Benefits of prenatal and postnatal vitamin D supplementation

Alicja Kołodziejczyk-Nowotarska
Neonatal and Intensive Care Department, Medical University of Warsaw, Poland
https://orcid.org/0000-0002-9380-4723
Corresponding author: zuzialicja@gmail.com

Renata Bokiniec
Neonatal and Intensive Care Department, Medical University of Warsaw, Poland
https://orcid.org/0000-0002-1164-8406

Joanna Seliga-Siwecka
Neonatal and Intensive Care Department, Medical University of Warsaw, Poland
https://orcid.org/0000-0002-4628-0541

ABSTRACT
The best evidence for the role of vitamin D in infants is its influence on skeletal growth, however, the pleiotropic actions of vitamin D in the foetus and neonates are under-researched. The systematic reviews, based mostly on observational studies, suggest correlations between prenatal and postnatal supplementation and the occurrence of allergy, respiratory infections, sepsis or mental and behavioural development. Some of these studies focused on subgroups of neonates, such as preterm infants, investigating the influence inter alia on sepsis, bronchopulmonary dysplasia, and necrotising enterocolitis. Currently, there is a need for randomised trials for proof of the skeletal and pleiotropic effects of vitamin D in infants.

Introduction
The best evidence for the role of vitamin D (vit D) is its influence on skeletal growth [1]. Dietary or supplemental intake of vitamin D after intestinal absorption or from 7-dehydrocholesterol in the skin is bonded to vit D binding protein(DBP) in blood and converted to 25-hydroxyvitamin D (25(OH)D) in the liver, which is hydroxylated to the active form 1,25‐dihydroxycholecalciferol in the kidney. The active form increases intestinal calcium absorption, renal calcium and phosphate reabsorption, regulating mineral homeostasis and parathormone secretion. Conversely, parathormone, calcium and phosphorus regulate the level of the active form. Severe vit D deficiency in children can lead to the development of nutritional rickets. In the first half of the 20th century, vit D supplementation during infancy became common, accompanied by a huge decrease in the incidence of nutritional rickets [2]. Conversely, the available data does not provide definitive evidence that vit D influences bone mineral density (BMD) in children [3]. Indeed, the data from
the most recent Cochrane database systematic review does not provide sufficient evidence to assess the influence of vit D deficiency in breast-fed term infants on biochemical or radiological rickets and BMD. However, there is low-certainty evidence of maternal supplementation on the incidence of biochemical markers of rickets (14% decrease) in a subgroup of term infants with a high risk of vit D deficiency [4].

Preterm infants are particularly at risk of metabolic bone disease and vit D deficiency [5,6]. Additionally, vit D deficiency at birth due to lack of supplementation during pregnancy is a risk factor for reduced intrauterine bone growth due to inferior placentation [7]. The most recent meta-analysis of observational studies considered the influence of vit D deficiency (below 20 ng/ml) during pregnancy on the occurrence of small for gestational age infants and preterm birth [8]. The benefits of maintaining higher vit D levels in pregnant women to decrease preterm birth and small for gestational age infants were observed inter alia in studies with a large sample size conducted in California and Sweden [9,10]. However, other meta-analyses which also included randomised trials suggest that a deficiency rather than insufficiency is associated with preterm birth [11]. Low birth weight is associated with increased illness and mortality in infancy, consequently, reduced height in later life [12]. A lower areal BMD in early adulthood is more frequently observed in studies of preterm and very low birth weight infants [13,14] but it is not clear whether this can lead to osteoporosis in adulthood. Systematic reviews which evaluate the impact of vit D supplementation in pregnancy on infant BMD remain inconclusive [15], only confirming the prevention of neonatal hypocalcaemia in infants born to mothers who received vit D supplements [16]. A double-blind randomised trial with a good rate of follow-up conducted in Denmark demonstrated an association between high vit D supplementation during pregnancy (2400 IU) and 50% reduced odds of enamel defects in children at six years old [17].

Currently, the most prevalent role of non-skeletal vit D under investigation is its immunomodulatory impact. The vit D receptor is present on B cells, T cells, macrophages, and dendritic cells and can play a role in the immune response [18]. An inappropriate immune response influences the development of autoimmune disease. A systematic review based on observational studies suggests a correlation between early vit D supplementation in children and protection against the occurrence of type 1 diabetes, with dose response effects [19]. In a large sample size birth-cohort study conducted in Finland, children with high dose vit D supplementation (2000 IU) had a significantly reduced risk of type 1 diabetes [20]. The meta-analysis investigating inter alia the influence of prenatal and postnatal early vit D supplementation on allergic rhinitis, wheezing and asthma in children concluded that due to limited information, an early prevention impact still remains uncertain [21]. Nevertheless, a combined analysis of two large, randomised trials of vit D supplementation in pregnancy performed in the United States shows a significant 26% decrease in wheezing or asthma in the offspring by 3 years of age and was more pronounced for children whose mothers had achieved a sufficient 25(OH)D level [22]. However, in a Danish study, the protective effect of high vit D supplementation during pregnancy on persistent wheezing and the occurrence of asthma in the offspring at the age of 3 years was not observed at 6 years of age (limitation: target sample size was not achieved on follow-up). The Finnish researchers performed the study based on the hypothesis of a positive correlation between vit D supplementation in infancy and an increased risk of atopy and allergic rhinitis in adult life [23]. Also, the potential vit D impact on food allergy among infants through promotion of immunological tolerance is under investigation. Since data from different observational studies are contradictory [24], there is a need to undertake a randomised trial targeted at this potential correlation.

Secondly, the vit D dependent immune response modulates the development of infectious disease. Vit D receptors can be found not only within the immune system but also on airway epithelial cells. Respiratory tract infections among neonates are mostly viral in origin, typically manifesting as wheezing, pneumonia or bronchiolitis. The influence of vit D supplementation in pregnancy and the neonatal period on the development and severity of the upper or lower respiratory tract infections in early childhood is currently under investigation in clinical trials. However, most studies concur that vit D status in young children modulates the occurrence and severity of respiratory infections [25,26]. In a
recent metanalysis, investigators examined the hypothesis that vit D can modulate the immune response in neonatal sepsis (NS) [27], an infection in the first 28 days of life including bloodstream infections, meningitis, and pneumonia. However, the analysis was based solely on observational studies and there was significant heterogeneity among the studies. Furthermore, an analysis was performed in a subgroup for an association between cord blood and maternal vit D level and the development of early-onset sepsis in term infants, showing a positive correlation between vit D deficiency during pregnancy and at birth and incidence of NS including early onset.

The influence of vit D on the immune response in preterm infants is a separate discussion. The most recent studies consider an association between maternal, cord or neonatal blood vit D level in a group of premature neonates and the occurrence of NS as well as necrotising enterocolitis (NEC), which in origin favour a pro-inflammatory mechanism [28,29]. In Cetinkaya's study, the maternal vit D level was a significant predictor of NEC, whereas in Say's study, the cord blood vit D level did not correlate with the risk of NS. Furthermore, antenatal vit D deficiency is linked to both airway inflammation and impaired anatomical and functional lung development which can lead to bronchopulmonary dysplasia in preterm infants. A meta-analysis based on four trials detected a significant association between vit D deficiency at birth and the development of bronchopulmonary dysplasia based on oxygen dependency at 28 days of age or 36 weeks of corrected age with no significant heterogeneity existing between the studies [30].

The last potential effect of vit D described in this short review is the effect on brain development, including neurotrophic and neuroprotective actions and changes in brain structure. A prospective study conducted on mother-child pairs reported a correlation between insufficient vit D pregnancy level and offspring language impairment at 5 and 10 years of age without offspring behavioural and emotional difficulties at any age [31]. Another large-scale prospective cohort study showed that higher 25(OH)D concentrations in pregnancy are associated with improved offspring mental and psychomotor scores in infancy [32]. The limitations of the study included the residual possibility of confounding by parental intelligence and lack of information on neonatal vit D supplementation. However, these results suggest that an optimal 25(OH)D level could improve early foetal brain development. Contrary to the latter research, a prospective cohort study with long term follow-up did not provide evidence inter alia that a higher maternal vit D status can support scholastic achievement among offspring [33].

Conclusions

The influence of vit D on neonatal health is one of the hot topics of the previous decade. The investigation of the skeletal and pleiotropic roles of vit D among infants is based on an increasing number of observational studies and their systematic reviews but there is a great need for randomised trials.

Abbreviations

Vit D - vitamin D; BMD - bone mineral density; NS - neonatal sepsis; 25(OH)D - 25-hydroxyvitamin D; NEC - necrotising enterocolitis

Acknowledgements

Conflict of interest statement

The authors declare no conflict of interest.

Funding sources

There are no sources of funding to declare.

References


