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Role of Vitamin D in Pregnancy and Its Impact on Maternal and Perinatal Outcomes

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Abstract: ***Pregnancy is a critical time in the lifecycle of a woman where she is responsible not only for her own well-being, but also that of her developing fetus. Until recently, the impact of vitamin D status during this period had not been fully appreciated. 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. Vitamin D through its effect on immune function and surveillance plays a role beyond calcium and bone metabolism on the health status of both the mother and her fetus. Thus by learning effect of supplementing vitamin D on maternal and perinatal outcomes, we can individualize its role in a safe manner. Interventional studies have also evaluated the effect of vitamin D for reduction on preterm birth and asthma programming. Thus maternal deficiency predicts fetal and infant deficiency of vitamin D. The importance and impact of this on maternal and fetal outcomes will be discussed in this review.***

Keywords: Vitamin D, Pregnancy, Maternal, Fetal

1. Introduction

Pregnancy is a state with change in physiology, change in physical structure with additional requirement for both mother and fetus. As deficiency and supplementation of iron, folic acid and vitamin B12 are well known in pregnant women, it is not so for obscured vitamin D. Vitamin D is known to play an important role in bone metabolism through regulation of calcium and phosphate equilibrium. Vitamin D has an increasingly recognized repertoire of non-classical actions, such as promoting insulin action and secretion, immune modulation and lung development. It therefore has the potential to influence many factors in the developing fetus. Vitamin D is mainly produced in the body by exposure to sunlight but is also found in dietary products like oily fish, eggs and fortified foods. 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 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 fetus 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 fetal development [2]. Actually, we have a large prevalence of vitamin D deficiency/insufficiency among adolescents and women of reproductive age most of these adolescents will become pregnant and then vitamin D deficiency will play a negative role on the fetal programming of next generations [3].

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. Its deficiency has been found to be linked with increased risk of pre-eclampsia, gestational diabetes mellitus, post-partum hemorrhage, preterm birth, low birth weight etc [4]. However current evidences are limited. We will discuss vitamin d physiology and metabolism, role of vitamin d in pregnancy and fetomaternal outcome, its daily requirement dose, diseases linked to its deficiency and how to prevent those for successful outcome of pregnancy.

Vitamin D Physiology & Metabolism

There are two forms of vitamin D available that is vitamin D2 and D3. The first step in the formation of vitamin D occurs in the skin by conversion of 7-dehydrocholesterol to pre-vitamin D following UVB exposure. Once formed, pre-vitamin D undergoes a thermal reaction and is converted into vitamin D. Most vitamin D is converted in the liver to 25(OH) D through the action of 25-hydroxylase. The 25(OH) D is taken up by the kidney and converted to dihydroxy vitamin D (1, 25 [OH] 2D or calcitriol), the active hormonal form of vitamin D, by the action of the enzyme 1-a-hydroxylase. Its endocrine effects are increased calcium and phosphorus absorption from the intestine, increased calcium re-absorption from urine and regulation of parathyroid hormone by negative loop feedback.

Vitamin D Intake Recommendations during Pregnancy

The amount of vitamin D that is required to meet the physiological needs of humans is an ongoing subject of debate. Current recommendations show no consensus regarding it. The Institute of Medicine (IOM) defining serum 25(OH) D levels of 50 nmol/L as adequate [5], and others advocating a threshold of 75 nmol/L [6]. 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 [6]. 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. Nevertheless, both societies agree to consider the upper limit of intake as 4, 000 IU/day.

Dietary vitamin D intake usually reaches only about 5 µg per day (200 IU/day) [7], 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 [8]. Supplementation with 1, 000 IU/day could be a safe option to treat vitamin D deficiency. The problem of excessive vitamin D intake during pregnancy is linked to the risk of hypercalcemia in the fetus, 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.

Vitamin D supplementation and Feto-maternal bone health

Maternal vitamin D and calcium levels are modified during pregnancy to support fetal calcium homeostasis. Hypovitaminosis D is associated with impaired growth and bone development in the fetus. Evidence is accruing to show that less profound maternal 25(OH) D insufficiency may lead to suboptimal bone size and density after birth without overt rachitic change. This is likely to lead to an increased risk of osteoporotic fracture in later life. Maternal serum 25(OH) D levels below 30ng/mL are associated with maternal periodontal disease during pregnancy [9]. Moreover, osteoporosis is an important public health problem. 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 fetal 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 [10].

The MAVIDOS study, a multi-center, double-blind, randomized, 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. 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 [11].

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. A comment piece in The Lancet argued that routine supplementation of vitamin D should be reserved for at-risk women rather than for all women. 68 This was on the basis of a large prospective cohort study showing no association between maternal serum vitamin D levels and bone mineral content in the children [12].

Vitamin D Supplementation during Pregnancy and Perinatal Outcomes

25(OH) D serum levels with higher risk of preeclampsia, gestational diabetes, caesarean sections, preterm birth (PTB) or IUGR [13, 14]. In addition, there is growing evidence on the association with offspring risk of asthma, bone health, allergies and impaired neurodevelopment [15-18]. In a recent Cochrane meta-analyses 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 [19, 20].

Preeclampsia Risk

In a recent Cochrane review, results from two trials involving 219 women suggested that women who received vitamin D supplements may have a lower risk of pre-eclampsia 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].

Impaired glucose tolerance in pregnancy

Hypovitaminosis D is associated with impaired glucose tolerance and diabetes in the general population. However, the evidence for an association between low vitamin D levels and gestational diabetes mellitus (GDM) is conflicting. A meta-analysis of 31 studies demonstrated vitamin D insufficiency was associated with a higher risk of GDM [21].

Low Birth Weight

Maternal vitamin D levels have been shown to positively correlate with birth-weight centile [22].

However, other studies demonstrated no relationship between maternal vitamin D levels in the first trimester and birth-weight but did demonstrate that low vitamin D levels in late pregnancy were associated with reduced intrauterine long bone growth and lower gestational age at delivery [23].

Preterm Birth

Recent meta-analyses of observational studies also support that vitamin D insufficiency (<30 ng/dL) is associated with risk of PTB. With regard to spontaneous abortion and stillbirth, the available evidence suggests that there is no association with low vitamin D levels [24]. The possible biological mechanisms of vitamin D involved in the prevention of PTB are presumably related to its immunomodulatory capacity during embryo implantation [25], calcium homeostasis in the endometrium for the

maintenance of pregnancy [26], as well as its role in the prevention of infection during pregnancy [27].

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 signaling may have a role in brain development and function [64, 65]. Its deficiency may be related to low global intelligence quotient (IQ) or cognitive development, psychomotor Outcomes, attention deficit hyperactivity disorder and autism spectrum disorder but results are still inconsistent.

Prenatal Vitamin D Status and Asthma Risk

Nevertheless, doses higher that 400 or 600 IU/day during pregnancy seemed to be needed to achieve a potential benefit to fight against childhood wheeze or respiratory infections. Since growing evidence supports a preventive role of vitamin D during pregnancy on offspring wheeze and/or respiratory tract infections [30 [.

Safety of vitamin D

In pregnancy there is enhanced intestinal calcium absorption. Vitamin D toxicity is manifested through hypercalcaemia and hypercalciuria. Therefore, there is a hypothetical concern that when secondary hyperparathyroidism follows vitamin D deficiency, calcium given with vitamin D may be associated with temporary hypercalcaemia. However, this is self-limiting due to the associated hungry bone and has not been demonstrated to represent a clinical problem.

2. Conclusions

Large intervention studies are warranted to determine the appropriate levels of vitamin D supplementation during pregnancy on maternal and fetal outcomes. Optimal levels of vitamin D could be essential as early as from the beginning of pregnancy for the risk reduction of preeclampsia and other pregnancy complications.

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