REVIEW

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Relationship between total 25(OH)D and interleukin-2 contents in preterm conversion patients

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ABSTRACT

The most essential nutrient for pregnant women is vitamin D. A lack of vitamin D can cause preterm labor and other issues like low birth weight, preeclampsia, and issues with the baby's bones. According to some research, there is no safe top level and a 75–80 nmol/L range. According to additional studies, an ideal range is between 75 and 110 nmol/L and a daily dosage of 1800 to 4000 IU of vitamin D3. In both early and late pregnancies, women with sufficient vitamin D levels (at least 30 ng/mL) exhibited a significant decrease in the incidence of preeclampsia. It is also known that vitamin D modulates the immune system in several ways. T-cell proliferation can be suppressed, and pro-inflammatory cytokines, including IL-2, IFN-, and IL-17, can be produced less frequently when vitamin D is present. A lack of vitamin D may lead to a rise in cytokines that promote inflammation, such as IL-2. This paper will, therefore, examine the relationship between vitamin D, IL-2 levels, and the risk of premature labor.

Keywords: vitamin D, interleukin-2, pregnancy.
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INTRODUCTION

Sunlight and diet are the two primary sources of vitamin D, essential in many bodily metabolic functions. A normal range of 30-100 ng/mL is found for the blood's 25(OH)D level, which is used to monitor vitamin D activity.[1,2] A lack of vitamin D, insufficient sun exposure, poor absorption, or the kidneys' incapacity to convert 25(OH)D into its active metabolite form can all contribute to a vitamin D deficit. A shortage of vitamin D during pregnancy can lead to preeclampsia, gestational diabetes, early delivery, low birth weight, and problems with the bones in newborns.[3]

Premature delivery, which is defined as giving birth before the baby reaches the age of 37 weeks of pregnancy as determined by the first day of the preceding menstrual cycle, is a serious global health concern. According to World Health Organization projections from 2018, 1 million babies die as a result of preterm birth complications out of an estimated 15 million premature births annually.[4,5] Premature birth is caused by a complicated and multifaceted theory that includes activation of the maternal hypothalamic-hypophyses-adrenal system, infections, inflammation, uterine straining, and decidua hemorrhage. According to studies, 90% of moms at risk of premature childbirth have a vitamin D deficiency, which can raise the risk of premature labor.[5,6] By lowering oxidative stress, limiting excessive apoptosis, and regulating pro-inflammatory cytokines, vitamin D plays an immunological function in preventing premature labor. A lack of vitamin D can increase the levels of pro-inflammatory cytokines, such as IFN-γ and IL-2, which can lead to premature birth and induce uterine contractions.[2] All things considered, vitamin D is crucial for the health of expectant moms and for delaying early labor by controlling the immune system, lowering oxidative stress, and decreasing inflammation.[7]

LITERATURE REVIEW

Vitamin D is one of the essential micronutrients for various metabolic processes in the body. Vitamin D can be absorbed by diet, generated by the skin when exposed to sunshine and utilized in the immune system. Vitamin D also regulates calcium and phosphate absorption in the intestines to maintain blood calcium concentrations and bone mineralization.[3] Vitamin D metabolism comprises numerous phases of transformation. In metabolism, the vitamin D component must be transformed into its active metabolite form, namely 1,25(OH)2D3. This procedure involves hydroxylation twice. When vitamin D is introduced into the plasma, it does so as 2-globulin, a protein-bound form. The liver microsome is then hydroxylated to produce 25-hydroxyvitamin D (25(OH)D). Compared to vitamin D, whose blood levels are momentarily increased during absorption or skin production, 25(OH)D has more stable levels. The addition of a third hydroxyl group (OH) to the carbon atom 1 is the next step required to convert the 25(OH)D molecule into an active metabolite form. In the kidneys, in the mitochondria of the proximal tubules,

an enzyme known as 1-hydroxylase adds this hydroxyl group, resulting in the production of 1,25-dihydroxide vitamin D (1,25(OH)2D), or calcitriol.[7]

The kidney enzyme 1-hydroxylase has strict control over the production of 1,25(OH)2D, which is the active form of vitamin D. By raising the activation of the enzyme 1-hydroxylase, other hormones, including fibroblast growth factor-23 (FGF-23) and 1,25-dihydroxy vitamin D can reduce the activity of these enzymes.[8] As vitamin D and its metabolites travel through the bloodstream, they bind to albumin and vitamin D binding protein (VDBP), two types of carrier proteins. Vitamin D interacts with the vitamin D nuclear receptor (VDRn) in the target cells after the complex reaches those cells. The body contains these VDRn in a range of tissues and cell types. By binding to the RXR receptor, the VDRn ligand will affect gene expression through nuclear transcription processes.[9]

Besides its genetic regulation-mediated effects, vitamin D has non-genomic actions that involve controlling the vitamin D receptor (VDR) and activating the intracellular signal pathway. Components like STAT1 (signal transducer and activator of transcription 1) and IKK-β (inhibitor of nuclear factor kappa-b kinase subunit Beta) may be involved in these non-genomic effects. The VDR receptor in the cell membrane, known as VDRm, is responsible for this non-genomic technique.[9] Thus, vitamin D plays a crucial role in controlling the body's calcium homeostasis through genetic regulation and non-genetic mechanisms in many tissues and cells.[10]

The body needs different amounts of vitamin D based on characteristics like age, gender, and personal risk factors. There are two bioequivalent forms of vitamin D: vitamin D3 (cholecalciferol) obtained from sunlight, fish oil, and fortified foods, and vitamin D2 (ergocalciferol) from herbal sources and oral supplements. The biological activity of both forms of vitamin D is equal and is expressed in international units of micrograms (μg). Table 1 displays the recommended daily consumption of vitamin D per age group.[11]

Measuring serum 25(OH)D levels during pregnancy is rare in certain nations. Numerous recommendations exist on the body's ideal concentration of 25(OH)D. According to some research, there is no safe top level and a 75–80 nmol/L range. Other research indicates that a daily dosage of 1800–4000 IU of vitamin D3 is recommended, with an optimal level of 75–110 nmol/L. In contrast, the Institute of Medicine (IOM) considers a blood level of approximately 50 n mol/L of 25(OH) D a suitable rate. Therefore, advice from research and health agencies regarding the ideal level of 25(OH)D during pregnancy varies.[12,13] It is necessary to supplement with 1500–2000 IU of vitamin D according to the US Endocrine Society's guidelines to maintain 25(OH)D levels above 75 nmol/L, which is deemed sufficient for pregnant mothers.[14,15]

Low levels of vitamin D in expectant mothers have been associated with several challenges the developing child faces, such as short gestational age (SGA), early birth, and problems with the development of the teeth and bones. Maternal hypovitaminosis D (25(OH)D levels <20 ng/ml or <50 nmol/l) is a substantial risk factor for adverse neonatal external effects, as per multiple observational studies.[12]

In order to meet the fetal calcium requirements, the amount of 1,25(OH)2D increases during pregnancy. Certain data suggest a connection between the mother's vitamin D levels and contested neonatal outcomes, like a decline in 25(OH)D after pregnancy. Because the fetus depends on the mother for vitamin D consumption, the mother's vitamin D level is still significant. Three meta-analyses of observational research have been released in the past few years.[16–18] On the relationship between birth weight and vitamin D levels during pregnancy, the first study could not reach a definitive result. The incidence of SGA appeared to be higher in women who were deficient in vitamin D, most likely because various criteria were utilized to define vitamin D deficiency or inadequacy.[16] According to the second study, women's odds of developing SGA were higher when their levels of 25(OH)D were less than 50 nmol/l than when they were more than 50 nmol/l (Odds Ratio [OR] 1.52; 95% CI 1.08–2.15).[17] A third meta-analysis supported this risk, finding that mothers with 25(OH)D levels less than 50 nmol/l had higher odds of premature birth and SGA (OR 1.85; 95% CI 1.52-2.26).[18] Effects of maternal vitamin D levels and neonatal

Table 1. Daily recommendation of vitamin D intake by age group[11]

Age	Gender		Pregnancy	Breastfeeding
	Male	Female		
0-12 Month	400 IU (10 μg)	400 IU (10 μg)		
1-13 Year	600 IU (15 μg)	600 IU (15 μg)		
14-18 Year	600 IU (15 μg)	600 IU (15 μg)	600 IU (15 μg)	600 IU (15 μg)
19-50 Year	600 IU (15 μg)	600 IU (15 μg)	600 IU (15 μg)	600 IU (15 μg)
51-70 Year	600 IU (15 μg)	600 IU (15 μg)		
>70 Year	800 IU (20 μg)	800 IU (20 μg)		

Table 2. Effects of maternal vitamin D levels and neonatal birth weight of risk of SGA in neonates

Researchers, Year	Neonatal outcome	Number of trials included	Risk Reduction	Findings
Thorne-Lyman and Fawzi (2012).[16]	Low birth weight	3	RR 0.40; 95% CI 0.23–0.71	Protective
	SGA	2	RR 0.67; 95% CI 0.40–1.11	Protective
De-Regil et al. (2016).[19]	Low birth weight	3	RR 0.40; 95% CI 0.24–0.67	Protective
	Preterm birth	3	RR 0.36; 95% CI 0.14–0.93	Protective
Perez-Lopez et al. (2015).[20]	Low birth weight	4	RR 0.72; 95% CI 0.44–1.16	No effect
	Preterm birth	3	RR 1.26; 95% CI 0.60–2.63	No effect
	SGA	3	RR 0.78; 95% CI 0.50–1.21	No effect

birth weight of risk of SGA in neonates are shown in Table 2.

The perinatal and fetal stages of development may be negatively impacted by inadequate vitamin D during pregnancy. Low levels of 25(OH)D in the mother's serum have been linked in several studies to an increased risk of preeclampsia, gestational diabetes, cesarean delivery, and delayed fetal growth (IUGR).[21,22] In some of Cochrane's meta-analyses of vitamin D intervention studies, there was no clear association with gestational diabetes (risk ratio [RR] 0.43; 95% CI 0.05-3.45), cesarean sex action (RR 0.95; 95% IC 0.06-1.99) or fetal mortality (RR 0.27; 95 % CI 0.04–1.67).[6]

Currently, several studies are assessing how vitamin D functions as an immunomodulator to lower the incidence of preeclampsia. Results from two studies, including 219 women who received vitamin D, indicated a decreased incidence of preeclampsia (8.9 versus 15.5%; RR 0.52; 95% CI 0.25–1.05, poor quality) compared to individuals without intervention or placebo in several Cochrane reviews. The topic is still confined to a small number of preeclamptic pregnant populations, however. One VDAART (Vitamin D Antenatal Asthma Reduction Trial) study in the United States involving 408 placebos and 408 samples given 4400 IU of vitamin D3 at the beginning of pregnancy at the age of 10-18 weeks, found that there was no decrease in the incidence of preeclampsia (8.08 vs. 8.33%; relative risk (RR) 0.97; 95% CI 0.61–1.53). Maternal plasma in the intensive group had high levels of 25(OH)D during childbirth (39.2 ± 15.3 vs. 26.8 ± 10.7 ng/dL in the control group), but this did not reduce the risk of preeclampsia. In contrast to women without vitamin D levels at the time, those with adequate vitamin D (at least 30 ng/mL) in both early and late pregnancies demonstrated a substantial reduction in preeclampsia-related incidence (2.25 vs. 11.92%; RR 0.20; 95% CI, 0.06–0.66; p<0.008). The study's findings indicate that taking a vitamin D supplement for certain pregnant women can lower their chance of developing preeclampsia. The initial levels of vitamin D in the body determine the difference in reaction, though, with women who had adequate levels before becoming pregnant typically experiencing a significant risk reduction.[6]

Whereas the metabolite 25(OH)D is prepared to cross the placenta and enter the fetal compartment, the metabolite 1,25(OH)2D, also referred to as calcitriol, does not. Through its 1-α-hydroxylase enzyme, the placenta may convert 25(OH)D to 1.25(OH)2D, vital for controlling placenta tissue's vitamin D levels. Moreover, the placenta may convert 24-hydroxylate 25(OH)D to 24(OH)2D. This regulates vitamin D levels locally in the placental tissue, influencing perinatal output and pregnancy development. Additionally, the placenta has anti-inflammatory properties. Numerous studies demonstrate that during the mother's blood in the latter trimester of pregnancy, the concentration of 1,25(OH)2D increases. While the placenta can create 1,25(OH)2D, the mother's kidneys are primarily responsible for the elevated levels of this substance during pregnancy. The kidney primarily mediates the generation of 1,25(OH)2D in the mother's blood. A high amount of 1,25(OH)2D functions in immune system regulation throughout gestation, enhances intestinal calcium absorption during pregnancy and supports calcium metabolism in both mothers and fetuses.

T-regulating lymphocytes play an essential role in limiting the immune system's response, can be damaging during pregnancy and in preventing the risk of premature childbirth. Premature delivery is a major cause of neonatal morbidity and mortality, and many are initiated by inflammatory responses involving immune cells and activated T cells. Activated cytokines, chemokines, and T-cells trigger inflammation reactions that can negatively affect pregnancy and lead to premature delivery. T cells with phenotype Th1, involved in pro-inflammatory immune responses, are found in premature babies but not in babies born enough months.[23,24] It suggests that regulating the immune system, mainly through vitamin D and T-cell regulators, is vital in a healthy pregnancy and in preventing premature delivery.[21]

Several observational studies indicate that vitamin D deficiency (<30ng/dL) is associated with the risk of premature childbirth (preterm birth, PTB).[6] Pregnant women (n = 1064) were randomized to major RCTs using vitamin D3 free supplementation at levels of 25(OH)D ≥ 40 ng/mL, which demonstrated a 62% reduction in the risk of premature labor when compared to values of <20 ng/ml. Comparable findings revealed a decreased risk of preterm labor in the community of women with a history of preterm labor as well as in some subtypes of premature labor. Additionally, it was observed that the rate of premature delivery was approximately 20% for women whose 25(OH)D was less than 20 ng/mL, 12% for women whose 25(OH)D was between 20 and 30 ng/mL, 13% for women whose 25(OH)D was between 40 and less than 40 ng/mL, and 9% for women whose 25(OH)D was greater than 40 ng/mL. It involves the molecular mechanisms of calcium hemostasis in the endometrium to sustain pregnancy, vitamin D's role as an immunomodulator during embryo implantation, and avoiding infection throughout pregnancy. These findings bolster the recommendation for vitamin D supplementation during pregnancy to avoid preterm birth.[5,6]

Through several different ways, vitamin D regulates the immune system in a significant way. Vitamin D can inhibit T-cell proliferation and decrease the generation of pro-inflammatory cytokines like IL-2, IFN-γ, and IL-17. A shortage in vitamin D may lead to elevated levels of pro-inflammatory cytokines such as interferon-γ and IL-2.[25,26] Pro-inflammatory cytokines such as IL-1, IL-2, IL-6, and TNF-α may trigger the production of prostaglandins (PGE2 and PGF2-α) that can trigger uterine contractions and contribute to premature delivery.[27] In addition to playing a role in the immune response, vitamin D also affects the integrity of cells and cell connections, such as tight junctions, gap junctions, and adherents, which can act as a physical barrier in the cellular immune system.[28]

Numerous immune cell types, such as monocytes, dendritic cells, T and B lymphocytes, and macrophages, are also impacted by vitamin D. It can control the synthesis of antimicrobial peptides that help fight infections, like μ-defensin-2 and cathelicidin. Research indicates a

connection between low vitamin D levels and the emergence of viral illnesses such as dengue, hepatitis, herpes, influenza, and other infections. In order to keep the immune system in balance and prevent infections, vitamin D is essential. A study by Shao, dkk (2019) determined normal reference levels of serum IL-2 based on confidence intervals of 90% in healthy subjects and obtained the lower normal limit of IL-2 levels was 1.30 pg/mL in the study.[29] Previous research supports the idea that subclinical infections can lead to premature childbirth. Recent data suggest that premature delivery has been associated with intrauterine or systemic infections, with special attention to interleukin (IL), such as IL-1, IL-2, IL-6, IL-8, and IL-2R.[30] Althouginterleukin pro and anti-inflammatory coexist during pregnancy; this study did not find an increase in serum interleukine concentrations associated with gestation age. However, IL-2R was detected in all samples, indicating the presence of particular immune activation in the pregnancy environment. Although IL-2 levels are low and difficult to detect, research indicates that IL2R can be a good marker for premature delivery, especially in cases without clinical signs of infection.[31,32] Those studies concluded that interleukin may have a good or bad effect on pregnancy, depending on its concentration. The mother's interleukin does not appear to be contaminated by the interleukine produced by the fetus, and therefore, the mother's serum IL, IL-2R, can be used as a marker of premature delivery, especially in cases without clinical infection.[33,34]

One essential vitamin that may impact pregnancy is vitamin D. Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are two important forms of vitamin D that the body needs to activate to operate. Vitamin D insufficiency may contribute to preterm delivery for a variety of causes, including low vitamin D levels that increase the risk of bacterial vaginitis, diabetes, amniotic membrane rupture, and gestational hypertension. However, research on the relationship between vitamin D deficiency and premature childbirth is inconsistent, and studies yield varying results.[34] Several studies show differences in vitamin D levels in the premature group compared to the timely group. However, other studies found no significant correlation. Environmental factors, such as seasons, also affect vitamin D levels, making comparing studies difficult.[29]

The immune system is also regulated by vitamin D because immune cells use 1-alpha-hydroxylase to control the amounts of calcitriol in their local environments. Given that sufficient serum levels of 25(OH)D have been linked to higher levels of the anti-inflammatory cytokines IL-4 and 10 and lower levels of the pro-inflammatory cytokines IL-1, IL-2, and IL-6, these effects have been linked to the cytokine environment. Conversely, pro-inflammatory cytokine profiles and chronic inflammatory diseases have been connected to vitamin D insufficiency.[35,36] Whether vitamin D regulates hormonal variables during pregnancy directly or indirectly is still unknown. As a result, research on the connection between vitamin D insufficiency and early birth is ongoing.[37]

Most likely, vitamin D's impact on the innate immune response is the primary mechanism underlying its ability to prevent premature delivery. Immune cells that identify chemicals generated from microorganisms, such as dendritic cells and macrophages, have receptors for vitamin D. These immune cells generate antimicrobial peptides after becoming activated. These antimicrobial pathways might be crucial in avoiding prenatal infections linked to preterm delivery. Furthermore, it has been demonstrated that 1,25(OH)2D suppresses several inflammatory cytokines, including IL-2, IFN-γ, and tumor necrosis factor (TNF). This ketosteroid hormone also seems to have additional immunomodulatory effects, which are thought to be the mechanism via which a mother's vitamin D insufficiency is linked to a higher risk of preterm birth.[38,39] Three of eight meta-analyses, according to a prior study, did not find any connection between mothers' vitamin D deficiency and a higher risk of preterm birth. A significant correlation was discovered in five out of eight meta-analyses between a mother's low vitamin D levels and her chance of having a premature birth. This is significant due to the heterogeneity of the research (varying levels of vitamin D supplementation, gestational age at blood collection, and test methodology); the more significant heterogeneity, the more challenging it is to interpret the findings.[40]

CONCLUSION

Low intake, insufficient exposure to sunlight, insufficient absorption, or the kidney's incapacity to transform 25(OH)D into its active form can all lead to vitamin D deficiency. Premature birth, low birth weight, hypertension, gestational diabetes, and fetal bone abnormalities have all been linked to vitamin D insufficiency during pregnancy. Additionally, vitamin D affects how immune cells—particularly T lymphocytes—are modulated. It has been demonstrated that taking vitamin D supplements during pregnancy lowers the risk of preterm birth and other issues.

ETHICAL CLEARANCE

Not Applicable.

AUTHOR CONTRIBUTION

All authors contributed equally to this manuscript writing and publication.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest regarding this study publication.

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