. Pregnancy. Complications. Obstetric labor. Preterm birth.

Introduction

Pregnancy and its prognosis are highly influenced by maternal nutritional status before and during pregnancy. In addition, maternal age, parity, weight, height, environmental and genetic factors, smoking and alcohol and drug abuse, and also the influence on the puerperal pregnancy cycle **[1]**.

The importance of adequate macronutrient intake and micronutrient supplementation in the preconception period is known, during pregnancy and in the puerperium so that we have a healthy pregnancy, a delivery with a lower rate of complications, a fetus with good intrauterine development and well-nourished at birth, in addition to a puerperium that allows satisfactory breastfeeding for the newborn **[1,2]**.

Here, the importance of vitamin D during pregnancy will be addressed, and more specifically, the consequences of its deficiency in preterm birth (PTB). PTB labor is defined as that which occurs before the 37th week of gestation, being the main cause of neonatal morbidity and mortality, with a prevalence of 9.6% globally **[1]**. Prematurity is the most common cause of death among children under 5 years of age and one of the greatest Public Health indicators in a country.

According to the World Health Organization (WHO), prematurity rates in countries range from 5 to 18%. The incidence of necrotizing enteritis, retinopathy, neonatal jaundice, hypoxic encephalopathy, and other diseases in preterm infants was significantly higher in preterm infants than in full-term newborns (NB). Up to 40% of surviving preterm infants have bronchopulmonary dysplasia, cerebral palsy, epilepsy, cognitive

impairment, and other neurological disorders **[2]**.

Depending on the weeks of gestation, it can be designated as extreme prematurity below 28 weeks, severe prematurity between 29 and 30 weeks, moderate prematurity between 31 and 33 weeks, and late prematurity between 34 and 36 6/7 weeks of gestation **[1]**.

Currently there is a need for supplementation of other micronutrients such as iron, iodine, calcium and zinc, in addition to folic acid supplementation three months before conception to avoid fetal malformations at the central nervous system level. Studies have associated prematurity with low levels of vitamin D during pregnancy. Vitamin D can be obtained in several ways: by endogenous synthesis in the skin resulting from exposure to ultraviolet rays from the sun, by the conversion of 7-dehydrocholesterol into cholecalciferol (vitamin D3), and by ingestion of fatty fish, which contain cholecalciferol, and of plants and mushrooms containing ergocalciferol (D2). An adequate level of vitamin D 25(OH) is above 30 ng/mL, 21-29 ng/mL is insufficient and below 20 ng/mL is deficient **[3]**.

This literature review aimed to study the relationship between preterm birth and hypovitaminosis D.

Methods

Literature review carried out in Google Scholar, Virtual Health Library (BVS), SciELO, and PubMed databases, using the terminologies registered in Health Sciences Descriptors (DeCS), translated from MeSH Terms (Medical Subject Headings (MeSH) of the National Library of Medicine (NLM), which allows the use of common terminologies in Portuguese, English, Spanish, and French. The keywords used in the searches were "vitamin D deficiency" "complications in pregnancy" and "premature labor". articles from the last 5 years (2017 to 2020 (June), and the result was filtered for review articles and always guided by the initial proposal.

Results

Vitamin D

It is a steroid hormone, whose main function is to regulate calcium and phosphorus homeostasis, bone formation, and resorption, in addition to interacting with the parathyroid, kidneys, thyroid, and liver. Its absorption is most effective in the small intestine by passive diffusion. After its incorporation into lipids, vitamin D enters the lymphatic system, and plasma, upon reaching the bloodstream, is incorporated by a binding protein, which transports the vitamin and its metabolites to target tissues. It is activated by the kidneys and liver, where little storage takes place. Data show that 50 to 80% of ingested vitamin D is absorbed **[4]**.

It is primarily involved in the functioning of the musculoskeletal system, regulating calcium and phosphorus metabolism, along with parahormone and calcitonin (thyroid). Its production depends on sun exposure (ultraviolet B-UVB radiation). More than 90% of vitamin D comes from skin synthesis. Its dietary sources are scarce, represented by vegetables (mushrooms, etc.) and, mainly, products of animal origin, such as fish liver oil, cod, salmon, mackerel, tuna, sardines, oysters, liver, milk and cheese, egg and fortified products (milk, juices, cereals, fortified yogurt, and margarine). Currently, it is known that vitamin D is the necessary factor for the development and maintenance of bone tissue, and for the maintenance of normal homeostasis of calcium and phosphorus. As food sources of vitamin D are scarce, humans depend mainly on cutaneous synthesis, resulting from ultraviolet B radiation, which tends to decrease with aging, placing elderly individuals in a risk group for vitamin D deficiency **[4]**.

Vitamin D Physiology and Metabolism

It is a fat-soluble vitamin that has two forms, both obtained through the diet, vitamin D3 (cholecalciferol), of animal origin, in particular, fatty fish and eggs, and vitamin D2 (ergocalciferol), of vegetable origin, in the form of supplements dietary supplements **[1]**. Given its greater impact on the body, the synthesis and respective activation of vitamin D3 stands out in this context. In humans, it begins its biosynthesis in the skin and results from the conversion of its epidermal form, 7-dehydrocholesterol, through exposure to ultraviolet B radiation, this endogenous source being very effective and responsible for more than 80% of its production **[5,6]**.

Initially metabolized in the liver, in the first activation step, vitamin D3 undergoes hydroxylation and becomes its immediate precursor, 25(OH)D3, which is the biomarker of vitamin D status with a long half-life (2 to 3 weeks). Subsequently, this pre-hormone is converted in the kidney into 1,25(OH)2D3, or calcitriol, becoming biologically active. This second step of activation is mediated in the kidney by enzymes of the cytochrome P450 complex, namely 25(OH)D-1alpha-hydroxylase (CYP27B1), which is independently present in extrarenal tissues, including the placenta, cardiovascular, neurological and respiratory systems **[5,6]**.

CYP27B1 activity is closely regulated by mineral metabolism, especially by parathyroid hormone (PTH), which aims to maintain plasma levels of 1,25(OH)2D3 adequate for needs and with a half-life of 4-6 hours, in

such a way that these do not correctly reflect vitamin D status **[5]**. Vitamin D and its metabolites are transported in the bloodstream mainly bound to vitamin D binding protein (DBP), and a lesser extent by serum albumin or circulating in a free form. However, entry into cells is mainly carried out by free metabolites, for this reason, measurement of free 25 (OH) D3 can be useful in special conditions with altered levels of BPD (for example in pregnancy, hormonal contraception, or liver cirrhosis **[5,6]**.

Changes in Vitamin D Homeostasis During Pregnancy

Vitamin D metabolism during pregnancy shows significant changes. Its homeostasis is adapted to respond to two inherent needs: allowing bone mineralization of the fetus in the last trimester by increasing maternal calcium absorption and reinforcing maternal systemic and local immunological tolerance to fetal antigens. Three potential adaptive modifications of vitamin D during pregnancy have been suggested, and the mechanism that originates them is still unknown **[6]**.

The first adaptation consists of a gradual increase in maternal 1,25(OH)2 D3, approximately two to three times during pregnancy, reaching a maximum peak in the third trimester. It has mainly a renal origin, independent of PTH levels, but without affecting ionized or corrected calcium levels. One of the proposed mechanisms for this increase incorporates the high expression of CYP27B1 in the maternal-fetal interface and in fetal tissues that originate active vitamin D in circulation, since it does not cross the placenta **[7]**. Renal macrophages perform an immune response and are important mediators of the inflammatory process, increasing circulation during normal pregnancy **[6]**.

The second adaptation involves the passage of maternal 25(OH)D3 through the placenta, representing the main source of vitamin D in the fetus. Embryologically, the placenta is formed from the fourth week of gestation and is crucial in providing nutrients for the developing embryo. From that moment until delivery, 25(OH)D3 is transported and reaches concentrations in fetal umbilical cord blood equivalent to approximately 50-75% of the maternal blood value **[6]**.

The third adaptation consists of increasing maternal BPD by 40-50%, which reaches its maximum at the beginning of the third trimester and then decreases until delivery. This protein is expressed in placental trophoblast cells during a normal pregnancy, which suggests that its increase may result from a high turnover rate of trophoblasts that are in direct contact with maternal blood **[6]**.

To complement the study by Karras et al. **[6]**, it is proposed that possible adaptive biological phenomena of vitamin D homeostasis during pregnancy may be related to several obstetric outcomes. As an example, BPD dysregulation may be involved in the pathogenesis of preterm labor, preeclampsia, and type 1 diabetes in offspring.

Vitamin D and Its Implications For Pregnancy and the Fetus

Vitamin D deficiency in pregnant women is very prevalent. There is evidence that increased body mass index, low sun exposure, and minorities, in particular those with dark skin pigmentation, are risk factors for low vitamin D levels **[8,9]**. As previously mentioned, 25(OH)D is considered to be the main functional indicator of vitamin D status and includes both 25(OH)D2 and 25(OH)D3 forms, reflecting a balance of endogenous and exogenous synthesis. The definition of vitamin D insufficiency and deficiency is based on the serum concentration of 25(OH)D. Deficiency below 20 ng/mL and insufficiency between 20 and 30 ng/mL and sufficiency above 30 ng/mL.

In pregnant women, the need and effectiveness of supplementation with vitamin D remain questionable, in contrast to other nutrients such as folic acid and iron, which are unanimous in terms of recommendations **[8]**. When vitamin D deficiency is identified, according to the committee of the American College of Obstetricians and Gynecologists, supplementation with 1000 to 2000 IU/day of vitamin D should be started. However, the dose of vitamin D supplementation is not well defined as essential to adequately increase its level in pregnancy, which suggests the need for more randomized clinical trials. In the study, although inconclusive, there is a probability that even higher levels in the order of 4000 IU / day are needed **[10]**.

During pregnancy, there is a need for an inflammatory balance in the immune system, and deregulation in this system causes an excessive pro-inflammatory response that can lead to preterm labor. Vitamin D has anti-inflammatory and immunoregulatory properties, thus potentially having the potential to modulate the placental inflammatory response **[1]**. Budhwar et al. carried out a study to evaluate the impact of changing the concentration of 25(OH)D in the umbilical cord and its correlation with placental concentration during preterm labor **[11]**.

In the premature group, there was an increase in the expression of placental inflammation markers and a decrease in the expression of vitamin D signaling mediators. Regarding histological changes in preterm labor, the syncytiotrophoblast layer was distorted, with

the deposition of fibrous tissue in the stroma and reduced vascularization, in addition to a decrease in the expression of vitamin D markers. In term pregnancies, the architecture of the placenta remained vascularized and the levels of vitamin D were normal **[11]**.

Vitamin D in the Health of the Premature Newborn

After birth, with the sudden cessation of the source of vitamin D by transplacental transfer, especially in the last trimester of pregnancy, the premature newborn is at risk of a lack of this and other micronutrients. Their nutritional needs differ from those of full-term infants, as their metabolism shows immaturity of various organs and an accelerated growth rate.

Effectively, preterm infants show a decline in the concentration of 25(OH)D in the umbilical cord blood compared to full-term newborns, with a positive correlation with gestational age ($r = 0.936$, $p < 0.0001$) and with the birth weight ($r = 0.9559$, $p < 0.0001$). Therefore, the relationship between lower gestational age at delivery and low levels of 25(OH)D makes preterm newborns a vulnerable population due to diminished vitamin D reserves **[12]**.

Preterm birth (PTB)

Birth at less than 37 completed gestational weeks (less than 259 days) is the leading cause of neonatal morbidity and mortality. A lower limit of 20 or 22 weeks is adopted. The lower the gestational age at birth, the greater the neonatal complications. The prevalence of prematurity varies according to the characteristics of the population, but, in general, it has been rising in recent years. According to WHO, there are about 15 million premature births per year. In Brazil, the prevalence of prematurity is 11.7% **[12]**.

The consequences of prematurity represent a serious public health problem. The most common neonatal complications include respiratory distress syndrome (RAS), intracranial hemorrhage, necrotizing enterocolitis, and neonatal death. These intercurrences are more frequent at gestational ages below 32 weeks, becoming critical below 28 weeks. Mortality is also high in the group of newborns who directly survive respiratory disorders and infectious and neurological complications **[12]**.

Risk Factors for Preterm Labor

Risk factors are smoking, maternal obesity, and gestational diseases, but even among healthy women, a certain percentage of babies can be born prematurely. Risk factors are complex and prevention is a global health issue. Among the risk factors, we also found low body mass index, asymptomatic bacteriuria, black ethnicity, cervical surgery, in vitro fertilization techniques, bacterial vaginosis, and cervical shortening. Below is a list of risk factors for preterm delivery **[2]**.

Pathophysiology of PTB Work

There are four mechanisms for the pathophysiology of preterm delivery: activation of the hypothalamic-pituitary-adrenal axis (stress), inflammation and infection, decidual bleeding, and pathological uterine distension or contraction. Fetal or maternal stress can trigger the release of hypothalamic (corticotropin-releasing hormone, oxytocin) and adrenal (cortisol, adrenaline) hormones. Inflammatory and infectious processes (chorioamnionitis, cervicitis) promote the release of endotoxins and inflammatory cytokines, such as TNF-alpha and interleukins. Decidual bleeding with the production of thrombin increases uterine contractility. Abnormal uterine contractility may involve oxytocin receptors, a relative decrease in progesterone, or gap junctions **[9]**.

Etiology of Preterm Labor

Consists of chorioamnionitis, intrauterine infection, anomalies of the placenta, anomalies of the uterus, cervical isthmus incompetence, pathology of the fetus, uterine hypertension, frequent uterine contractility before term, and other causes. The onset of labor can be triggered when local uterine factors stimulate the uterine contractility cascade early and dilate the cervix, or when factors that inhibit it are suppressed. Therefore, a pro-inflammatory response originates with the release of a considerable amount of cytokines, such as the tumor necrosis factor (TNF-alpha) and interleukins (IL-1, IL-6, and IL-8), and with the activation of T cells in the maternal-fetal interface and the uterine cervix. In particular, a subtype of TH 1 cells has been studied and found to be present in the umbilical cord blood of premature newborns, in contrast to those born at term. Due to this, premature activation of these inflammatory pathways justifies preterm labor, being the most relevant mechanism **[1]**.

Vitamin D deficiency has also been identified as a risk factor for the development of preterm labor, suggesting that it plays an important role in suppressing the maternal immune response and TH 1 -mediated inflammatory pathways, which lead to at the start of childbirth **[1]**.

Discussion

A meta-analysis conducted by Mansur et al.

concluded that the risk of preterm birth and low birth weight along with small size for gestational age would increase with 25(OH)D deficiency during pregnancy **[12]**. Another study showed that pregnant women with 25(OH)D less than 20 ng/mL at 35 weeks of gestation had a 1.8 times greater risk of preterm delivery compared to women with 25(OH)D greater than or equal to 30 ng/mL, and this risk was 2.1 times greater for 25(OH)D less than 12 ng/mL. The risk of preterm birth has been assessed in supplementation studies without finding any association with vitamin D deficit in Asian women, so it is unclear whether differences in skin pigmentation and baseline levels can alter the results **[13]**.

Wagner et al. observed a 60% decline in preterm births in US mothers with vitamin D concentrations greater than 40 ng/mL. The authors concluded that the prescription of supplementation of at least 4000 IU/day was necessary to reach these levels **[14]**. According to five observational studies that analyzed the association between vitamin D and preterm delivery, the highest level of evidence was found with vitamin D values below 20 ng/mL and the lowest level of evidence with vitamin D values above 30 ng/mL **[15]**.

Lian et al. **[2]**, in their meta-analysis, found evidence to suggest that vitamin D deficiency in the second trimester of pregnancy is associated with an increased risk of preterm delivery and that there is a small relationship between vitamin D deficiency in the second trimester of pregnancy. first and third trimester of pregnancy and prematurity.

Conclusion

It is known that hypovitaminosis D during pregnancy can be a risk factor for preterm birth and all its complications for the newborn. But its isolated supplementation during pregnancy is still not a preventive action with statistically significant benefits in preterm birth. Researchers and physicians should be made aware of this issue to improve prenatal care. Strategies adopted to prevent preterm birth are scarce, and it is hoped that in the posterity the evidence mentioned in this article on the role of vitamin D may help to reduce its incidence and, consequently, mortality and, as such, improve the health of women pregnant women and their respective descendants.

Acknowledgement

Not applicable.

Ethical Approval

Not applicable.

Informed consent

Not applicable.

Funding

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

References

1. Rodrigues BF. Fisiopatologia da vitamina D3 no parto pré-termo [Internet]. Coimbra, Portugal: Faculdade de Medicina, Universidade de Coimbra; 2020. [cited 2022 May 24]. Tese. Available from: TF MIM - Fisiopatologia da vitamina D3 e o PPT - Bárbara R..pdf (uc.pt)
2. Lian RH, Qi PA, Yuan T, Yan PJ, Qiu WW, Wei Y, et al. Systematic review and meta-analysis of vitamin D deficiency in different pregnancy on preterm birth: deficiency in middle pregnancy might be at risk. Medicine (Baltimore) [Internet]. 2021[cited 2022 May 27];100(24):e26303. Available from: Systematic review and meta-analysis of vitamin D deficiency in different pregnancy on preterm birth - PMC (nih.gov)
3. Dutra LV, Affonso-Kaufman FA, Cafeo FR, Kassai MS, Barbosa CP, Santos Figueiredo FW, et al. Association between vitamin D plasma concentrations and VDR gene variants and the risk of premature birth. BMC Pregnancy Childbirth [Internet]. 2019 Dec 31[cited 2022 May 21];20(1):3. Available from: Association between vitamin D plasma concentrations and VDR gene variants and the risk of premature birth - PMC (nih.gov)
4. Goulart PA, Goulart RN. Gestação e deficiência de vitamina D: artigo de revisão na literatura. Arq Catar Med [Internet]. 2017[cited 2022 Mar 18];46(1): Available from: Vista do GESTAÇÃO E DEFICIÊNCIA DE VITAMINA D: ARTIGO DE

REVISÃO NA LITERATURA (acm.org.br).

5. Pilz S, Zittermann A, Trummer C, Theiler Schwetz V, Lerchbaum E, Keppel MH, et al. Vitamin D testing and treatment: a narrative review of current evidence. Endocr Connect [Internet]. 2019[cited 2022 Jul 21];8(2):R27–43. Available from: Vitamin D testing and treatment: a narrative review of current evidence - PMC (nih.gov)
6. Karras SN, Wagner CL, Castracane VD. Understanding vitamin D metabolism in pregnancy: from physiology to pathophysiology and clinical outcomes. Metabolism. 2018;86:112–23.
7. Institute of Medicine (US). Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Editors Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Dietary reference intakes for calcium and vitamin D [Internet]. Washington (DC): National Academies Press (US); 2011 [cited 2022 Apr 19]. (The National Academies Collection: Reports funded by National Institutes of Health). Available from: Dietary Reference Intakes for Calcium and Vitamin D - NCBI Bookshelf (nih.gov)
8. Sotunde OF, Laliberte A, Weiler HA. Maternal risk factors and newborn infant vitamin D status: a scoping literature review. Nutr Res. 2019;63:1–20.
9. Bittar RE. Parto pré-termo. Rev Med (São Paulo). 2018;97(2):195-207.
10. ACOG Committee Opinion No. 495: Vitamin D: Screening and supplementation during pregnancy. Obstet Gynecol. 2011;118(1):197–8.
11. Budhwar S, Verma P, Verma R, Gupta S, Rai S, Rajender S, et al. Altered cord serum 25-hydroxyvitamin D signaling and placental inflammation is associated with pre-term birth. Am J Reprod Immunol. 2020;83(2):e13201.
12. Mansur JL, Oliveri B, Evangelina G Fusaro D. Vitamina D: before, during and after pregnancy: effect of neonates and children. Nutrients [Internet]. 2022[cited 2022 Jun 2];14(9):1900. Available from: Vitamin D: Before, during and after Pregnancy: Effect on Neonates and Children - PMC (nih.gov)
13. Abrams SA. Vitamin D in preterm and full-term infants. Ann Nutr Metab [Internet]. 2020[cited 2022 Jan 21];76 Suppl 2:6-14. Available from: Vitamin D in Preterm and Full-Term Infants (karger.com)
14. Wagner CL, Baggerly C, McDonnell S, Baggerly KA, French CB, Baggerly L, et al. Post-hoc analysis of vitamin D status and reduced risk of preterm birth in two vitamin D pregnancy cohorts compared with South Carolina March of Dimes 2009-2011 rates. J Steroid Biochem Mol Biol [Internet]. 2016;155(Pt B)>245-51. [cited 2022 May 21];155(Pt B):245-51. Available from: Post-hoc analysis of vitamin d status and reduced risk of preterm birth in two vitamin d pregnancy cohorts compared with south carolina march of dimes 2009-2011 RATES - PMC (nih.gov)
15. Bialy L, Fenton T, Shulhan-Kilroy J, Johnson DW, McNeil DA, Hartling L. Vitamin D supplementation to improve pregnancy and perinatal outcomes: an overview of 42 systematic reviews. BMJ Open [Internet]. 2020 [cited 2022 Jul 27];10(1):e032626. Available from: Original research: Vitamin D supplementation to improve pregnancy and perinatal outcomes: an overview of 42 systematic reviews - PMC (nih.gov).