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Vitamin D Deficiency-Related Reproductive Consequences

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Abstract

Background: Vitamin D deficiency during pregnancy is common and threatens the woman and her developing fetus. As a pregnancy progresses, the requirements for vitamin D increase, thus, increasing the risk of hypovitaminosis D. Consequently, the majority of women become or remain vitamin D deficient and remain vitamin D deficient during pregnancy and the postnatal period.

Rationale/Objectives: Despite some awareness of the problem, in a high percentage of pregnancies, vitamin D deficiency remains unidentified and unaddressed. Consequently, this review explores the risks and complications associated with vitamin D during pregnancy and highlights the importance of having physiological levels of serum 25-hydroxy vitamin D [25(OH)D] during pregnancy to minimize risks to mothers and fetuses.

Outcomes: Hypovitaminosis D during pregnancy leads to an increased incidence of a variety of pregnancy-related complications leading to adverse reproductive outcomes. These include higher incidences of pregnancy loss, preeclampsia, placental insufficiency, gestational diabetes, impaired immune tolerance, increased risk for cesarean delivery, bacterial vaginosis, impaired fetal growth and development, small-for-date neonates, and premature deliveries. In addition, the effects of maternal vitamin D deficiency on the fetus may continue beyond delivery.

Wider implications: There are clear medical as well as ethical reasons for clinicians to diagnose and treat vitamin D deficiency during pregnancy. Given that lives and otherwise uncomplicated pregnancies are at stake, identifying and effectively addressing vitamin D deficiency during pregnancy is not optional but essential.

Abbreviations: 25(OH)D; 1,25(OH)2D; Biology; Clinical Trials; Human; Personalized Therapy; Physiology; Supplements

Introduction

The active form of vitamin D, 1,25(OH)2D, is a secosteroid hormone, intimately involved in a multitude of genomic and nongenomic effects. These effects expand from facilitating fertilization and implantation to issues related to fetal well-being [1]. Vitamin D maintains the health of all reproductive tissues, including the endometrium [1], and encourages fertilization [2] as well as immune neutrality in the event of implantation [3].

Deficiency of vitamin D (hypovitaminosis D), increases the incidence and severity of many pregnancy-associated risks and complications, leading to negative outcomes. Therefore, early identification and correction of vitamin D deficiency is essential [4], ideally, before a women becomes pregnant. However, many pregnancies, if not most, are allowed to continue under the shadow of hypovitaminosis D; this is not uncommon in both industrialized and agricultural countries.

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Vitamin D metabolism

Vitamin D is created following exposure to ultraviolet B (UVB) radiation in the dermis and epidermis, effecting a conformational change in a 7-dehydro-cholesterol to become 9,10-secosterol, previtamin D3 [5]. Previtamin D enters the circulation bound to vitamin D binding protein (DBP) and is transported to the liver, where it is hydroxylated to become 25(OH)D in the parenchymal cells. This precursor undergoes further modification in the renal tubular cells with 1α-hydroxylation to form active vitamin D, 1,25(OH)2D [6].

The transformation of vitamin D to 25(OH)D and 1,25(OH)2D customarily occurs through the actions of specific cytochrome P450 (CYP) enzymes located within renal mitochondria: CYP27A1, CYP27B1, and CYP24A1 [7]. A number of tissues containing target cells also possess the intracellular enzymatic mechanisms to convert 25(OH)D to its hormonally active form 1,25(OH)2D, calcitriol [6, 8]. Apart from UVB exposure, small quantities of vitamin D are obtainable by diet and supplementation as D3 and D2. D3 is of animal origin, whereas D2 is derived from plant and fungi sources. Because of its longer half-life, vitamin D3 is considered more effective than D2 in maintaining physiologically healthy 25(OH)D levels [7, 9].

Vitamin D Sufficiency vs. Deficiency

The terminology of "insufficiency" and "deficiency" is arbitrary. Neither vitamin D insufficiency nor deficiency is physiological, because with either condition, the biological needs of vitamin D in humans are not met. Various organs and tissues require different concentrations of 25(OH)D in serum to function optimally. Because negative reproductive outcomes occur when serum 25(OH)D levels fall within the insufficiency range, hypovitaminosis D should be identified and not allowed to persist in pregnant and pre-pregnant women [10].

For optimal pregnancy-related outcomes, it is recommended that serum 25(OH)D concentrations be maintained above 40 ng/mL [11, 12]. Vitamin D deficiency negatively affects the pregnant woman and the fetus in a variety of ways [13-15], including prevention of infections [16]. Evidence supports having serum 25(OH)D concentrations between 40 and 60 ng/mL; this is achievable by daily supplementation of vitamin D on the order of 4,000 IU/day (range 3000 to 6000 IU/day) of vitamin D3 [17-19]. However, there are a handful of studies that disagree with the above findings [20].

Vitamin D requirements during Pregnancy

Current recommendations for vitamin D supplementation during pregnancy are insufficient [13]. A more favorable response was reported when pregnant women were supplemented with 4,000 IU/day of vitamin D, starting in the 12th to 16th week and continuing to completion of pregnancy, compared with doses of less than 800 IU/day [17].

This study and others suggest studies of vitamin D during pregnancy strongly support that the minimal vitamin D level for optimal outcomes during pregnancy is 40 ng/mL. The goal of supplementation with 4,000 IU/day for pregnant women is to increase the serum 25(OH)D levels to near or above 40 ng/mL in most women during pregnancy [10].

However, in 2010, the Institute of Medicine (IOM) issued guidelines for vitamin D supplementation suggesting an intake of 600 IU/day is adequate for adults regardless of their circumstances; yet, this is substantially below the physiological needs of pregnancy that have been shown to prevent complications and protect the fetus [21]. Such intake is far from adequate to maintain the serum 25(OH)D levels needed for a healthy pregnancy and favorable reproductive outcomes [13,22].

Recommendations by Various Scientific Societies

The IOM defined vitamin D insufficiency as a value between 10 and 19 ng/mL, and severe vitamin D deficiency is defined as a value below 10 ng/mL [21]. It should be noted that the IOM cutoff value of below 20 ng/mL for vitamin D insufficiency was based on requirements for bone health only (Endocrine Society recommendations; [23]). Therefore, applying the IOM recommendations to the requirements of vitamin D during pregnancy (or other diseases or conditions) is inappropriate and is, in fact, harmful to women during pregnancy [13].

Following the publication of the IOM public health recommendations, the Endocrinology Society and other societies took the initiative to defined vitamin D deficiency as any value below 20 ng/mL, with vitamin D insufficiency defined as a value between 20 and 30 ng/mL [21, 24, 25]. The authors and others believe a value of at least 30 ng/mL, and perhaps closer to 40 ng/mL, addresses the needs of pregnant women and their fetuses [17, 22]. In the absence of laboratory testing, the vitamin D status of an expectant mother remains unknown, complications are not prevented or relieved, and appropriate intervention is less likely to occur [10].

Prevalence of vitamin D deficiency during pregnancy

Estimates suggest that the incidence of maternal vitamin D deficiency is on the order of 20% to 40% [21]); whilst others report a prevalence of more than 60% of pregnant women [26]. A much higher incidence of vitamin D deficiency occurs among

pregnant African American and Latina American women because of higher levels of melanin in darker-skinned individuals, which is an impediment to UVB penetration and thus places a limitation on the generation of vitamin D [5].

Vitamin D Actions in Maternal and Fetal Systems

In general, vitamin D works in conjunction with calcium, particularly in nongenomic activities [18]. Active vitamin D initiates genomic and nongenomic events via a vitamin D receptor (VDR) [27]. Unlike many other receptors, VDRs populate both cell membranes and the nuclei and are distributed ubiquitously in a variety of cell types [7, 28]. Consequently, vitamin D has pleotropic effects [29].

Irrespective of the economic status, ethnicity, or proximity to the equator of populations, vitamin D deficiency is an epidemic affecting virtually all countries [30]. Not only vitamin D deficiency but also VDR abnormalities can lead to signs and symptoms of vitamin D deficiency [6]. With respect to pregnancy, alterations in gene expression, those normally mediated and modulated by active vitamin D [31], can place the pregnancy in jeopardy and lead to many negative pregnancy and fetal outcomes, such as miscarriage, preeclampsia, gestational diabetes, and preterm birth [32].

Reproductive Consequences of Vitamin D Deficiency

Vitamin D deficiency before and during pregnancy causes a variety of significant negative outcomes and threatens the lives of the woman and the fetus (e.g., preeclampsia) [32]. There are a number of threats and complications posed by maternal vi- amin D deficiency for both mother and the fetus; us, effectively resolving such is essential. Some of the common negative reproductive consequences secondary to vitamin D deficiency are Summarized in Figure 1 and will be briefly discussed below.

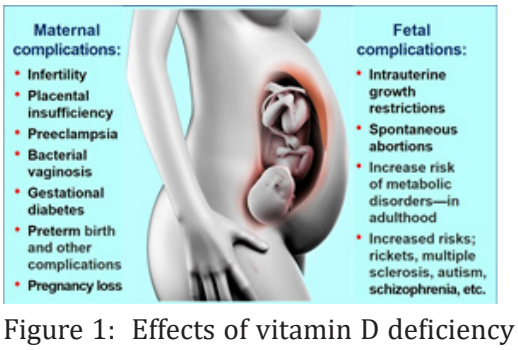

Figure 1: Effects of vitamin D deficiency on maternal and fetal outcomes

a) Fertilization and immune regulation

Fertilization is facilitated by 1,25(OH)2D/VDR-mediated nongenomic activity [27]. Accordingly, intracellular 1,25(OH)2D raises calcium levels and increases the likelihood of sperm–egg binding; it also increases the activity of acrosine, the enzyme responsible for digesting zona pellucida of the ovum, allowing sperm to penetrate and fertilize the egg [27, 33].

After successful fertilization, immune tolerance of the fertilized ovum is essential to reproductive success [34, 35]. Active vitamin D orchestrates immune tolerance by stimulating Treg activity and shifting the Th1 cytokine profile from a pro-rejection profile to a tolerance-promoting Th2 profile [35, 36].

b) Placental insufficiency:

Placental VDR expression and its interaction with 1,25(OH)2D is a critical regulator of the growth of the placenta and fetus [37]. Placental VDR/1,25(OH)2D interaction allows vitamin D to play key roles in regulating genes involved in early placental development [38], local immune suppression, and the production of vascular endothelial growth factor [39]. In addition, pregnant women with 25(OH)D concentrations less than 20 ng/mL are reported to have suboptimal levels of placental growth factor, which may contribute to the development of preeclampsia and fetal growth restriction [34, 35, 40].

Compromised placental growth and development leads to vascular insufficiency and placental inflammation; the combination predisposes women to preeclampsia and associated negative consequences [41]. Whereas, vitamin D adequacy is reported to play a decisive role in preventing and suppressing placental inflammation [41].

c) Preeclampsia:

Multiple studies have reported that vitamin D deficiency is associated with an increased risk of preeclampsia [42-44]. A five-fold increase in preeclampsia was reported in pregnant women with a 25(OH)D level of 15.2 ng/mL compared with those with substantially higher 25(OH)D levels [45].

Underscoring the value of vitamin D in the prevention of preeclampsia, one study found a 27% reduction in preeclampsia risk in women who supplemented with vitamin D compared with those who did not supplement [32]. Not to lose sight of the individual most at risk, a neonate born to a preeclamptic woman is five times more likely die during the first birth month [46], which underscores the extreme seriousness of maternal vitamin D deficiency and preeclampsia.

d) Bacterial vaginosis:

Vitamin D deficiency is associated with an increased risk of bacterial vaginosis [32, 36, 47]. One

study reported a threefold increase in bacterial vaginosis in pregnant women who had a vitamin D level of less than 30 ng/mL [47]. Bacterial vaginosis is clearly a threat to a pregnancy and to the life of the fetus, and is strongly associated with reproductive failure, fetal loss, premature rupture of membranes, and premature birth [48, 49]. Given the roles vitamin D plays in shaping the immune response to bacteria in the placenta, vitamin D sufficiency is one answer to this common reproductive threat [32].

e) Gestational diabetes:

Gestational diabetes is more common than reported and may occur in more than 14% of pregnancies in the United States; it can increase the need for cesarean section delivery [50]. Vitamin D deficiency is positively associated with an increased risk of gestational diabetes [51] and risks of fetal abnormalities (e.g., macrosomia), birth trauma, neonatal respiratory distress syndrome, and other negative outcomes [50].

Levels of serum 25(OH)D below 20 ng/mL have been linked to a 2.7-fold increase in gestational diabetes [52]. In patients with gestational diabetes, doses of 4,000 IU of vitamin D per day have been shown to decrease insulin resistance and fasting insulin levels, whereas a daily dose of 2,000 IU was ineffective [53]. These data also suggest the need for vitamin D supplementation of 4,000 IU/day and maintaining serum 25(OH)D levels above 30 ng/mL.

f) Intrauterine growth restriction:

Intrauterine growth restriction affects as many as 1 in 12 pregnancies, is associated with placental insufficiency, and can lead to fetal loss, perinatal asphyxia, and impaired cognition and cerebral palsy [54]. Affected infants are predisposed to disease in their later life, including type 2 diabetes, hypertension, stroke, and coronary artery disease [54]. In addition, maternal vitamin D deficiency has been associated with an increased risk of type 1 diabetes, multiple sclerosis, schizophrenia, autism, and asthma in offspring [32, 52].

In one study, the risk for small-for-gestational-age neonates was 2.4 times higher when the mother has a serum 25(OH)D level below 12 ng/mL compared with mothers with levels of 20 ng/mL [39, 55, 56]. According to one source, women who supplemented with vitamin D during pregnancy have a greater than 50% reduction in low–birthweight infants compared with women who did not supplement with vitamin D during pregnancy [55].

g) Spontaneous abortion and preterm birth:

Pregnancy loss may terminate as many as 31% of all pregnancies [57]. Studies involving in vitro fertilization have revealed the importance of vitamin D to the maintenance of pregnancy. Remarkably, one such study found the vitamin D levels in patients who achieved clinical pregnancy were substantially higher than were those who experienced pregnancy loss via spontaneous abortion, with those with a high vitamin D level achieving a fourfold greater pregnancy success rate than those with low vitamin D levels [33].

To underscore the value of adequate vitamin D supplementation in the prevention of premature birth, one study found a 50% reduction in preterm birth in pregnant women who received 4,000 IU vitamin D per day, as opposed to those who received lesser amounts (e.g., 400 or 2,000 IU) of daily supplementation [17,22,26].

Conclusion

Vitamin D deficiency is a major threat to maternal and fetal well-being, yet the epidemic of vitamin D deficiency continues. Clinicians are uniquely responsible for safe care and delivering appropriate instruction but overall are receiving a failing grade because of a lack of knowledge or attention to this matter. There are consequences, born out in the lives of mothers and their offspring, including the loss of life. Given the weight of the evidence, there is a pressing need for clinicians to recognize the dangers of maternal vitamin D deficiency and effectively identify and address this threat in the women under their care.

Guidance:

Levels of 25(OH)D should be measured before or during early pregnancy, with monitoring and retesting during pregnancy. Based on the findings, prescribing adequate oral supplementation of vitamin D_3 to maintain serum vitamin D concentration of more than 30 ng/mL (or preferably keep above 40 ng/mL) is recommended to mitigate risks. Awareness of such should be expanded to minimize the harm caused by what has been recognized as a global epidemic of maternal vitamin D deficiency.

Disclosure

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