

Implications of maternal vitamin D deficiency for the fetus, the neonate and the young infant

Nicola Principi · Sonia Bianchini · Elena Baggi ·
Susanna Esposito

Received: 9 September 2012 / Accepted: 23 November 2012
© Springer-Verlag Berlin Heidelberg 2012

Abstract

Background It has recently been demonstrated that vitamin D (VD) deficiency during pregnancy and lactation can give rise to problems in mothers and their children.

Aim To discuss the implications of VD deficiency during pregnancy and the best VD supplementation to use in order to avoid risks for the mother and child.

Methods PubMed was used to select all of the clinical studies published in the last 15 years concerning VD deficiency in pregnant women and its impact on the fetuses, neonates and infants, as well as the use of VD supplementation during pregnancy.

Results Several studies have suggested that VD deficiency is associated with possible major outcomes in the preconception period, during pregnancy, perinatally and in childhood. A 25(OH)D concentration of >32 and <50 – 60 ng/mL seems to be associated with the lowest risk of disease, and the administration of 2,000 IU/day to pregnant and breastfeeding women seems to maintain adequate 25(OH)D levels. However, not all the experts agree with these conclusions because some of them do not think that VD deficiency can really cause extraskelatal manifestations and consider that the traditionally suggested 400–600 IU/day can be enough to permit an adequate bone development.

Conclusions Despite an increasing amount of data seems to suggest that pregnant women need a greater amount of VD than recommended in the past, further studies are

needed to determine how much VD has to be given to assure a regular evolution of the pregnancy and an adequate development of the fetus and the young child.

Keywords Bone development · Pregnancy · Respiratory infection · Vitamin D · Vitamin D deficiency · Vitamin D supplementation

Introduction

Vitamin D (VD) has long been considered an essential nutrient for bone health. Its role in pregnant women and children has been clearly defined by the demonstration that VD deficiency during intrauterine life and early childhood can lead to rickets, growth retardation, skeletal deformities and an increased risk of fractures risk [1, 2]. However, it is only recently that systematic VD supplementation became universally recommended for pregnant women. As late as 2004, the UK National Institute for Clinical Excellence in Antenatal Care recommended that VD supplementation should not be routinely offered to pregnant women [3], but now most of the experts worldwide suggest that women should be given VD supplements during pregnancy, although there is no agreement on the amount useful for assuring optimal pregnancy outcomes and childhood growth [4].

It has recently been demonstrated that VD can generate a number of biological responses other than those relating to bone metabolism, and that VD deficiency during pregnancy and lactation can give rise to problems in mothers and their children. Low maternal 25(OH)D levels have been associated with early-onset severe preeclampsia and poor effects of infertility treatment. On the contrary, VD supplementation seems to reduce the risk of primary

N. Principi · S. Bianchini · E. Baggi · S. Esposito (✉)
Pediatric Clinic 1, Department of Pathophysiology
and Transplantation, Università degli Studi di Milano,
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,
Via Commenda 9, 20122 Milan, Italy
e-mail: susanna.esposito@unimi.it

cesarean section, gestational diabetes and preeclampsia [5–9]. Downstream effectors of VD have been detected in fetuses with a gestational age of as young as 14 weeks, and it has been found that VD modulates early lung development and surfactant production [10, 11]. It has also been shown that serum 25(OH)D levels during pregnancy can condition the expression of tolerogenic genes, which suggests that the immunomodulatory function of VD (widely demonstrated in vitro and in vivo in experimental animals and humans of any age) occurs prenatally [12]. Moreover, diseases of neonates and young infants other than congenital rickets have been associated with a low VD intake by pregnant mothers, thus confirming that substantial VD supplementation is necessary to assure optimal baby health.

This new knowledge has convinced various experts that greater VD supplementation than usually recommended is needed during pregnancy in order to assure optimal maternal health, adequate fetal development and a healthy postnatal life. The main aim of this review is to discuss the implications of VD deficiency during pregnancy and the best VD supplementation to use in order to avoid risks for the mother and child. PubMed was used to select all of the studies published in the last 15 years using the following combinations of text words: “VD” and “pregnant women” or “pregnancy” or “fetus” or “neonate” or “infant.” More than 1,500 articles were found, but only papers published in English as well as those showing evidence-based data or presenting recommendations from Scientific Societies were included.

Prevalence of VD deficiency in pregnant women

About 40 years ago, it was decided that, despite 1,25(OH)D was the active form of VD, serum 25(OH)D levels could provide the best measure of VD status and that evaluating their Gaussian distribution in the healthy general population could establish the cut-off level for defining so-called VD deficiency. At that time, it was thought that 25(OH)D concentrations of <10 ng/mL were indicative of deficiency in otherwise healthy adults, whereas higher values always indicated normality [13].

However, a more recent and detailed analysis of the ways in which VD becomes available to the body has led to the conclusion that the old methods of assessing VD status were grossly inaccurate because factors such as limited ambient ultraviolet radiation, inadequate sun exposure and host factors could significantly influence the final results and lead to a wrong cut-off value [14]. Moreover, data collected in studies evaluating the correlation between plasma 25(OH)D levels and a series of biomarkers [intestinal calcium absorption, maximal parathyroid hormone (PTH) suppression, bone fracture prevention and optimal bone turnover] clearly indicate that only concentrations

significantly higher than 10 ng/mL can permit an adequate bone metabolism [15]. However, there is no definite consensus about the minimum normal 25(OH)D value for healthy humans of different ages and whether and how this minimum level has to be increased for particular subjects such as pregnant women. The Institute of Medicine of the USA (IOM) that bases its recommendation on what is needed to maintain skeletal integrity indicates that if a pregnant woman exhibits a circulating level of 20 ng/mL, she should be considered replete [16]. On the contrary, the Endocrine Society that consider also other VD-dependent factors recommends a circulating level ≥ 30 ng/mL in order to assure a satisfactory evolution of the pregnancy and an optimal fetal development [17]. Other experts consider suboptimal all the 25(OH)D serum values lower than 32 ng/mL and distinguish deficiency when the 25(OH)D is <20 ng/mL from insufficiency if it is between 20 and 29 ng/mL (Table 1) [18]. On the basis of these premises, most studies of 25(OH)D levels in pregnant and breastfeeding women have found that deficiency is an ongoing epidemic, although its prevalence may vary significantly depending on the characteristics of the enrolled populations, the role played by factors influencing VD skin synthesis and the amount of VD supplementation (Table 2). In most cases, the studies have clearly shown that the dose of solar irradiation, skin phototype and dietary VD intake can significantly condition serum 25(OH)D levels in pregnant women [18–21]. Figure 1 summarizes VD pathway. Black women living at latitudes of more than 51° who do not receive VD supplementation during pregnancy and lactation are at the highest risk of deficiency; furthermore, because of their high melanin pigmentation, they remain at higher risk even when they live at lower latitudes and receive VD supplementation [18–21]. Bodnar et al. [18] measured serum 25(OH)D levels in 200 white and 200 black pregnant Americans living in the north of the USA and classified them as having deficient (≤ 10 ng/mL), insufficient (11–32 ng/mL) or adequate levels (> 32 ng/mL). At the time of delivery, VD deficiency and insufficiency were recorded in 29.2 and 54.1 % of the black women and in 5 and 42.1 % of the white women, respectively. The results were similar at <22 weeks of gestation. After adjusting for their pre-pregnancy body mass index (BMI) and peri-conceptual multivitamin use, the black

Table 1 Vitamin D reference values

Stage	Serum 25(OH)D, ng/mL
Deficiency	<20
Insufficiency	20–29
Adequacy	30–99
Toxicity	≥ 100

Table 2 Risk factors for vitamin D deficiency

Major risk factor	Specific risk factor
Low ambient ultraviolet radiation	Northern latitudes
	Winter season
	High level of air pollution
Limited sun exposure	Excessive sun avoidance (i.e., shade, sunscreen)
	Extensive clothing cover
	Built or indoor environment
Host factors	Dark skin
	Obesity
	Aging
	Inappropriately low dietary intake
	Malabsorptive syndrome (i.e., celiac disease, Whipple's disease, cystic fibrosis, inflammatory bowel syndrome, short gut syndrome)
	Liver and renal diseases
	Use of certain drugs (i.e., glucocorticoids, phenytoin, phenobarbital, highly active antiretroviral therapy, rifampin)

women showed a smaller mean increase in maternal 25(OH)D from winter to summer ($p < 0.01$) and remained significantly more frequently VD deficient [18]. Johnson et al. [19] evaluated pregnant women of different races living at a southern latitude in the USA and found that, although most of them had 25(OH)D levels of <32 ng/mL, almost all of the African-Americans had inadequate VD concentrations. Similarly, Hamilton et al. [20] studied 559 women living in South Carolina at a latitude of 32°N (48 % African-Americans, 38 % Hispanics and 14 % white or belonging to other races) and found that 48 % were VD deficient, and an additional 37 % had insufficient 25(OH)D levels. Finally, Ginde et al. [21] who conducted a secondary analysis of 928 pregnant and 5,173 nonpregnant women aged 13–44 years from the National Health and Nutrition Examination Survey 2001–2006 found that minority race as well as ethnicity were independently associated with significant lower 25(OH)D levels.

However, together with these factors, nutritional status could also contribute to the development of VD deficiency. It has been found that increases in serum 25(OH)D concentration following exposure to UV-B radiation correlate positively with cholesterol levels, regardless of skin phenotype, suggesting that a very low cholesterol serum concentration could cause problems in natural VD synthesis [22].

Impact of VD deficiency in pregnant women on fetuses, neonates and infants

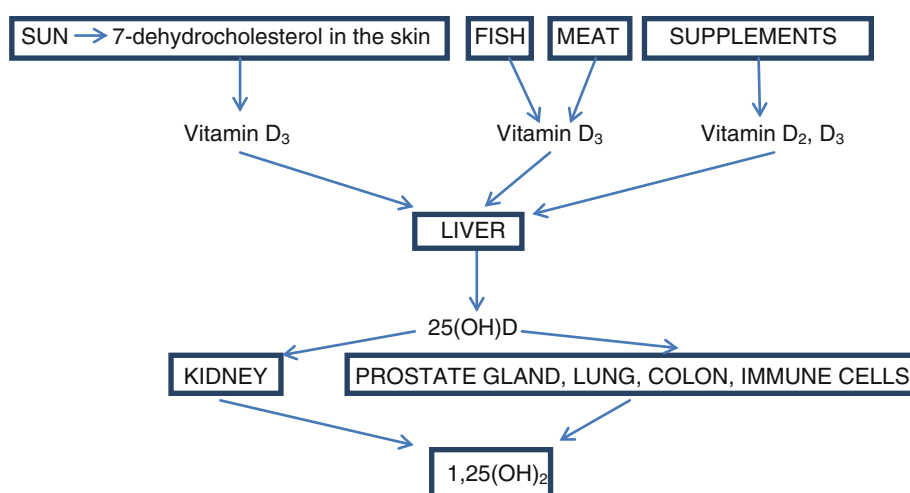
Body weight and bone development

Fetuses depend entirely on the mother for the supply of calcium and 25(OH)D, which crosses the placenta and

reaches cord blood concentrations similar to or only slightly lower than those found in women at delivery [23]. Consequently, VD concentrations are lower in black neonates than in those born to white mothers although, as in the mothers, the differences are more evident during the winter. Basile et al. [23] measured 25(OH)D levels in 100 cord blood samples and found that African-American infants had significantly lower levels than their white counterparts (10.5 ± 6.0 vs. 19.5 ± 9.6 ng/mL; $p < 0.0001$). The mean 25(OH)D level in the white born in November–March (15.7 mg/mL) was 11.3 ng/mL lower than that in those born in April–October (29.0 ng/mL), whereas the difference among the African-American infants was 3 ng/mL (10.1 and 13.1 ng/mL) [23].

Albeit with some exceptions [24], most of the studies carried out over the last 30 years have clearly shown that children whose mothers had higher levels of 25(OH)D in the third trimester of pregnancy [25] or who received VD supplementation, while their child was in utero [26], showed better postnatal growth or a higher whole body and lumbar spine bone mineral content. More than 20 years ago, it was found that VD-supplemented Asian women living in India [27] or London [25] gained significantly more weight and had infants with higher birth weights than those not receiving supplementation living in Asia. The increases in birth weight ranged from 80 to 410 g, and one study showed a twofold reduction in low birth weight [23]. More recently, Burris et al. [28] found that second trimester 25(OH)D levels of <10 ng/mL were associated with higher odds of neonates who were small for their gestational age. As such very low 25(OH)D levels were significantly more frequent among black women, the authors suggested that VD status might contribute to racial disparities in the prevalence of infants who were small for their gestational

Fig. 1 Metabolic pathway of vitamin D (VD)



age. Moreover, a number of studies have shown that women who drink a significant amount of milk during pregnancy are more likely to have babies who are large for their gestational age, whereas those who restrict milk drinking have infants with lower birth weights (~ 80 g) [29], thus suggesting that milk consumption and VD intake are both significant predictors of birth weight. Moreover, in line with the increased PTH levels associated with VD deficiency, a small study of 30 VD-deficient Pakistani *gravidae* found an inverse correlation ($r = -0.39$; $p = 0.05$) between lower birth weights and higher maternal PTH levels [30].

Together with birth weight, it has been found that VD deficiency during pregnancy is associated with poor skeletal mineralization and bone defects. Low maternal 25(OH)D levels predispose to hypocalcemia in the immediate postpartum period and rickets during over the next few months [31]. Craniotabes with impaired skull ossification and larger fontanels was first described some years ago in neonates born to VD-deficient mothers [31], and these findings have been repeatedly confirmed. It has also been reported that postnatal VD supplementation can improve VD status but only partly eliminates the differences in bone variables induced by maternal deficiency during the fetal period [32, 33]. In a 9-year longitudinal study, Javaid et al. [32] followed up 198 children whose VD status-related neonatal characteristics were well defined and found that reduced 25(OH)D levels in the mothers during late pregnancy were associated with reduced whole body ($r = 0.21$; $p = 0.008$) and lumbar spine bone mineral content ($r = 0.17$; $p = 0.03$) in their 9-year-old children. Viljakainen et al. [33] followed up 87 children from birth to 14 months of age when they measured bone variables using peripheral computed tomography of the left tibia and compared serum 25(OH)D and bone turnover markers with maternal VD status during

pregnancy. Serum 25(OH)D concentrations, bone mineral density and bone mineral concentration were similar in all of the children regardless of their baseline values, but the total tibial bone cross-sectional area, which was greater in the neonates with higher 25(OH)D levels, remained greater (multivariate analysis of variance: $p = 0.068$) [33]. Finally, Ioannou et al. [34] performed a study to detect correlations between bone characteristics and maternal VD concentration. They evaluated 357 pregnant women at 34 weeks of gestation and fetal femur volume (FV) together with proximal metaphyseal diameter (PMD) immediately after birth and found that 25(OH)D concentrations could be considered independent predictors of both variables with a strict correlation between the amount of VD, FV and PMD.

Respiratory diseases

Young infants are frequently affected by respiratory diseases, and given the important function of VD in innate and adaptive immunity, it has been suggested that inadequate 25(OH)D levels at birth or in the first months of life due to insufficient VD intake by pregnant or breastfeeding women may condition susceptibility to, and the severity of, respiratory tract infections in the first months of life and later. Various studies have clearly confirmed this hypothesis in healthy children [35–38] and those with severe underlying diseases [39]. Roth et al. [35] found that serum 25(OH)D concentrations were inversely associated with the risk of lower respiratory tract infection in breastfed children aged 1–13 months living in Bangladesh. Karatekin et al. [36] observed that neonates admitted to an intensive care unit because of acute lower respiratory tract infection had lower 25(OH)D concentrations than age-matched healthy controls. Camargo et al. [37] analyzed the 25(OH)D content in cord blood taken from 922 newborns and correlated the

values with their clinical history of respiratory infections at 3 months or wheezing at 15 months and then annually. After adjusting for the season of birth, they found that the cord blood 25(OH)D concentrations were inversely associated with the risk of respiratory infection by the age of 3 months (odds ratio: 1.00 [reference] for ≥ 32 ng/mL, 1.39 for 10–32 ng/mL and 2.16 for < 10 ng/mL) and inversely associated with the risk of infectious wheezing by 15 months, 3 and 5 years of age (all $p < 0.05$) [37]. Finally, Belderbos et al. [38] found that cord blood VD deficiency is associated with an increased risk of respiratory syncytial virus (RSV) bronchiolitis during infancy, an effect that is explained by the fact that VD decreases the RSV induction of NF- κ B-linked chemokines and cytokines in the airways epithelium while maintaining an antiviral state, thus reducing viral inflammation without affecting viral clearance [40].

The possible relationship between 25(OH)D concentrations at birth or in the first months of life and the occurrence of wheezing and asthma is much less clear. Most studies have found that VD deficiency is frequently associated with the wheezing that follows respiratory infections, whereas the association between VD and allergic diseases (including asthma) is still widely debated. Camargo et al. [41] studied the relationship between total VD intake during pregnancy and the incidence of recurrent wheezing associated with respiratory infections in children before the age of 3 years. In comparison with the mothers in the lowest quartile of daily intake (median: 356 IU), those in the highest quartile (724 IU) were at a lower risk of having a child with recurrent wheezing (odds ratio [OR] 0.39; 95 % confidence interval [CI] 0.25–0.62; p for trend < 0.001) [41]. A 100 IU increase in VD intake was associated with a lower risk (OR 0.81; 95 % CI 0.74–0.89), regardless of whether the VD came from the diet (OR 0.81; 95 % CI 0.69–0.96) or supplements (OR 0.82; 95 % CI 0.73–0.92) [41].

On the contrary, the same authors found that low cord blood 25(OH)VD levels had no association with incident asthma at the age of 5 years [37]. Moreover, there are data that seem to indicate that both high and low cord blood 25(OH)D levels are associated with aeroallergen sensitisation in children, and studies that suggest that 25(OH)D levels might lead to increased markers of atopy and an increased risk of allergic conditions [42–44]. Rothers et al. [42] found that cord blood 25(OH)D levels of ≤ 20 and > 40 ng/mL were both associated with increased total IgE levels and detectable inhalant allergen-specific IgE levels up to the age of 5 years.

On the other hand, Hypponen et al. [43] found that supplementation with high daily doses of VD ($\geq 2,000$ IU/day) in the first year of life was associated with an increased skin prick test response and allergic rhinitis in more than 5,000 subjects aged 31 years.

It has been suggested that the apparent nonlinear relationship between VD status and allergic/asthmatic outcomes may be due to the fact that VD supports a TH₂-mediated anti-inflammatory cytokine profile, and so increased 25(OH)D levels may lead to sustained TH₂ skewing in immune system markers in the circulation, while simultaneously creating opposing anti-inflammatory effects in the lung [44]. However, a recent elegant study found no significant associations between maternal late-pregnancy 25(OH)D level and either asthma or wheeze at age 6 years [45], which indicates that further research into these complex relationships is clearly warranted.

Other diseases

A number of studies of experimental animals and humans have clearly suggested that VD deficiency or VD supplementation can be associated with an increased or reduced risk of developing type 1 diabetes [46, 47]. There are few data concerning the long-term effects of VD status in pregnant or lactating women, but observational studies conducted during pregnancy indicate that VD insufficiency is associated with an increased prevalence of islet cell antibodies and modified insulin sensitivity in the offspring, and that a history of VD supplementation in pregnant women may lead to a lower childhood incidence of type 1 diabetes [48].

Experimental studies suggest that VD is also involved in brain development, and that VD deficiency during pregnancy can lead to larger lateral ventricles, reduced nerve growth factor protein content, and the lower expression of a number of the genes involved in neuronal structure or neurotransmission [49, 50].

In humans, an increased risk of schizophrenia and multiple sclerosis has been observed at increasing latitudes, and in patients born in winter or spring, which is consistent with the low maternal 25(OH)D levels [49]. Moreover, Whithouse et al. grouped the serum 25(OH)D concentrations of 743 white women after 18 weeks of gestation into quartiles and assessed the behavior of their offspring using the Child Behavior Checklist at the ages of 2, 5, 8, 10, 14 and 17 years (numbers: 412–652); receptive language was assessed using the revised Peabody Picture Vocabulary Test at the ages of five ($n = 534$) and 10 years ($n = 474$). Although the statistical analyses did not reveal any significant associations between the maternal serum 25(OH)D quartiles and offspring behavioral/emotional problems at any age, there was a significant linear trend between the quartiles and language impairment at 5 and 10 years of age: the risk of VD-deficient women having a child with clinically significant language difficulties was almost twice that of women whose 25(OH)D levels were > 32 ng/mL [50]. Moreover, recently, a positive linear relationship was

found by Morales et al. [51] between circulating maternal 25(OH)D concentrations in pregnancy and mental and psychomotor scores in the offspring. After adjustment for potential confounders, infants of mothers with 25(OH)D concentrations in pregnancy >30 ng/mL showed higher mental score ($\beta = 2.60$; 95 % CI 0.63–4.56) and higher psychomotor score ($\beta = 2.32$; 95 % CI 0.36–4.28) in comparison with those of mothers with 25(OH)D concentrations <20 ng/mL.

Recommendations for monitoring and supplementation

Given the possible major outcomes related to VD deficiency at different stages of life, VD supplementation is usually recommended during pregnancy (Table 3). However, the amount of the VD supplement is not clearly defined. The UK National Institute for Clinical Excellence stated in 2008 (and confirmed in 2011) that pregnant women should receive 400 IU/day of VD [52], whereas the IOM recommends a dietary intake of 600 IU/day for all adults regardless of whether they are pregnant or not [16]. Moreover, it is stated that this intakes can be obtained in most of the cases through the diet so that only subgroups of women, particularly those with poor nutrition, those living at northerly latitudes or in institutions, or those with very dark skin pigmentation might require supplementation [53]. Different recommendations, reporting significant higher VD supplements, were, on the contrary, prepared by other scientific Societies that have based their statements on a series of clinical trials indicating that 400 or 600 IU/day could be largely insufficient to reach adequate serum VD levels. Lee et al. [54] studied healthy pregnant women that in most of the cases had received a daily prenatal intake of 400/600 IU of vitamin D and found VD deficiency (<12 ng/mL) in 50 % of mothers and 65 % of their newborn infants, with a positive correlation between maternal and infant plasma 25(OH)D concentrations. Similar results have been reported by Cockburn et al. [55] studying pregnant women that were given 400 IU/day, and in whom at delivery, lower than normal 25(OH)D levels were found. Moreover, studies of VD supplements of 800–1,600 IU/day during the third trimester of pregnancy in women with 25(OH)D levels of <15 ng/mL have shown that VD levels only increase by 5.8–11 ng/mL and remain lower than required [56]. On the basis of these observations, in 2007 (and subsequently in 2010), the Canadian Pediatric Society recommended administering 2,000 IU/day to pregnant and breastfeeding women in order to maintain VD and calcium sufficiency [57]. This suggestion (which is now accepted by a great number of experts) [58] seems to be strongly supported by the findings of a recent trial. Women were randomised during the first trimester of pregnancy to receive VD 400,

2,000 or 4,000 IU per day until delivery, and it was found that a supplementation of 2,000 IU/day was adequate in most cases [59]. In particular, it was reported that mean 25(OH)D concentrations at delivery and 1 month before delivery were significantly different ($p < 0.0001$), and that the percentage of women achieving VD sufficiency was significantly different by group and highest in the 4,000 IU group ($p < 0.0001$) [59]. The relative risk (RR) of achieving a concentration of ≥ 32 ng/mL 1 month before delivery was significantly different between the 2,000 and 400 IU group (RR = 1.52; 95 % CI 1.24–1.86) and between the 4,000 and 400 IU group (RR = 1.60; 95 % CI 1.32–1.95), but not between the 4,000 and 2,000 IU group (RR = 1.06; 95 % CI 0.93–1.19) [59].

A relevant amount of VD is suggested even to maintain normal VD milk concentrations during breastfeeding and to assure what is needed for an optimal development. Wagner et al. [60] reported that with limited sun exposure a VD intake of 400 IU/day did not sustain circulating maternal 25(OH)D levels and thus supplied only extremely limited amounts of VD to the nursing infant via breast milk. Only a maternal VD intake of 6,400 IU/day elevated circulating 25(OH)D in both mother and nursing infant to normal levels [60].

Furthermore, the administration of a greater than usual amount of VD was safe and well tolerated [61]. No significant adverse event has been associated with the use of either 2,000 or 4,000 IU/day, and a risk assessment based on well-designed clinical trials of VD has calculated that a dose of $\geq 10,000$ IU/day could be considered the tolerable upper intake level and a serum 25(OH)D level of 100 ng/mL the maximum acceptable blood concentration [61]. On the other hand, the possibility of humans to tolerate without relevant clinical problems 25(OH)D levels significantly higher than that traditionally recommended seems supported by the findings of the study by Luxwolda et al. [62]. These authors studied VD concentrations in several African populations and found different mean values according to age, sex, pregnancy, delivery and sunlight exposure. However, these 25(OH)D concentrations were in most of the cases near 100 ng/mL and never lower than 70 ng/mL. However, the problem of the best amount of VD to administer to pregnant women is far from to be solved, and the controversy between favorable and negative researchers seems at the moment irremediable. Those that are adverse to a greater supplementation of VD to pregnant women think that the evidence that higher dosages of VD are needed because they confer benefit for or are casually related to extraskelatal health outcomes is not compelling. Consequently, they think that only the amount needed to assure adequate bone development and maintenance has to be administered. Moreover, they are critical toward the studies that seem to indicate a positive effect of the

Table 3 Possible major outcomes related to vitamin D (VD) deficiency at different life stages

Life stage	Outcome
Preconception	Unsuccessful in vitro fertilization
Pregnancy	Reduced activation of innate immunity in the placenta Increased risk of gestational diabetes and preeclampsia Delay in fetal lung development and surfactant production Delay in fetal bone development
Perinatal	Increased risk of cesarean delivery Reduced body size and shape at birth Poor skeletal mineralization and bone defects at birth
Childhood	Lower bone mineral content with skeletal deformities and increased risk of fracture Growth retardation Rickets Increased risk of respiratory tract infections Increased risk of wheezing and asthma Increased risk of type 1 diabetes Increased risk of central nervous system disorders

administration of higher doses of VD because in many cases, they have been carried out on small groups of subjects and with debatable methods [16]. Finally, the risk of toxicity with higher doses given for a prolonged time is not completely excluded mainly because it is not defined the role of the 25(OH)D baseline level on the final concentrations. It could be supposed that in pregnant women with normal 25(OH)D baseline levels, higher amounts of VD can lead to toxicity. On the other hand, those who support the systematic use of higher doses think that the extra-skeletal effects of VD have been clearly demonstrated in vitro and in vivo both in the experimental animals and in the humans. Moreover, they think that there are no risks of adverse events, and that some negative conclusions regarding the clinical trials that seem to show that higher doses of VD are need during pregnancy are largely debatable. The best example at this regard is the recently published Cochrane review in which it was concluded that, even if VD supplementation in a single or continued dose during pregnancy increases serum 25(OH)D concentrations at term, the clinical significance of this finding and the potential use of this intervention as a part of routine antenatal care are yet to be determined as the number of high quality trials and outcomes reported is too limited to draw conclusions on its usefulness and safety [63]. In this case, the most important randomized clinical trial that enrolled about 500 pregnant women receiving different amounts of VD was not included because the study did not have a control group of patients without VD supplementation. This can be considered a relevant mistake leading to wrong conclusions on the effectiveness, safety and tolerability of VD in pregnancy because a control group receiving the

standard of care of giving 400 IU VD/day as part of the prenatal supplement was, on the contrary, included.

Conclusions

Serum 25(OH)D concentrations in pregnant women were frequently found much lower than those considered normal. This is mainly true of black women, but has also been frequently demonstrated in white, particularly those living in northern regions. Dietary intake can be very poor because the VD content in food is limited. Moreover, skin synthesis is frequently insufficient to assure adequate serum levels. Although not fully known, the consequences of low 25(OH)D levels in pregnant women seem to be many and are sometimes very severe for both mother and child. Further studies are urgently needed in order to evaluate the role of VD during pregnancy, and the amount of VD needed to eliminate any risk of negative consequences more precisely.

Acknowledgments S.E. and N.P. designed the review and co-wrote the manuscript. E.B. and S.B. collected the references, participated in the evaluation of the collected papers and helped to draft the manuscript. All authors read and approved the final manuscript. This review was supported by a grant from the Italian Ministry of Health (Bando Giovani Ricercatori 2007).

Conflict of interest The authors have no conflict of interest to declare.

Ethical statement All the works cited in this manuscript have been approved by the appropriate ethical committees related to the institution(s) in which they were performed and subjects gave informed consent to the work.

References

- Centers for Disease Control and Prevention (2001) Severe malnutrition among young children—Georgia January 1997–June 1999. *JAMA* 285:2573–2576
- Kreiter SR, Schwartz RP, Kirkman HN Jr, Kirkman HN Jr, Charlton PA, Calikoglu AS et al (2000) Nutritional rickets in African American breast-fed infants. *J Pediatr* 137:153–157
- Moy R, Shaw N, Mather I (2004) Vitamin D supplementation in pregnancy. *Lancet* 363:574
- Hollis BW (2007) Vitamin D requirement during pregnancy and lactation. *J Bone Miner Res* 22(Suppl 2):V39–V44
- Wagner CL, Taylor SN, Dawodu A, Johnson DD, Hollis BW (2012) Vitamin D and its role during pregnancy in attaining optimal health of mother and fetus. *Nutrients* 4:208–230
- Urrutia RP, Thorp JM (2012) Vitamin D in pregnancy: current concepts. *Curr Opin Obstet Gynecol* 24:57–64
- Bischoff-Ferrari HA (2011) Vitamin D: role in pregnancy and early childhood. *Ann Nutr Metab* 59:17–21
- Robinson CJ, Alanis MC, Wagner CL, Hollis BW, Johnson DD (2010) Plasma 25-hydroxyvitamin D levels in early-onset severe preeclampsia. *Am J Obstet Gynecol* 203:366.e1–366.e6
- Hollis BV, Wagner CL (2012) Vitamin D and pregnancy: skeletal effects, nonskeletal effects, and birth outcomes. *Calcified Tiss Int* (Epub 24 May 2012)
- Nguyen TM, Guillozo H, Marin L, Tordet C, Koite S, Garabedian M (1996) Evidence for a vitamin D paracrine system regulating maturation of developing rat lung epithelium. *Am J Physiol* 271(3pt1):L392–L399
- Nguyen TM, Guillozo H, Marin L, Dufour ME, Tordet C, Pike JW et al (1990) 1,25-Dihydroxyvitamin D₃ receptors in rat lung during the perinatal period: regulation and immunohistochemical localization. *Endocrinology* 127:1755–1762
- Rochat MK, Ege MJ, Plabst D, Steinle J, Bitter S, Braun-Fahrlander C et al (2010) Maternal vitamin D intake during pregnancy increases gene expression of ILT3 and ILT4 in cord blood. *Clin Exp Allergy* 40:786–794
- Haddad JG, Chyu K (1971) Competitive protein-binding radioassay for 25-hydroxycholecalciferol. *J Clin Endocrinol Metab* 33:992–995
- Hollis BW (2005) Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr* 135:317–322
- Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R (2004) Vitamin D round table. In: Burckhardt P, Dawson-Hughes B, Heaney R (eds) *Nutritional aspects of osteoporosis*, 2nd edn. Elsevier Science and Technology Books, Burlington, MA, pp 263–270
- Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK et al (2011) The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 96:53–58
- Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP et al (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96:1911–1930
- Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM (2007) High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. *J Nutr* 137:447–452
- Johnson DD, Wagner CL, Hulsey TC, McNeil RB, Ebeling M, Hollis BW (2011) Vitamin D deficiency and insufficiency is common during pregnancy. *Am J Perinatol* 28:7–12
- Hamilton SA, McNeil R, Hollis BW, Davis DJ, Winkler J, Cook C et al (2010) Profound vitamin D deficiency in a diverse group of women during pregnancy living in a sun-rich environment at latitude 32°N. *Int J Endocrinol* 2010:917428
- Ginde AA, Sullivan AF, Mansbach JM, Camargo CA Jr (2010) Vitamin D insufficiency in pregnant and nonpregnant women of childbearing age in the United States. *Am J Obstet Gynecol* 202:436.e1–436.e8
- Bogh MK, Schmedes AV, Philipsen PA, Thieden E, Wulf HC (2010) Vitamin D production after UVB exposure depends on baseline vitamin D and total cholesterol but not on skin pigmentation. *J Invest Dermatol* 130:546–553
- Basile LA, Taylor SN, Wagner CL, Quinones L, Hollis BW (2007) Neonatal vitamin D status at birth at latitude 32 degrees 72': evidence of deficiency. *J Perinatol* 27:568–571
- Mallet E, Gugi B, Henocq A, Basuyau JP, Lemeur H (1986) Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstet Gynecol* 68:300–303
- Davis LM, Chang SC, Mancini J, Nathanson MS, Witter FR, O'Brien KO (2010) Vitamin D insufficiency is prevalent among pregnant African American adolescents. *J Pediatr Adolesc Gynecol* 23:45–52
- Brooke OG, Butters F, Wood C (1981) Intrauterine vitamin D nutrition and postnatal growth in Asian infants. *Br Med J* 283:1024
- Marya RK, Rathee S, Lata V, Mudgil S (1981) Effects of vitamin D supplementation in pregnancy. *Gynecol Obstet Invest* 12:155–161
- Burris HH, Rifas-Shiman SL, Camargo CA Jr, Litonjua AA, Huh SY, Rich-Edwards JW et al (2010) Plasma 25-hydroxyvitamin D during pregnancy and small-for-gestational age in black and white infants. *Ann Epidemiol* (Epub 31 May 2012)
- Olsen SF, Halldorsson TI, Willett WC, Knudsen VK, Gillman MW, Mikkelsen TB et al (2007) Milk consumption during pregnancy is associated with increased infant size at birth: prospective cohort study. *Am J Clin Nutr* 86:1104–1110
- Brunvand L, Quigstad E, Urdal P, Haug E (1996) Vitamin D deficiency and fetal growth. *Early Hum Dev* 45:27–33
- Congdon P, Horsman A, Kirby PA, Dibble J, Bashir T (1983) Mineral content of the forearms of babies born to Asian and white mothers. *Br Med J (Clin Res Ed)* 286:1233–1235
- Javaid MK, Crozier SR, Harvey NC, Gale CR, Dennison EM, Boucher BJ et al (2006) Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *Lancet* 367:36–43
- Viljakainen HT, Korhonen T, Hytinantti T, Laitinen EK, Andersson S, Mäkitie O et al (2011) Maternal vitamin D status affects bone growth in early childhood—a prospective cohort study. *Osteoporos Int* 22:883–891
- Ioannou C, Javaid MK, Mahon P, Yaqub MK, Harvey NC, Godfrey KM et al (2012) The effect of maternal vitamin D concentration on fetal bone. *J Clin Endocrinol Metab* 97:E2070–E2077
- Roth DE, Shah R, Black RE, Baqui AH (2010) Vitamin D status and acute lower respiratory infection in early childhood in Sylhet, Bangladesh. *Acta Paediatr* 99:389–393
- Karatekin G, Kaya A, Salihoğlu O, Balci H, Nuhoglu A (2009) Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. *Eur J Clin Nutr* 63:473–477
- Camargo CA Jr, Ingham T, Wickens K, Thadhani R, Silvers KM, Epton MJ et al (2011) Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics* 127:e180–e187

38. Belderbos ME, Houben ML, Wilbrink B, Lentjes E, Bloemen EM, Kimpen JL et al (2011) Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. *Pediatrics* 127:e1513–e1520
39. Finkelstein JL, Mehta S, Duggan C, Manji KP, Mugusi FM, Aboud S et al (2012) Maternal vitamin D status and child morbidity, anemia, and growth in human immunodeficiency virus-exposed children in Tanzania. *Pediatr Infect Dis J* 31:171–175
40. Hansdottir S, Monick MM, Lovan N, Powers L, Gerke A, Hunninghake GW (2010) Vitamin D decreases respiratory syncytial virus induction of NF-kappaB-linked chemokines and cytokines in airway epithelium while maintaining the antiviral state. *J Immunol* 184:965–974
41. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR et al (2007) Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr* 85:788–795
42. Rothers J, Wright AL, Stern DA, Halonen M, Camargo CA Jr (2011) Cord blood 25-hydroxyvitamin D levels are associated with aeroallergen sensitization in children from Tucson, Arizona. *J Allergy Clin Immunol* 128:1093-9.e1–1093-9.e5
43. Hyppönen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL et al (2004) Infant vitamin D supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. *Ann N Y Acad Sci* 1037:84–95
44. Wintergerst ES, Maggini S, Hornig DH (2007) Contribution of selected vitamins and trace elements to immune function. *Ann Nutr Metab* 5:301–323
45. Pike KC, Inskip HM, Robinson S, Lucas JS, Cooper C, Harvey NC et al (2012) Maternal late-pregnancy serum 25-hydroxyvitamin D in relation to childhood wheeze and atopic outcomes. *Thorax* (Epub 15 June 2012)
46. Hyppönen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM (2001) Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 358:1500–1503
47. Zipitis CS, Akobeng AK (2008) Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Arch Dis Child* 93:512–517
48. Stene LC, Joner G (2003) Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. *Am J Clin Nutr* 78:1128–1134
49. Staples J, Ponsonby AL, Lim L (2010) Low maternal exposure to ultraviolet radiation in pregnancy, month of birth, and risk of multiple sclerosis in offspring: longitudinal analysis. *BMJ* 340:c1640
50. Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM, Hart PH (2012) Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics* 129:485–493
51. Morales E, Guxens M, Llop S, Rodríguez-Bernal CL, Tardón A, Ríaño I et al (2012) Circulating 25-Hydroxyvitamin D3 in pregnancy and infant neuropsychological development. *Pediatrics* 130:e913–e920
52. National Institute for Clinical Excellence (2011) Improving the nutrition of pregnant and breastfeeding mothers and children in low-income households, NICE public health guidance, July 2011. Available at: <http://www.nice.org.uk/nicemedia/live/11943/40097/40097.pdf>. Accessed on 14 June 2012
53. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Ross AC, Taylor CL, Yaktine AL, Del Valle HB (eds) (2011) Dietary reference intakes for calcium and vitamin D. National Academies Press (US), Washington DC, USA
54. Lee JM, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF (2007) Vitamin D deficiency in a healthy group of mothers and newborn infants. *Clin Pediatr (Phila)* 46:42–44
55. Cockburn F, Belton NR, Purvis RJ, Giles MM, Brown JK, Turner TL et al (1980) Maternal vitamin D intake and mineral metabolism in mothers and their newborn infants. *Br Med J* 281:11–14
56. Vieth R, Chan PC, McFarlane GD (2001) Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 73:288–294
57. First Nations, Inuit and Métis Health Committee, Canadian Paediatric Society. Vitamin D supplementation: recommendations for Canadian mothers and infants. Reference no. FNIMH 07-01. Available at: www.cps.ca/english/statements/ii/fnimh07-01.htm. Accessed on 14 June 2012
58. Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C (2010) Implications of vitamin D deficiency in pregnancy and lactation. *Am J Obstet Gynecol* 202:429.e1–429.e9
59. Hollis BW, Johnson D, Hulsey TC, Ebeling M, Wagner CL (2011) Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. *J Bone Miner Res* 26:2341–2357
60. Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW (2006) High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed Med* 1:59–70
61. Hathcock JN, Shao A, Vieth R, Heaney R (2007) Risk assessment for vitamin D. *Am J Clin Nutr* 85:6–18
62. Luxwolda MF, Kuipers RS, Kema IP, van der Veer E, Dijck-Brouwer DA, Muskiet FA (2012) Vitamin D status indicators in indigenous populations in East Africa. *Eur J Nutr* (Epub 10 Aug 2012)
63. De-Regil LM, Palacios C, Ansary A, Kulier R, Peña-Rosas JP (2012) Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2:CD008873