www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2013;2(2):e020202
doi: 10.7363/020202 Received: 2013 Jun 06; accepted: 2013 Jul 03; advance publication: 2013 Aug 12

Review

Vitamin D in the perinatal period: an update

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Abstract

Vitamin D is a pleiotropic hormone modulating calcium and phosphorous metabolism. Numerous extraskeletal functions of vitamin D have been shown in recent years and the role of an adequate vitamin D status during pregnancy in terms of benefits for mother and child has been investigated. Presumed effects on pregnancy course include reduction in risk of pre-eclampsia, caesarian and preterm delivery and gestational diabetes mellitus. Short term outcomes in the offspring such as skeletal development, birthweight, and incidence of infections have also been postulated. Finally, long term effects of maternal vitamin D status during pregnancy on infant and child health would include bone health, neurodevelopment and incidence of asthma, infections and autoimmune diseases such as type 1 diabetes mellitus. As vitamin D deficiency is widespread among pregnant women all over the world, supplementation during pregnancy is a hot topic in literature, also in the light of these recent acquisitions. This review will summarize the most recent advances in this field.

Keywords

Vitamin D, pregnancy, newborn, infant, child, supplementation.

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How to cite

Fanos M, Vierucci F, Saggese G. Vitamin D in the perinatal period: an update. J Pediatr Neonat Individual Med. 2013;2(2):e020202. doi: 10.7363/020202.

Introduction

Vitamin D has traditionally been viewed as a fundamental hormone in the regulation of phosphorus and calcium and bone metabolism. In recent years, the discovery of a new world of extraskeletal and particularly immunomodulatory effects renewed the interest of research on vitamin D. In this light, an adequate vitamin D status appears to be relevant to health at

all ages, and even in prenatal life. In fact, maternal vitamin D levels in pregnancy may have an impact on its course and on the health of fetus, newborn and even child in a longer term. Since vitamin D deficiency is commonly observed in pregnant women around the world [1], there is growing interest in the definition of vitamin D health benefits and supplementation during pregnancy.

Vitamin D physiology

Vitamin D production starts in the skin, where vitamin D_3 is synthesized from 7-dehydrocholesterol after sun exposure. Vitamin D_2 and vitamin D_3 may also be introduced with food but the relative contribution of dietary sources is scarce compared to endogenous production [2, 3]. These compounds are hydroxylated in the liver and converted into 25-hydroxy-vitamin D (25(OH)D), which is in turn converted into 1,25-dihydroxy-vitamin D ($1,25(OH)_2D$) by 1-alpha-hydroxylasis in the proximal tubules of the kidney. The last hydroxylation reaction may actually occur in several other tissues and organs, particularly the placenta [4]. $1,25(OH)_2D$ is the active form of vitamin D that acts binding to vitamin D receptors (VDRs) both in the nucleus and in plasma membrane of target cells [5]. Classic genomic effects of $1,25(OH)_2D$ involve calcium and phosphorus homeostasis and account for their absorption through the intestinal wall, calcium reabsorption from ultrafiltrate in the kidney, activation of preosteoclasts into active osteoclasts in bone turnover and negative feedback regulation of parathormone [4]. Numerous new functions of vitamin D besides bone metabolism have been discovered in recent years. At least 37 types of tissues express VDRs [4] and vitamin D has been recently shown to regulate up to 291 genes in vivo [6]: these data support the existence of pleiotropic effects. These include a role for vitamin D in the cardiovascular system, muscles, and the immune system. The immunomodulatory role of vitamin D is of particular interest, as it contributes to activate innate immune response while inactivating the adaptive immune system and these effects have been implicated in several autoimmune conditions [7].

During pregnancy, vitamin D maternal metabolism undergoes a series of adaptations as the fetus is completely dependent on placental delivery and therefore on maternal intake and production [8]. Vitamin D synthesis increases not only in the kidney, but also in the placenta [9]. However, $1,25(OH)_2D$ is not able to cross the placenta while 25(OH)D enters fetal circulation and is then hydroxylated into the corresponding active form in the fetal kidney [10]. Traditionally, these changes in the mother and the fetus have been interpreted as a response to fetal need of calcium. Given the wide distribution of VDRs in the organism, and considered the already mentioned wide variety of extraskeletal effects of vitamin D, it has been suggested that other biological responses might be regulated by the physiologically increased levels of $1,25(OH)_2D$ in pregnancy [9].

The question of adequate levels of vitamin D has been largely discussed over years. Besides the issue of the use of different 25(OH)D dosing methods and the problem of inter-assay disagreement [11], there is still no consensus on which levels should define vitamin D sufficiency or deficiency. The Institute of Medicine (IOM) sets the cutoff for vitamin D sufficiency at a serum level of 20 ng/ml [12] in the adult, while the Endocrine Society identifies three categories: deficiency < 20 ng/ml, insufficiency 21-29 ng/ml, sufficiency > 30 ng/ml [13]. The same definitions apply to vitamin D levels in pregnant women.

Hypovitaminosis D is prevalent in 18-84% of women, depending on country of origin and lifestyle [14] and recent surveys in European countries found a prevalence of levels < 30 ng/ml of 10-30% in pregnant women [15]. A reasonable practice seems to screen pregnant women at risk for hypovitaminosis D to ensure that their serum 25(OH)D level is higher than 30 ng/ml. Risk factors include reduced or inefficient sun exposure (i.e. season, latitude, lifestyle, non-caucasian ethnicity, concealing clothing) or pathological conditions (i.e. malabsorption, liver and kidney diseases) [16].

Effects of vitamin D status on the mother and the course of pregnancy

Numerous recent studies suggested that maternal vitamin D levels during pregnancy affect the course of pregnancy and the health of the offspring. Presumed effects of vitamin D during pregnancy are outlined in **Tab. 1**. With regards to the course of pregnancy, an adequate maternal vitamin D status has been related to a lower risk of pre-eclampsia, gestational diabetes mellitus (GDM), caesarian section and preterm delivery.

First of all, vitamin D deficiency has been associated with a higher incidence of pre-eclampsia in several observational studies [17-19] and in two recent meta-analysis [20, 21]. Besides

Table 1. Presumed effects of vitamin D during pregnancy on maternal and child outcomes.

Effects on the mother and the course of pregnancy • Pre-eclampsia • Gestational diabetes mellitus (GDM) • Caesarian section • Preterm delivery
Short-term effects on the fetus, the newborn and the infant • Bone metabolism • Birth length and weight • Immunomodulatory effects: infections
Long-term effects on the child • Bone mineral content and growth • Immunomodulatory effects: asthma, allergy and diabetes mellitus • Neurodevelopment

regulating gene expression relevant to placental development [18], vitamin D would be implicated in immunoregulation and hypovitaminosis D would therefore lead to an inappropriate activation of lymphocyte Th_1 response, which is typical of pre-eclampsia [22]. Furthermore, Wei et al. found that women with vitamin D deficiency (< 20 ng/ml) were more likely to have low levels of placental growth factor, which were associated with an increased risk of preeclampsia. Further research should elucidate whether this association indicates a possible role for vitamin D deficiency in impaired angiogenesis [23]. As the exact role of vitamin D in the pathogenesis of pre-eclampsia is still not clear [18] and clinical trials are limited in number and design [14], several Authors urge for further research in this field [22].

GDM has also been investigated in connection with vitamin D status. In spite of mixed views [24], several studies hint to a correlation between maternal hypovitaminosis D and a higher risk of disease, primarily a 2008 observational study by Zhang et al. (25(OH)D < 20 ng/ml, OR = 2.66) [25]. A noteworthy paper by Lau et al. in 2011 confirmed previous results and further showed an inverse association between 25(OH)D and glycated hemoglobin HbA1c [26]. Parlea et al. in the same year showed a double risk of having GDM in women with low vitamin D levels and defined a threshold serum level of 30 ng/ml for GDM to become apparent, suggesting that not only vitamin D deficiency but even insufficiency would increase the risk of developing GDM [27]. These observational results were confirmed in a recent study by Burris et al. [24]. In fact, vitamin D would regulate insulin secretion through a calcium-mediated mechanism and insufficiency would therefore lead to altered glucose homeostasis [27]. Three recent meta-analysis also confirmed that 25(OH)D levels are significantly lower in pregnant women with GDM than controls [20, 28, 29]. Nevertheless, the actual role of vitamin D in the pathogenesis of GDM is still a matter of debate [28].

A two to four times higher risk of caesarian delivery has been associated to low maternal vitamin D levels in recent years [30, 31]. Observational studies suggest that vitamin D deficiency would undermine pelvic muscle strength and thus pushing ability at delivery [32], as well as preventing the initiation of labor, which depends on high serum calcium. Finally, low vitamin D levels would represent a risk factor for pre-eclampsia and infections in pregnancy and would thus indirectly increase the resort to caesarean section [30]. However, some Authors did not find any association between maternal vitamin D status and caesarian delivery [33, 34] so this topic remains controversial.

Preterm delivery has also been associated to vitamin D deficiency in a few studies (< 20 ng/ml, [31]) (< 15 ng/ml, [35]). Vitamin D would be involved in immune tolerance and placental implantation and its deficiency would increase the risk of preterm child birth. The exact mechanism however is still not known [31] and considering controversial results obtained in different observational studies [36], these data still have to be confirmed.

Low vitamin D serum levels (< 10 ng/ml) have been associated to several other maternal adverse effects, such as bone reabsorption, myopathy and inadequate calcium homeostasis. Not only severe vitamin D deficiency, but also mild insufficiency (11-32 ng/ml) would be enough to determine bone loss and subclinical myopathy [14].

Short-term effects on the fetus, the newborn and the infant

Bone metabolism

Severe vitamin D deficiency in the mother during pregnancy has long been associated to impaired bone metabolism and development in the fetus [37]. A series of observational studies support this correlation showing abnormal fetal skeletal markers, such as fetal femoral or tibial cross-sectional area measured by ultrasound, in mothers with low vitamin D levels (< 20 ng/ml, [38]; < 17 ng/ml, [39]). As a result, as neonatal vitamin D adequacy is strictly dependent on the mother's status during pregnancy, congenital rickets, craniotabes

and osteopenia may present in newborns of mothers with severe vitamin D deficiency [14, 40].

Birth length and weight

A correlation between birth weight and maternal vitamin D status during pregnancy has been proposed. Several observational studies have shown that adequate vitamin D levels correlate with heavier neonatal birth weight [15]. A recent observational study including 2,146 mothers found that maternal 25(OH)D levels > 15 ng/ml were associated to higher neonatal birth weight [41]. With regards to supplementation, Scholl et al. in 2009 demonstrated that women ingesting less than 200 IU/day of vitamin D gave birth to newborns of lower birth weight, compared to mothers who had higher plasma vitamin D levels in the third trimester of pregnancy [42]. Kalra et al. recently showed that birth weight and length were greater in mothers supplemented in the second and third trimesters of pregnancy (n = 48, one dose of 1500 μg; n = 49, two doses of 3000 μg) than in the untreated control group [43].

Leffelaar et al. in 2010 further showed an increased risk of small for gestational age (SGA) births in mothers with low vitamin D levels (< 12 ng/ml) in early pregnancy [44]. Among other Authors, this fact was recently confirmed by Burris et al. in 2012 [45] and a role for single-nucleotide polymorphisms (SNPs) of the VDR gene were suggested to account at least in part for SGA births [46]. However, not all studies support these findings and as results are still controversial, large interventional studies are needed [15].

Immunomodulatory effects: infections

A series of observational clinical studies suggested a role for vitamin D in the immune response against respiratory tract infections. Belderbos et al. in a 2011 longitudinal study showed that vitamin D deficiency (< 20 ng/ml) at birth is associated to a higher risk of lower respiratory tract infections (LRTI) by Respiratory Syncytial Virus (RSV) [47]. Camargo et al. in the same year showed a correlation between low neonatal vitamin D levels at birth and a higher risk of respiratory tract infections in the first three months of life (25(OH)D 10-30 ng/ml, OR = 1.39; 25(OH)D < 10 ng/ml, OR = 2.16) [48]. Finally, on the wake of these results, a recent cohort-study in more than 1,700 mother-children pairs showed an inverse association between maternal vitamin D levels during pregnancy and the risk of respiratory tract infections in the child during the first year of life [49].

Long-term effects on the child

Bone metabolism and growth

A few recent studies suggested a correlation between maternal vitamin D status and bone mass and growth in later childhood. A landmark observational study by Javaid et al. found that maternal 25(OH)D levels < 20 ng/ml during pregnancy were associated to reduced whole-body and lumbar-spine bone mineral content in their children at the age of nine years [50]. Even though this paper did not take into account confounding factors contributing to bone mass accrual during childhood [51], low vitamin D levels during pregnancy could indeed account for "fetal imprinting" in bone formation and development [10]. A study by Viljakainen et al. partially confirmed these results, reporting a correlation between lower vitamin D status during pregnancy and smaller distal tibial cross sectional area at 14th months [52]. However, a recent study by Lawlor et al. including 3,960 mother and child pairs found no association between maternal 25(OH)D levels during pregnancy and bone mineral content in their children at 9 years of age, contradicts the work by Javaid et al. and remarks some confounding factors that could possibly explain the inconsistency of the results [53]. Interestingly, partly on the basis of the recent denial of these vitamin D long term effects on the offspring bone health, a Comment on the Lancet questioned on the advisability of vitamin D supplementation during pregnancy [54].

Immunomodulatory effects: asthma, allergy and diabetes mellitus

Immunomodulatory effects of vitamin D during pregnancy have been claimed to have a long-term effect on child health. Vitamin D during pregnancy would contribute to establish and maintain fetal T-cell repertoire and would affect lymphocyte Th_1-Th_2 balance, affecting the pattern of the immune responses of the child later in life [22].

For example, claims are that higher maternal vitamin D levels in pregnancy are protective against the risk of asthma in the child later in infancy [48, 55, 56]. A conflicting result was found by Gale et al. in a work on children of 9 years of age [55], but the analysis included only a small number of subjects and confounding factors were not examined [57].

The relationship between allergy and vitamin D during pregnancy is still a controversial issue. Some Authors recently suggested that vitamin D may not be protective against food allergy, claiming that high vitamin D levels during pregnancy enhance the risk within the first two years of life [58]. On the other hand, one study measuring maternal vitamin D intake during pregnancy assessed through questionnaires suggested that high levels of vitamin D could be protective against allergic rhinitis and asthma in childhood [59]. Other works simply found no correlation between vitamin D at birth and allergic rhinitis [60].

T1DM has also been considered. Observational studies have associated maternal vitamin D low levels during pregnancy to higher prevalence of auto-antibodies against islet cells in the baby [9]. A recent work by Sorensen et al. found that the risk of developing T1DM is twofold higher in children born from mothers with low vitamin D levels during pregnancy, compared to mothers with high levels [61]. These Authors however suggest further research on this point, as other observational works such as one by Marjamäki et al. [62] or another by Miettinen et al. [63] did not find any correlation between auto-antibodies against islet cells in the child and maternal vitamin D status during pregnancy.

Neurodevelopment

Finally, vitamin D has shown important extraskeletal functions regarding neurodevelopment. In fact, it is involved in several biological pathways, such as synaptic plasticity and neurotransmission [9] and regulation of neurotrophic factors [64]. Morales et al. found that maternal high levels of vitamin D during pregnancy were associated to improved mental and psychomotor development in infants [65]. Whitehouse et al. found an association between maternal 25(OH)D levels < 18 ng/ml during pregnancy and language difficulties in children of five and ten years of age [64].

Vitamin D deficiency has also been claimed to play a role in a few neurological and psychiatric pathologies since fetal life. Schizophrenia and multiple sclerosis in particular have been considered – however more studies are needed to draw conclusions on this issue [66, 67].

Evidence for supplementation

Current IOM guidelines recommend an intake of 600 IU/day in pregnant women [68]. The Endocrine Society in 2011 confirmed the IOM recommendations, but opened to a dose of 1,500-2,000 IU/die for women at risk for vitamin D deficiency [69]. In 2011 the American College of Obstetricians and Gynecologists also stated that a dose up to 1,000-2,000 IU/day would be safe in vitamin D deficient pregnant women, while quoting the IOM indications of 600 IU/day as the adequate intake for the general population of pregnant women [70].

Hollis et al. recently claimed that these doses may be too cautious and inefficient to gain vitamin D sufficiency during pregnancy. They pointed out that recommendation on the upper safe intake limit, which is stated 4,000 IU/day for IOM and 10,000 IU/day for the Endocrine Society, is by far lower than vitamin D concentrations that may be endogenously produced daily from natural sun exposure in humans, particularly in pregnant women, such as 10,000-20,000 IU of vitamin D/day [71]. These Authors recently conducted two RCTs comparing groups of pregnant women receiving different vitamin D doses (400 IU/day, 2,000 IU/day, 4,000 IU/day in the NICHD trial, 2,000 IU/day and 4,000 IU/day in the Thrasher Research Trial) [72, 73]. A combined analysis of both RCTs suggests that vitamin D supplementation of 4,000 IU/day in pregnant women is safe and allows to obtain adequate maternal and neonatal vitamin D levels, while seemingly reducing the risk of preeclampsia and infections [74]. Remarkably, supplementation started only after the 12th week of gestation, therefore no data is available on the safety of such high doses during the first trimester of pregnancy. Another recent RCT by Roth et al. found that a weekly dose of 35,000 IU would safely raise maternal vitamin D levels and suggested to consider this supplementation regimen in future trials [75]. Finally, a recent RCT by Dawodu et al. confirmed that 4,000 IU/day would be the most effective dose to raise vitamin D levels in vitamin D deficient pregnant women and their offspring [76].

Besides contrasting opinion about the dose, the importance of vitamin D supplementation in pregnant women is now widely accepted, even more in the light of the widespread deficiency in the general population. However, the new acquisitions on the health benefits for mother and child discussed earlier should be revised before they become the basis for clinical practice. First of all, most of the works on vitamin D during pregnancy are still observational studies and only a limited number of RCTs have been conducted

to date. Observational studies should be regarded as hypothesis generating papers and lay the foundation to further trials to confirm previous results [51, 77]. This is also the conclusion of two recent meta-analysis [78, 79], stating that currently there is only a low level of evidence that vitamin D supplementation during pregnancy would have positive effects on mother or child as the number of high quality trials is too low. Notably, however, no meta-analysis has yet included the aforementioned most recent RCTs. Finally, while all pregnant women should receive vitamin D supplementation, particular attention should be given to women at high risk of hypovitaminosis D. Consensus should be reached on tailored supplementation for women presenting with the aforementioned risk factors of reduced or inefficient sun exposure, particularly due to seasonality or pathological conditions impairing vitamin D metabolism [80, 81].

Conclusions

Several observational studies and a few recent RCTs suggested that maternal vitamin D levels during pregnancy affect the course of pregnancy and the health of fetus and child. Despite clear IOM and Endocrine Society recommendations, the adequacy of supplementation and suggested doses during pregnancy are a controversial issue. Recent favorable results should be confirmed in a larger number of RCTs before these promising acquisitions can translate into clinical practice. Nevertheless, current evidence suggests that 600 IU/day may not be enough to raise serum 25(OH)D level > 30 ng/ml in pregnant women and that 1,500-2,000 IU/day would safely allow to reach this target. At present, higher doses (4,000 IU/day) should only be considered in women with vitamin D deficiency (25(OH)D < 20 ng/ml) confirmed by laboratory testing. Screening for vitamin D deficiency is not advisable in all pregnant women and should be restricted to women at risk for hypovitaminosis D.

In conclusion, the issue of vitamin D effects during pregnancy and the adequacy of maternal supplementation is a fascinating and promising field of research. More investigations however are needed to guide clinicians through the mass of literature [77] as current studies are not yet conclusive. Hopefully such a simple and seemingly effective supplement would improve pregnancy outcomes and both child and maternal health in the near future.

Abbreviations

$1,25(OH)_2D$, 1,25-dihydroxy-vitamin D
25(OH)D, 25-hydroxy-vitamin D
GDM, gestational diabetes mellitus
IOM, Institute of Medicine
LRTI, lower respiratory tract infection
RCT, randomized controlled trial
RSV, Respiratory Syncytial Virus
SGA, small for gestational age
SNP, single-nucleotide polymorphism
T1DM, type 1 diabetes mellitus
VDR, vitamin D receptor

Declaration of interest

The Authors declare that there is no conflict of interest.

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