

Maternal and Foetal Health Implications of Vitamin D Status during Pregnancy

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Keywords

Vitamin D · 25-Hydroxyvitamin D Pregnancy · Preeclampsia · Preterm · Neurodevelopment · Wheezing · Asthma

Abstract

Background: To what extent does the circulating 25-hydroxyvitamin D (25[OH]D) concentration help to meet the physiological needs of humans is an ongoing subject of debate. Remaining unexposed to the sun to reduce melanoma cancer risk, current lifestyle with less outdoor activities, and increasing obesity rates, which in turn increases the storage of vitamin D in the adipose tissue, are presumably factors that contribute to the substantial upsurge in the prevalence of vitamin D deficiency in humans. Since evidence is lacking regarding the appropriate cut-off points to define vitamin D status during pregnancy, references used to establish the intake recommendations and vitamin D content of prenatal vitamin supplements are quite conservative. **Summary:** The foetus depends fully on maternal 25(OH)D supply. 25(OH)D readily crosses the placenta and it is activated into 1,25(OH)₂D by foetal kidneys. Moreover, 1,25(OH)₂D can also be synthesized within the placenta to regulate placental metabolism.

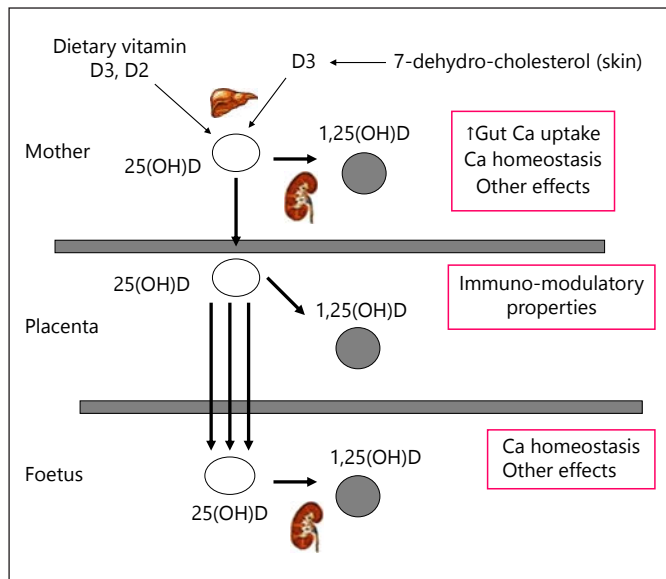
The importance of vitamin D during pregnancy for maintaining maternal calcium homeostasis and therefore for foetal bone development is well recognized; major discussions are in progress regarding the potential maternal detrimental effects on pregnancy outcomes, foetal development, and the long-term health of children. Interventional studies have also evaluated the effect of vitamin D for reduction on preterm birth and asthma programming. **Key Messages:** Clinically, by understanding the effects of vitamin D on perinatal outcomes, we could individualize antenatal counselling regarding vitamin D supplementation to ensure vitamin D repletion without increasing the risk of foetal hypercalcemia.

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Introduction

Maternal vitamin D insufficiency during pregnancy is a common issue and a significant public health problem at the global level [1]. Risk factors for vitamin D insufficiency are well described, and include ethnicity, extensive

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Fig. 1. Materno-foetal vitamin D transfer.

skin covering, liberal use of sun protection, overweight/obesity, low dietary vitamin D intake, and smoking, in addition to the seasonal variation that is observed at temperate latitudes.

The foetus depends on the maternal supply of vitamin D, calcium, and phosphorus, which is transmitted across the placenta. In fact, maternal and cord blood 25-hydroxyvitamin D (25(OH)D) are highly correlated in terms of supporting the importance of this vitamin for foetal development [2]. Actually, we have a large prevalence of vitamin D deficiency/insufficiency among adolescents and women of reproductive age [3]; most of these adolescents will become pregnant and then vitamin D deficiency will play a negative role on the foetal programming of next generations. Thus, it is important to discern the benefits of appropriate vitamin D levels on maternal and perinatal outcomes to support vitamin D screening and treatment during pregnancy.

Vitamin D Metabolism in Placenta

During pregnancy, maternal hemodilution is accompanied by a number of physiological changes into both vitamin D metabolism and maternal body composition; such adaptations lead to differences in the determinants of response to vitamin D supplementation between pregnant and non-pregnant women.

Although food may provide small amounts of both vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol), exposure to the sun is by far the major source of vitamin D to the body, the vitamin being synthesized from cholesterol derivatives. Vitamin D is carried up to the liver and hydroxylated to 25(OH)D or calcidiol; circulating 25(OH)D concentration is often used as an indicator of vitamin D status, due to its high concentration and larger half-life in comparison to the active form, but this inactive form of vitamin D requires further hydroxylation into the kidneys to 1,25-dihydroxyvitamin D (1,25(OH)₂D) or calcitriol, which is the active form of vitamin D [4, 5] (Fig. 1).

Placenta is a key organ that mediates not only nutrient transfer, but it is also essential for the immunotolerance adaptation during pregnancy. It is important to note here that 1,25(OH)₂D does not practically cross the placenta tissue, while its inactive precursor 25(OH)D readily crosses the tissue to the foetal compartment [4, 5]. Besides the kidneys, the placenta can potentially activate 25(OH)D, since it contains the enzyme 1- α -hydroxylase producing 1,25(OH)₂D [4, 5]. Moreover, placenta has a paracrine control of vitamin D metabolism and it may also inactivate 25(OH)D by 24-hydroxylation to 24,25(OH)₂D. This makes it possible for a local regulation of vitamin D levels within the placental tissue that may modulate anti-inflammatory effects and affect pregnancy development and/or perinatal outcomes [4, 5] (Fig. 1). Calcitriol exerts potent immunomodulatory properties by inhibiting adaptive T-helper 1 responses while stimulating innate antimicrobial reactions in human placental cells [5].

Some studies have described an increase in 1,25(OH)₂D maternal blood concentrations during the last trimester of pregnancy, while other studies have not [5, 6]. Seasonal variations greatly affect the circulating vitamin D levels [6–8]. Although placenta may synthesize 1,25(OH)₂D, most of this metabolite in maternal circulation is produced by maternal kidney. In fact, experiments using autosomal recessive 1- α -hydroxylase-deficient models indicate that maternal kidneys are likely to be the major source of increased maternal serum 1,25(OH)₂D observed in pregnancy [9]. Some case reports of pregnant women with impaired renal function showed that during pregnancy their circulating levels increased slightly but were much lower than those observed in normal pregnant women [10, 11]. Higher maternal levels of 1,25(OH)₂D are essential to increase intestinal calcium absorption during pregnancy and to support calcium for maternal and foetal metabolism [12], among other functions such

as regulating the immune systems during pregnancy [4, 13].

In the foetus, foetal kidneys may synthesize 1,25(OH)₂D from 25(OH)D. In fact, umbilical artery levels of 1,25(OH)₂D are slightly higher than those in venous cord levels, suggesting a role for foetal kidneys to activate vitamin D [14]. Moreover, foetal nephrectomy reduces foetal levels of 1,25(OH)₂D in sheep and rat models [15], emphasizing the importance of the foetal kidneys in maintaining the circulating levels of active vitamin D (Fig. 1).

Vitamin D Intake Recommendations during Pregnancy

The circulating 25(OH)D concentration that is sufficient to meet the physiological needs of humans is an ongoing subject of debate. Current recommendations show no consensus with regard to the optimal vitamin D status during pregnancy, with the Institute of Medicine (IOM) defining serum 25(OH)D levels of 50 nmol/L as adequate [16, 17], and others advocating a threshold of 75 nmol/L [18].

The IOM recommends an intake of 600 UL of vitamin D to pregnant women with the goal to achieve in serum more than 50 nmol/L (20 ng/mL) 25(OH)D considered by them as a sufficient level [16]. However, the US Endocrine Society suggests that at least 1,500–2,000 IU of vitamin D may be needed to maintain blood levels of 25(OH)D above 75 nmol/L (30 mg/dL) and that should be considered the sufficient level for pregnant women [18]. Nevertheless, both societies agree to consider the upper limit of intake as 4,000 IU/day [16, 18]. Since evidence is lacking regarding appropriate cut-off points to define vitamin D status during pregnancy, levels used to establish intake recommendations and vitamin D content of prenatal vitamin supplements are quite conservative.

In fact, depending on the cut-off points used to define the sufficient vitamin D serum levels, the prevalence of vitamin D deficiency/insufficiency estimated around the world is greatly affected. In fact, in England, pregnant women who require vitamin D supplementation may differ from 31% if a cut-off point of 20 ng/mL of circulating 25(OH)D is considered to 67% if 30 ng/mL is considered [3]. Similarly, in Spain, the prevalence of vitamin D deficiency among pregnant women may change from 20 to 52%, and similarly for many countries [3, 19].

The question to be answered is to define what circulating level of 25(OH)D during pregnancy is adequate to improve foetal development and prevent maternal com-

plications. In fact, maternal and foetal health endpoints might even differ in the appropriate time for supplementation during pregnancy and required dose. Future studies should establish the exact 25(OH)D level that can be deemed sufficient for improved maternal and perinatal health owing to the lack of consensus in the literature.

Dietary vitamin D intake usually reaches only about 5 µg per day (200 IU/day) [19], which is usually lower than the current 600 IU/day of Recommended Dietary Allowance of vitamin D from either IOM or the European Food Safety Agency [16, 20]. Nevertheless, the Estimated Average Requirement from IOM is 400 IU/day [16], while the World Health Organization recommended dietary intakes of 200 IU/day [21].

Multivitamin supplements for pregnancy usually include only 200–400 IU. This dose is sufficient for the general population who adequately expose themselves to the sun, but it is too low to treat situations of vitamin D deficiency, especially in mothers and newborns with genetic variation in genes involved in vitamin D metabolism [22], or with a goal to achieve vitamin D levels higher than 30 ng/mL. In fact, some health organizations suggest that at least 400 IU/day is used as a supplement, and the total intake should be in the range of 1,000–2,000 IU/day from dietary sources (e.g., oily fish) and supplements [23]. Supplementation with 1,000 IU/day could be a safe option to treat vitamin D deficiency. Doses of 2,000 and 4,000 IU have been used in trials with subjects under endemic vitamin deficiency obtaining vitamin levels above the 30 ng/mL and with significant increases in cord blood [24].

In the MAVIDO Study in the United Kingdom, supplementation during pregnancy with 1,000 IU Vitamin D reduced the deficient level of vitamin D in all the subjects, but even in summer they did not reach more than 30 ng/mL of serum levels of 25(OH)D [25]. The benefits of vitamin D supplementation during pregnancy should be evaluated through rigorous intervention studies, and it is crucial to define ethnicity, season and period of supplementation.

The problem of excessive vitamin D intake during pregnancy is linked to the risk of hypercalcemia in the foetus, which is not a minor disease. The highest daily dose evaluated in pregnancy is 4,000 IU/day. Higher doses might be used but just for short limited periods during the third trimester (since doses are cumulative) and always under the supervision of an obstetrician and with monitoring of calcium levels.

Foetal hypercalcemia is an old concept that is confusing [26]; some reported hypercalcemias could have been not due to vitamin D excess leading to supravulvar aor-

tic stenosis but due to a disease known as William's Syndrome in which patients exhibit an exaggerated response of circulating 25(OH)D to orally administered vitamin D [27–30]. However, in the 1950s, the policy to fortify milk and cereals with Vitamin D in the United Kingdom increased the number of cases of Infantile Hypocalcemia that was half reduced when the fortification was limited [31]. This is an important point of caution. Experiments in animals have shown teratogenic effects but using at very high doses far from those in humans [32]. Many studies support up to 4,000 IU vitamin D, but even in some of these studies and in case reports, some subjects with transient neonatal hypercalcemia that progressed without major adverse effects have been referred to, although the programming consequences are unknown [33].

Studies in endemic vitamin D deficiency countries have used bolus with macro-doses of vitamin D3 instead of daily vitamin D supplementation. Pharmacokinetic studies using doses of 25,000 IU/week have shown maximal 25(OH)D levels a day after vitamin dose administration (being very high and close to safe serum upper limits) and later on a decrease but with higher serum levels than those in placebo groups after 7 days [34]. The repetition of high doses of vitamin D3 every week is not very physiological, and daily vitamin D supplements would allow us to reach levels higher than 30 mg/dL in a more controlled way during pregnancy.

There are no studies with calcifediol (25(OH)D3 metabolite) supplementation during pregnancy. Calcifediol supplementation in older adults, rapidly and safely elevates serum 25(OH)D concentrations improving vitamin D status compared to vitamin D3 supplementation [35]. A significant association was observed between the changes in 25(OH)D and 24,25(OH)₂D ($R^2 = 0.83$, $p < 0.01$), but not between 25(OH)D and 1,25(OH)₂D ($R^2 = 0.04$, $p = 0.18$), which suggests the stimulation of the catabolic pathway to regulate 1,25(OH)₂D [35]. Thus, the use of calcifediol during pregnancy is not recommended until tolerance and safety of this compound is clarified in clinical trials conducted during this stage of development.

Vitamin D Supplementation and Maternal and Foetal Bone Health

Maternal vitamin D and calcium levels are modified during pregnancy to support foetal calcium homeostasis. Maternal parathyroid hormone levels increase when vitamin D levels are insufficient affecting bone resorption to

keep proper maternal serum calcium levels. The negative correlation between serum 25(OH)D and cross-linked C-terminal telopeptide of type 1 collagen in pregnant women with serum 25(OH)D <20 ng/mL also strengthened the relationship of bone resorption and low vitamin D levels in pregnancy, especially in the 2nd and 3rd trimesters [36]. Teeth are a source of calcium easily mobilized during this period; maternal serum 25(OH)D levels below 30 ng/mL are associated with maternal periodontal disease during pregnancy [37]. Moreover, it is classically known that tooth loss increased with increasing parity [38], which highlights to support mothers to achieve appropriate calcium and vitamin D levels during pregnancy.

Moreover, osteoporosis is an important public health problem. Its high prevalence makes necessary interventional strategies aimed to get an adequate bone mass peak [39]. Early growth and factors acting in utero and early postnatally during the first 1,000 days of life may contribute to optimise bone mass. Maternal serum 25(OH)D concentrations in pregnancy have been associated with offspring foetal femur volume and proximal metaphyseal diameter, measured by ultrasound. In fact, the Joannou's study in 357 pregnant participants showed that maternal height, adiposity and serum vitamin D were independent predictors of femoral size [40]. Besides, the Southampton Women's Survey study also investigated foetal femur length, distal metaphyseal cross-sectional area, and the ratio of femoral metaphyseal cross-sectional area to femur length ("femoral splaying index") in the offspring of 424 pregnant women [41]. In this study, lower maternal 25(OH)D levels were related at 19 weeks gestation to greater femoral metaphyseal cross-sectional area ($r = -0.16$, 95% CI -0.25 to -0.06) and femoral splaying index ($r = -0.17$, 95% CI -0.26 to -0.01) at 34 weeks gestation but not to foetal femur length [41]. Geometric mean femoral splaying indices increases in relation to smaller 25(OH)D concentrations in the mother [41]. These observations suggest that vitamin D levels in the mother are important in foetal bone health as early as 19 weeks gestation. Thus, probably it is necessary to assess vitamin D status in early pregnancy or in woman at pre-conception. Nevertheless, a recent systematic review on the role of maternal vitamin D in foetal bone growth has concluded that more studies are necessary, despite the numerous papers suggesting that low maternal vitamin D levels may affect bone growth, especially if there is simultaneously a low calcium intake [42, 43].

Concerning the healthy effect of maternal vitamin D levels on offspring during adolescence or young adults,

the results are still controversial. Javaid et al. [44] reported that the 25(OH)D status of mothers in late pregnancy predicts bone mass of their offspring 9 years later. However, in the ALSPAC cohort with 3,960 mothers-and-offspring pairs, mainly of white origin, authors did not find associations of serum 25(OH)D with total body less head and spinal bone mass content at the age of 9.9 years for any trimester, including the last one, which seems to be the most relevant [45]. However, recently, the Western Australian Pregnancy Cohort (Raine) Study in 341 mother and offspring pairs has concluded that vitamin D deficiency in pregnancy is associated with lower peak bone mass in their children at 20 years and this may increase fracture risk [46]. This study collected maternal serum samples at 18-weeks' gestation and the offspring outcomes were total body bone mineral content and bone mineral density, measured by dual-energy X-ray absorptiometry [46]. Thus, it is uncertain whether vitamin D levels in pregnant women may influence the bone mass of their children later in life.

Since, not all observational studies have demonstrated a benefit of higher maternal 25(OH)D concentrations in pregnancy on offspring skeletal health in childhood, intervention studies are important to address this issue. The MAVIDOS study, a multi-centre, double-blind, randomised, placebo-controlled trial of vitamin D supplementation in pregnancy in the United Kingdom, tested the hypothesis whether neonates born to mothers supplemented with vitamin D during pregnancy had increased whole body bone mineral content at birth and whether there was an interaction between season and treatment effect [25]; neonate whole body and lumbar spine by DXA was measured with the limitation of the lack of normative data in this age. Their findings demonstrated that gestational supplementation with 1,000 IU/day vitamin D did not improve offspring neonatal bone mass in infants born in the summer; however, foetal bone mineral accretion increased in infants born during the winter months; there was an interaction between treatment and season of delivery with greater effect of treatment (mean difference 5.5 g (95% CI 1.8–9.1, $p = 0,004$) in winter months. In addition, the intervention from 14 weeks gestation until delivery with this dose was safe and sufficient to achieve good levels of 25(OH)D repletion in the mothers [25].

In conclusion, the importance of vitamin D in pregnancy for maintaining maternal calcium homeostasis and hence for foetal bone development is well recognized, but more studies are warranted to know maternal vitamin D

levels that may affect bone mass in offspring, the appropriate time for supplementation and if this effect persists during lifespan.

Vitamin D Supplementation during Pregnancy and Perinatal Outcomes

Major discussions are on about the potential maternal detrimental effects of vitamin D deficiency on perinatal outcomes and foetal development. Observational studies have associated lower maternal 25(OH)D serum levels with higher risk of preeclampsia, gestational diabetes, caesarean sections, preterm birth (PTB) or IUGR [47, 48]. In addition, there is growing evidence on the association with offspring risk of asthma, bone health, allergies and impaired neurodevelopment [49–52].

Since vitamin D levels are affected by several factors as season, ethnicity and obesity (which is involved in the pathogenesis of some of these pathologies), intervention studies with vitamin D are essential to discern the role of vitamin D. In a recent Cochrane meta-analyses [1] on vitamin D intervention studies, no clear associations were reported for gestational diabetes (risk ratio [RR] 0.43; 95% CI 0.05–3.45, very low quality), caesarean section (RR 0.95; 95% CI 0.69–1.31; 2 trials; 312 women); stillbirths (RR 0.35; 95% CI 0.06–1.99; three trials, 540 women) or neonatal deaths (RR 0.27; 95% CI 0.04–1.67; 2 trials, 282 women) [1]. Similar results were also reported on 2 additional meta-analyses of vitamin D intervention studies [53, 54].

Vitamin D Supplementation and Preeclampsia Risk

Preeclampsia is a placenta-dependent disorder with a worldwide prevalence of 2–8% [55]. According to the American Congress of Obstetricians and Gynecologists guidelines preeclampsia is defined by the identification of high blood pressure with proteinuria (300 mg per 24-h collection or $\geq 1+$ on urine dipstick) or the presence of elevated liver enzymes, high platelet count, headache, or visual disturbances after 20 weeks of gestation [56]. It is a multifactor disease with altered immune and endocrine responses in which both defective placental trophoblast invasion and dysfunction of maternal vascular endothelium occur. Since vitamin D exerts potent immunomodulatory properties, and results of observational studies suggested that lower vitamin D levels could be associated with higher preeclampsia risk [47], some intervention studies have tried to evaluate this association. However, the results of meta-analyses on intervention

studies on vitamin D and risk of preeclampsia are still controversial.

In a recent Cochrane review [1], results from two trials involving 219 women suggested that women who received vitamin D supplements may have a lower risk of preeclampsia than those receiving no intervention or placebo (8.9 vs. 15.5%; risk ratio (RR) 0.52; 95% CI 0.25–1.05, low quality) [1]. Nevertheless, the number of subjects in the Cochrane review to determine the risk of preeclampsia was too limited ($n = 293$) for a disease of such prevalence. However, other meta-analyses of interventional studies [53, 54] and a further randomized control trial (RCT; VDAART study) [57] with more participants than in the previous meta-analysis, did not support previous results. The VDAART study (Vitamin D Antenatal Asthma Reduction Trial) in the United States including 408 placebo and 408 subjects receiving 4,400 IU vitamin D3 initiated early in pregnancy (10–18 weeks), did not find a reduction on the preeclampsia incidence (8.08 vs. 8.33%, respectively; relative risk (RR) 0.97; 95% CI 0.61–1.53) [57]. High levels of serum 25(OH)D were achieved on maternal plasma at delivery in the intervention group (39.2 ± 15.3 vs. 26.8 ± 10.7 ng/dL in the control group), yet the risk of preeclampsia was not lower. However, women who had sufficient vitamin D levels (at least 30 ng/mL) in both early and late pregnancy, regardless of the treatment group, showed a significantly lower incidence of preeclampsia as compared with those who had an insufficient level at these time points (2.25 vs. 11.92%; RR 0.20; 95% CI, 0.06–0.66; $p < 0.008$) [57]. These results are in agreement with other studies on preeclampsia using other intervention as aspirin intake (ASPREE Study) that have suggested the importance of early intervention to prevent the aberrant placentation in early pregnancy, and to reduce preterm preeclampsia, while term preeclampsia is more difficult to be reduced [58]. Thus, the time of supplementation with vitamin D before pregnancy for women with a high risk of vitamin D deficiency could be essential to reduce to preeclampsia risk. Since first trimester is a teratogenic period, it should be clarified whether vitamin D should be supplemented in this period or not. Maybe, more interesting is to perform clinical trials on vitamin D supplementation before pregnancy in order to reduce the risk of preeclampsia.

Vitamin D Supplementation during Pregnancy and Preterm Birth

Recent meta-analyses of observational studies also support that vitamin D insufficiency (<30 ng/dL) is associated with risk of PTB: PTB (<35–37 week, 20–30 ng/dL) RR 1.24 (95% CI 1.04–1.49), PTB (<35–37 week, <20 ng/

dL) RR 1.36 (95% CI 1.04–1.78), PTB (<32–34 week, <30 ng/dL) RR 1.83 (95% CI 1.23–2.74), PTB (<32–34 week, <20 ng/dL) RR 1.86 (95% CI 1.28–2.68) [59]. With regard to spontaneous abortion and stillbirth, the available evidence suggests that there is no association with low vitamin D levels [59].

With respect to meta-analyses from intervention studies, data from three RCTs involving 477 women in the Cochrane review [1] confirmed that vitamin D supplementation during pregnancy is associated with a reduced risk of PTB compared to no intervention or placebo (8.9 vs. 15.5%; RR 0.36; 95% CI 0.14–0.93, moderate quality), and with a decreased risk of low birth weight (<2,500 g; RR 0.40; 95% CI 0.24–0.67, moderate quality). According to other recent meta-analyses [54], vitamin D is related to a lower risk of small for gestational age, although no association is observed for PTB [54]. In addition, a significant dose-response effect has been found on birth weight in trials in which the mean baseline 25(OH)D was 30–50 nmol/L (12–20 ng/mL), but no effect is detected in RCTs with mean 25(OH)D <30 nmol/L (12 ng/mL) [54].

Free-vitamin D3 supplements in a very large RCT as the MUSC (Medical University of South Carolina) Study, offered to pregnant women ($n = 1064$) to achieve a goal of serum 25(OH)D ≥ 40 ng/mL resulted in 62% lower risk of PTB compared to those with levels <20 ng/mL [60]. Similarly, a lower risk of PTB was reported for PTB subtypes (spontaneous: 58%, $p = 0.02$; indicated: 61%, $p = 0.006$), and among women with a prior PTB (80%, $p = 0.02$). Among high-risk pregnancies, LOESS curve showed gestational age rising with increasing 25(OH)D vitamin D; PTB rates were 20% in women with 25(OH)D <20 ng/mL ($n = 248$), 12% in women with 25(OH)D 20 to <30 ng/mL ($n = 267$), 13% in women with 25(OH)D 30 to <40 ng/mL ($n = 255$) and 9% in women with 25(OH)D ≥ 40 ng/mL ($n = 294$) [60], which supports vitamin D supplementation during pregnancy to avoid PTB.

The possible biological mechanisms of vitamin D involved in the prevention of PTB are presumably related to its immunomodulatory capacity during embryo implantation [61], calcium homeostasis in the endometrium for the maintenance of pregnancy [62], as well as its role in the prevention of infection during pregnancy [63].

Prenatal Vitamin D and Neurodevelopment

Current evidence from observational studies indicates that vitamin D might affect brain development. The discovery of the vitamin D receptor (VDR) in multiple brain

regions of the neonatal and adult central nervous system of several species provided the first real clue that vitamin D signalling may have a role in brain development and function [64, 65]. Moreover, the presence of 1-hydroxylase in the human brain indicates that the central nervous system can synthesise the active form of vitamin D, 1,25(OH)₂D from its inactive precursor 25(OH)D, which suggests that vitamin D may also have paracrine properties in the human brain [66]. Further research has also shown that vitamin D plays a role in diverse brain developmental mechanisms and functioning, including neuronal differentiation, axonal connectivity, dopamine ontogeny, immunological modulation, and transcriptional control over a large number of genes [67, 68].

In the last decade, epidemiological literature on the potential impacts of prenatal vitamin D status on brain development, cognition and behaviour in the offspring has rapidly increased (Table 1), but at the moment, no intervention studies have evaluated the effect of vitamin D supplementation on neurodevelopment.

Global Intelligence Quotient (IQ) or Cognitive Development

Overall, 9 studies have evaluated the association of prenatal vitamin D status with global IQ or child cognitive development (Table 1). Seven studies did not find any association between prenatal vitamin D levels and global IQ or cognitive development at preschool [69–72] and school age [73, 74]. However, Keim et al. [75] reported a positive association between both maternal and cord blood 25(OH)D concentration and IQ at age 7, but the effect estimates were very small. Morales et al. [51] showed that at 14 months of age, infants of mothers with 25(OH)D concentrations in the first trimester of pregnancy >30 ng/mL had higher cognitive scores in comparison with those of mothers with 25(OH)D3 concentrations <20 ng/mL. Furthermore, a Chinese cohort study observed an inverted-U-shaped relation between neonatal vitamin D status and cognitive score in toddlers [76].

Psychomotor Outcomes

Seven studies assessed psychomotor development in relation to prenatal vitamin D status, showing inconsistent results. Two studies reported increased psychomotor scores at age 14 months [51] and at 30 months [74] associated with higher maternal vitamin D concentrations in pregnancy. However, 4 studies did not find any association [69, 71, 72, 75]. Furthermore, Zhu et al. [76] found an inverted-U-shaped relation between neonatal vitamin D status and psychomotor score in toddlers.

In summary, the current evidence of an association between prenatal vitamin D status and global IQ or cognitive development, psychomotor outcomes is inconsistent yet.

Attention Deficit Hyperactivity Disorder

In a population-based registry study of 850 women and their children born in 1988–1989, Strom et al. [77] found no indication that maternal 25(OH)D concentrations <50 nmol/L (20 ng/mL) versus ≥50–75 nmol/L (20–30 ng/mL; or higher) at gestational week 30 were associated with higher risk of attention deficit hyperactivity disorder (ADHD) disorder, defined as prescription of psychostimulant medication, among offspring during 22 years of follow-up. On the contrary, by analysing data from 1,650 mother-child pairs embedded in the INMA birth cohort in Spain, Morales et al. [78] found that the number of ADHD-like symptoms in preschoolers aged 4–5 decreased by 11% per 10 ng/mL increment of maternal 25(OH)D3 at 13 weeks of gestation. The inverse association was observed in the inattention subscale as well as in the hyperactivity-impulsivity subscale. Consistently, results from the Greek Rhea birth cohort [71] have also shown that higher maternal levels of vitamin D (>50.7 nmol/L) in early pregnancy (13 weeks) is associated with reduced hyperactivity-impulsivity symptoms and total ADHD-like symptoms in offspring at age 4.

Autism Spectrum Disorder

Four studies evaluated the association of prenatal vitamin D status with autistic traits or autism spectrum disorder (ASD). A case-control study carried out in China found that lower first trimester maternal circulating concentration of 25(OH)D was associated with increased risk of developing autism in offspring at age 3–7 [79]. A register-based total population study carried out in Sweden found a positive association between lifetime diagnoses of maternal vitamin D deficiency (serum 25(OH)D level of less than 25 nmol/L) and risk of ASD in children aged 4–17, which was especially noticeable for ASD with intellectual disability, and for children of non-immigrant mothers [80]. Accordingly, Vinkhuyzen et al. [81] also showed an association between both mid-gestational and neonatal vitamin D deficiency [25(OH)D concentration less than 25 nmol/L] with autism-related traits at 6 years of age in a large Dutch population-based birth cohort. Moreover, mid-gestation vitamin D deficiency was associated with a higher risk of being diagnosed with clinical ASD [82].

Table 1. Characteristics of epidemiological studies on prenatal vitamin D and neurodevelopment

Author, year	Country	Study's year of birth	Prenatal vitamin D assessment: time and levels	Age of offspring at assessment	Number	Neurodevelopment assessment of children and dimensions	Report
Gale et al. [73], 2008	UK	1991–1992	32 weeks Median 25(OH)D: 50 nmol/L (IQR 30–75.3)	9 years	178	Wechsler Abbreviated Scale of Intelligence (WASI) Strengths and Difficulties Questionnaire (SDQ)	Mother report
Morales et al. [51], 2012	Spain	2003–2008	13 weeks Median 25(OH)D3: 29.6 ng/mL (IQR 21.8–37.3)	14 months	1,820	Bayley Scales of Infant Development II	Psychologist report
Whitehouse et al. [52], 2012	Australia	1989–1991	18 weeks 25(OH)D: IQR 46–72 nmol/L	2 years 5 years 8 years 10 years 14 years 17 years	Range: 412–652	Peabody Picture Vocabulary Test Revised (PPVT-R) Child Behaviour Checklist (CBCL)	Parent report
Hanhie et al. [69], 2014	Vietnam	2010–2012	25(OH)D 32 weeks –	6 months	960	Bayley Scales of Infant Development III	Psychologist report
Keim et al. [75], 2014	US	1959–1973	≤26 weeks Median 25(OH)D: 45 nmol/L (IQR 34)	8 months 4 years 7 years	Range: 3,146– 3,587	Bayley Scales II Stanford-Binet Intelligence Scale and the Wechsler Intelligence Scale for Children (WISC) Wide Range Achievement Test (WRAT)	Psychologist report
Strom et al. [77], 2014	Denmark	1988–1989	>30 weeks Median 25(OH)D: 76.2 nmol/L (10th–90th percentiles 32.5–135.9)	22 years	850	ADHD (prescription for psychostimulant medication) Depression (prescription for antidepressant medication or registered with a diagnosis of depression) Scholastic achievement (Student Register)	Population-based registry
Morales et al. [78], 2015	Spain	1997–2008	13 weeks Median 25(OH)D3 (IQR): 29.1 ng/mL (21.7–36.8)	4.8 years	1,650	ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, fourth edition (ADHD-DSM-IV)	Psychologist report
Tylavsky et al. [70], 2015	USA	2006–2011	Second trimester Mean 25(OH)D: 22.3 ng/mL (range 5.9–68.4)	2 years	1,020	Bayley Scales III	–
Zhu et al. [76], 2015	China	2008	Cord blood at birth Mean 25(OH)D (range): 37.2 6 (5.56–111) nmol/L	16–18 months	363	Bayley Scales of Infant Development II	Certified examiners
Chen et al. [79], 2016	China	2014–2015	25(OH)D First trimester of gestation –	3–7 years	136	ASD diagnosis based on DSM-V criteria for autistic disorder	Child psychiatrist/ a neuropsychiatrist and a child psychologist

Table 1. (continued)

Author, year	Country	Study's year of birth	Prenatal vitamin D assessment: time and levels	Age of offspring at assessment	Number	Neurodevelopment assessment of children and dimensions	Report
Magnuson et al. [80], 2016	Sweden	2001–2011	25(OH)D –	4–17 years	509 639	ASD clinical diagnosis	National and regional registers
Vinkhuyzen et al. [81], 2016	The Netherlands	2002–2006	25(OH)D Mid-gestation Cord blood at birth –	6 years	2,866 1,712	Social Responsiveness Scale: Autism-related traits	Parental report
Daraki et al. [77], 2017	Creta	2006–2007	13 ± 2.4 weeks Mean 25(OH)D (SD): 46.3 (15.4) nmol/L	4 years	487	McCarthy Scales of Children's Abilities:	Maternal report
Darling et al. [74], 2017	UK	1991–1992	29.6 (IQR 12.7–33.3) weeks Median 25(OH)D: 61.3 (IQR 42.9–84.7) nmol/L	6–42 months 7–9 years	7,065	Gross and fine motor skills Social development Communication The Strengths and Difficulties Questionnaire (SDQ) WISC Neale Analysis of Reading Ability	Maternal report
Gould et al. [72], 2017	Australia	–	Cord blood at birth Mean 25(OH)D (SD): 55.9 (28.5) nmol/L	18 months 4 years	Range 299–323	Bayley Scales III The Differential Ability Scales Second Edition (DAS II) The Clinical Evaluation and Language Fundamentals Preschool, Second edition (CELF-P2)	Psychologist report
Veena et al. [104], 2017	India	1997–1998	30 weeks of gestation Mean 25(OH)D 38.9 (IQR: 23.5–58.3) nmol/L	9–10 years 13–14 years	468 472	Atlantis: Learning ability/long-term storage Word order: short-term memory, working memory Pattern Reasoning: Reasoning abilities Verbal fluency Kohs block design: Visuo-spatial ability Coding-WISC-III: attention and concentration	Psychologist report
Vinkhuyzen et al. [82], 2017	The Netherlands	2002–2006	Mid-gestation Mean 25(OH)D: 58.6 nmol/L Cord blood at birth Mean 25OHD: 35.9 nmol/L	6 years	3,957 2,916	Autism Spectrum Disorder (ASD) diagnosis	Clinical records

In summary, the current evidence indicates that prenatal vitamin D status may impact the risk of ADHD symptoms and ASD later in life; however, the evidence for other neurobehavioral problems is still inconsistent.

Although evidence is not yet conclusive and further research is needed, results from the latest epidemiological studies support the hypothesis that prenatal vitamin D status impacts the neuropsychological development of children, although this should be confirmed using intervention studies.

Prenatal Vitamin D Status and Asthma Risk

Changing lifestyle and environmental influences over the past few decades are most probably responsible for asthma upsurge worldwide [83]. Since immune and lung development occur largely in utero and during early childhood, diverse lifestyle and environmental exposures acting during these critical periods of life have been investigated as risk factors of developmental programming of asthma [84, 85]. To this regard, several reasons support the hypothesis that prenatal vitamin D status may play a role in programming the offspring's susceptibility to develop asthma later in life. First, VDRs are present in immune cells and the airways [86]. Second, vitamin D plays multiple effects on foetal maturation and the developing immune system [87, 88]. Third, polymorphisms in VDR and metabolism genes are associated with childhood asthma susceptibility [89, 90].

The levels of prenatal vitamin D on wheeze/asthma susceptibility in offspring have been extensively investigated in observational studies [49, 50, 91, 92]. There are two meta-analyses that have shown high dietary vitamin D intake during pregnancy to be associated with a reduced risk of wheeze in the offspring (Nurmatov et al. [91] OR 0.56, 95% CI 0.42–0.73; Beckhaus et al. [92] OR 0.58, 95% CI 0.38–0.88). However, the results of meta-analysis from observational studies but based on maternal serum 25(OH)D concentrations on asthma/wheeze outcome are controversial yet. Two other meta-analyses showed a trend to increased 25(OH)D to be inversely associated with the risk of asthma and wheeze during childhood, although associations did not reach statistical significance [50, 93]. Another meta-analysis based on 12 prospective studies suggested even a more complex association, in which a U-shaped relationship between maternal 25(OH)D levels and risk of asthma was described [49]. A more recent study meta-analyzing the results from 14 observational studies found no association between pre-

natal vitamin D concentrations and risk of asthma during childhood (Pacheco-Gonzalez et al. submitted [94]). Due to these controversial results, intervention studies are essential to clarify such associations.

To date, 4 independent randomized controlled trials have assessed the effect of vitamin D supplementation during pregnancy on the occurrence of wheezing and asthma. Chawes et al. [95] reported that supplementation with 2,800 IU/day of vitamin D3 during the third trimester of pregnancy, as compared with 400 IU/day, resulted in a non-significant reduced risk of persistent wheeze in the offspring through age 3. Both groups had sufficient maternal vitamin D levels at baseline (31 ng/mL), although the intervention increased in 13 ng/mL serum levels of 25(OH)D. The VDAART study assessed the effects of supplementation with 4,400 IU/day of vitamin D, as compared with 400 IU/day, at 10–18 weeks of gestation among pregnant women at high risk of having children with asthma and they found a non-significant 6.1% decreased incidence of asthma and recurrent wheezing by age 3 [96]. However, the combined analysis of the results obtained in these two RCTs has shown that vitamin D supplementation during pregnancy results in a significant reduced risk of asthma/recurrent wheeze in the offspring by age 3, especially among women with 25(OH)D level ≥ 30 ng/mL at randomization, where the risk was almost halved [54, 97].

Goldring et al. [98] randomized 180 pregnant women at 27 weeks gestation to either no vitamin D, 800 IU ergocalciferol daily until delivery or a single oral bolus of 200,000 IU cholecalciferol. Baseline median maternal 25(OH)D levels were deficient (around 25 nmol/L or 10 ng/mL) [99]. They found just a modest significant effect on cord blood and on maternal 25(OH)D at delivery (control 27 nmol/L (interquartile range [IQR] 27–39); daily dose 42 nmol/L (IQR 31–76); bolus dose 34 nmol/L (IQR 30–46) [99] and no effect on wheezing occurrence in offspring at age 3 [98]. A recent meta-analysis on intervention studies (including these previous 3 studies) supported the inverse association between the prenatal intake of vitamin D and the risk of developing recurrent wheeze in the offspring (Vahdaninia et al. [100] RR 0.812; 95% CI 0.67–0.98).

Grant et al. [101] randomized 260 woman/infant pairs to placebo/placebo, 1,000 IU/400 IU or 2,000 IU/800 IU. At enrolment, the mean serum 25(OH)D value was above the deficient level (63 nmol/L or 25 ng/mL). They achieved levels of maternal 25(OH)D at 36 week of gestation close to 40 ng/mL [102]. There were differences at 18 months in the proportion of children with primary care visits de-

scribed by the doctor as asthma (11, 0, and 4%, $p = 0.002$), but not for the other respiratory health outcomes. Thus, although some of the results tended to show an association between maternal vitamin D supplementation with lower wheeze risk, the different doses used limits to get robust results. Nevertheless, doses higher than 400 or 600 IU/day during pregnancy seemed to be needed to achieve a potential benefit to fight against childhood wheeze or respiratory infections [103].

Since growing evidence supports a preventive role of vitamin D during pregnancy on offspring wheeze and/or respiratory tract infections, recommendations in future intervention studies may need to work with large trials under defined ethnic, season and time of supplementation.

Conclusions

Large intervention studies are warranted to determine the appropriate levels of vitamin D supplementation during pregnancy on maternal, perinatal and foetal outcomes. Optimal levels of vitamin D could be essential as early as from the beginning of pregnancy for the risk re-

duction of preeclampsia and other pregnancy complications. However, to improve foetal programming of asthma and metabolism, maybe it could be more important to recommend vitamin D supplementation during the 2nd and 3rd trimesters of pregnancy.

Screening of vitamin D levels at the preconceptional period or at the first trimester should be recommended in pregnant women with high risk of vitamin D deficiency such as obese women, subjects with dark skin, hardly covered, under corticoid treatment, hypertension, pre-gestational diabetes mellitus, or autoimmune diseases so that they could receive appropriate treatment and monitored accordingly. For low-risk pregnancies, we must wait for more robust results that corroborate improved materno-foetal outcomes to recommend screening and supplementation with vitamin D at specific times during pregnancy.

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