REVIEW

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# Correlation between low level of vitamin d [25(OH)D] and high level of interleukin-2 (IL-2) in preterm birth: a systematic review

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## ABSTRACT

Preterm birth, characterized by uterine contractions and cervical changes before 37 weeks of gestation, is a leading cause of neonatal morbidity and mortality worldwide. Its multifactorial pathophysiological mechanisms include inflammatory responses. Emerging evidence suggests that vitamin D and interleukin-2 (IL-2), a pro-inflammatory cytokine, play significant roles in preterm birth by modulating immune responses. A systematic literature review was conducted using Google Scholar and PUBMED databases (2010–2023). Keywords included "vitamin D," "interleukin-2," and "preterm birth." Inclusion criteria covered observational, cohort, and case-control studies investigating the relationship between vitamin D, IL-2, and preterm labor. A total of eight studies met the eligibility criteria and were synthesized narratively. The review revealed that vitamin D deficiency is linked to increased IL-2 levels and heightened inflammatory cytokine activity, contributing to uterine smooth muscle contractions and preterm labor. Conversely, sufficient vitamin D levels suppress IL-2 transcription and reduce pro-inflammatory cytokines, potentially mitigating the risk of preterm birth. However, inconsistencies across studies were observed, attributed to population heterogeneity and varying definitions of preterm birth. Vitamin D may protect against preterm birth by modulating immune responses and reducing inflammation. Incorporating vitamin D supplementation into antenatal care, particularly for at-risk populations, could reduce preterm birth rates. Further randomized controlled trials are necessary to validate these findings and determine optimal supplementation strategies.

**Keywords:** cytokines, interleukin-2, preterm birth, vitamin D.
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## INTRODUCTION

Worldwide, there are an estimated 15 million preterm births annually, and the number is growing. Preterm birth (born before 37 complete weeks of gestation) and related complications are the leading cause of neonatal and child mortality among children under five, accounting for around one million child fatalities annually. The increasing development of science and technology currently facilitates increased survival of premature babies, but on the other hand, complications and treatment rates in the Neonatal Intensive Care Unit (NICU) are also increasing.[1]

Preterm birth is a complication of labor which is characterized by the opening of the cervix before term gestation. Uterine contractions occurring at least four times in 20 minutes or eight times in 60 minutes, along with progressive cervix alterations and thinning, are the hallmarks of this labor. Geographically, the prevalence of preterm birth in the Southeast Asia and Oceania region, including Indonesia, reaches 13.5%. Indonesia itself is listed as one of 11 countries with a prevalence of preterm birth of more than 15% and is specifically ranked ninth.[2] This WHO report was confirmed by *Laporan Riset Kesehatan Dasar* 2013 which stated that the prevalence of preterm birth in the period January 2010 to June 2013 was 36.4%.[3] Prevalence above 15% was also found at RSUP Prof. I.G.N.G Ngoerah, Denpasar in the period August 2015 to September 2015, where there were 70 preterm births out of 231 births, with a prevalence reaching 30.3%.[4]

The pathophysiological mechanism of preterm birth is multifactorial, and the latest theory classifies preterm birth as a syndrome with the name Premature Parturition Syndrome (PPS). One factor that is starting to be recognized as being associated with preterm birth is vitamin D. Vitamin D deficiency dramatically raises the chance of preterm birth, according to a meta-analysis study. Additionally, the study reported that at blood concentrations of greater than 20 ng/mL, vitamin D has a protective impact on premature birth.[5]

As a reaction to inflammatory responses, vitamin D in preterm delivery might lessen tissue oxidative stress reactions. Vitamin D serves to limit T cell proliferation by reducing the IL-2 gene transcription and inhibiting the production of pro-inflammatory Th

cytokines such as IFN-γ, IL-17, and IL-2. Therefore, vitamin D deficiency is associated with increased levels of pro-inflammatory cytokines such as IFN-γ and IL-2.[6,7] In the pathophysiology of preterm delivery, pro-inflammatory cytokines including IL-1, TNF-α, IL-6, and IL-2 are also known to raise PGE2 and PGF2-α levels and cause premature uterine contractions.[8] In addition, vitamin D also prevents excessive apoptosis and modulates infection-preventing factors. The presence of vitamin D deficiency in pregnancy can have adverse effects on perinatal outcomes and fetal development. Based on this description, this study aims to evaluate the correlation between vitamin D and the pro-inflammatory factor IL-2 in preterm birth.

## METHODS

The literature for this systematic review was sourced from Google Scholar and PUBMED databases, using the keywords vitamin D' OR '25-hydroxy vitamin D (25(OH)D)' and 'interleukin 2' OR 'IL-2' and 'preterm birth'. All clinical trial studies were included, and observational studies (case-control, cohort), case series, and case reports that examined the impact of vitamin D and interleukin-2 in preterm delivery were also taken into consideration because randomized controlled trial data was not readily available.

The inclusion criteria encompassed full-text articles written in English, published between 2010 and 2023, discussing the role of vitamin D or IL-2 in preterm birth. The exclusion criteria were applied to articles that were inaccessible in full text, not in English, or classified as review articles. After the evaluation, no studies were found that simultaneously assessed both variables (vitamin D and IL-2) concerning preterm birth; therefore, studies focusing on one variable were included in the review. Based on the search method, 262 publications in total were first found. Eight papers were chosen for in-depth examination after the inclusion and exclusion criteria were applied. A combination of case reports, clinical trials, and observational research are included in these articles. Figure 1 provides additional information on the selection procedure.

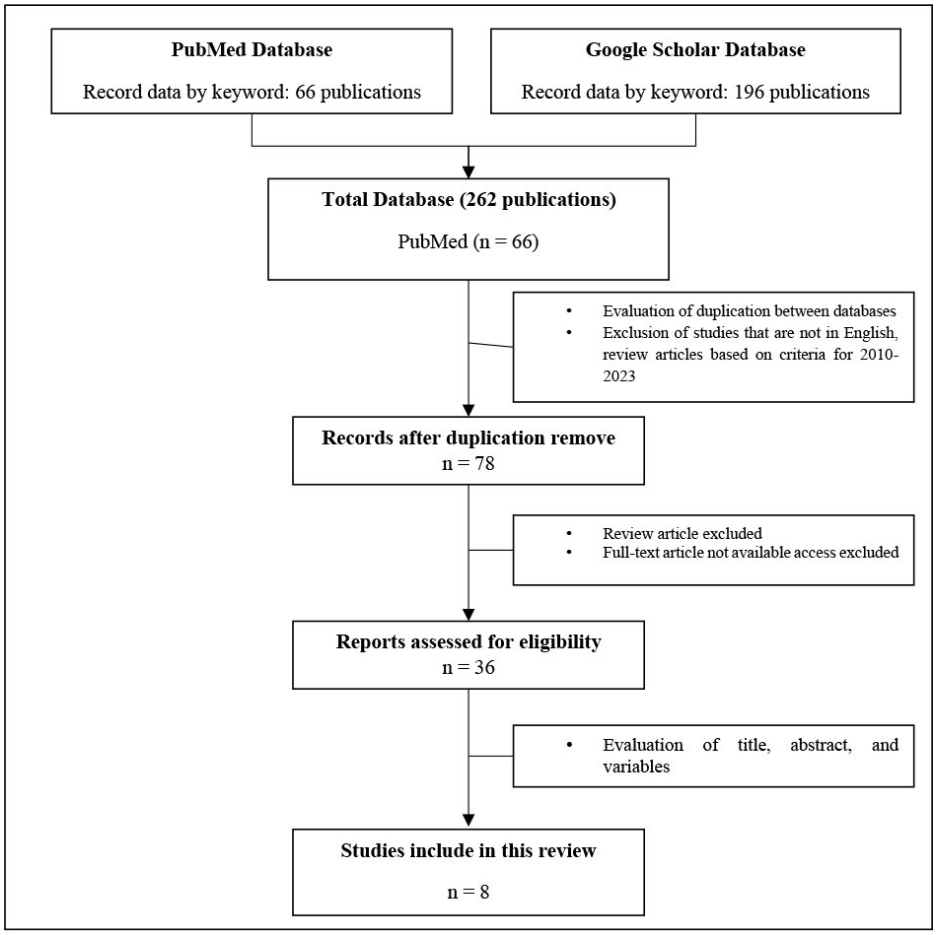


**Figure 1.** Flowchart of included studies.

## CORRELATION BETWEEN LOW LEVEL OF VITAMIN D [25(OH)D] AND HIGH LEVEL OF INTERLEUKIN-2 (IL-2) IN PRETERM BIRTH

Table 1 lists the attributes of the studies that were part of this review. This study reviewed eight full-text articles written in English that included eight cohort studies, two case-control studies, and seven case report publications. In the eight publications, there were differences in the time settings for establishing a diagnosis of preterm birth. Most research originated from European countries, namely the U.S.A. (4 studies), Bangladesh (1 study), and China (3 studies). The results of research conducted by Weinberg et al. showed that low vitamin D levels impact preterm labor. Low levels of vitamin D were related to inflammatory cytokines as biomarkers, namely sCD14, PG F2 alpha, and 5-HEPE, which increase smooth muscle contractions in reproductive organs, reduce macrophage metabolites, and increase infection risk leading to preterm labor.[9]

Wallenstein et al. evaluated three inflammatory biomarkers (sVEGFR3, sInterleukin-2, and sTNFR1) in pregnant women regarding the incidence of preterm birth. Elevated levels of interleukin-2 were associated with infectious, inflammatory, and autoimmune conditions, hypothesized to increase the risk of preterm birth.[1] Fučić et al. demonstrated that elevated IL-2 and decreased methylation site 1 of the IL-2 gene in cord blood were significant predictors of preterm birth risk. It has been demonstrated that IL-2 inhibits the development of T follicular helper cells, which is essential for immunity. Moreover, IL-2 was linked to neurological abnormalities that occurred during development and were connected to cognitive problems and autism.[10]

Serum 25(OH)D deficiency was found to be highly prevalent during the second trimester of pregnancy by Tahsin et al., and

**Table 1. Study Summary**

| Authors, Year | Type of Study, Number of sample (Period) | Region, Mother Age, Preterm birth definition (Characteristic) | Result and Reported Data |
|---|---|---|---|
| **Weinberg et al., 2019**[9] | **Observational (Case-Control)** n = 308 (2003-2013) | -U.S.A<br>- 29 years<br>- Women who give birth before the 35 weeks of GA | Vitamin D deficiency (D <20 ng/mL) has been linked to increased inflammatory PGF2α and decreased anti-inflammatory PGF2α, and it may serve as a marker for spontaneous preterm birth. Additionally, low vitamin D levels were linked to lower plasma levels of 5-HEPE as macrophages metabolite, higher levels of the pro-inflammatory PG-F2α leading to increased smooth muscle contraction, and moderately associated with higher levels of sCD14 which plays a crucial role in bacterial infection as a risk factor in preterm delivery. |
| **Wallenstein et al., 2016**[1] | **Observational (Case-Control)** n = 65 (2009-2010) | -U.S.A<br>-18–35 years<br>- Women with delivery occurring at < 32 weeks gestation | Soluble interleukin-2 receptor alpha-chain (sIL-2RA) and soluble tumor necrosis factor receptor 1 (sTNFR1) were linked to preterm birth. Obese women were associated with a higher risk of preterm delivery due to lower serum levels of sVEGFR3 and higher serum levels of sTNFR1 and sIL-2RA. |
| **Fučić et al., 2023**[10] | **Observational (Cross-sectional)** n = 50 preterm newborns (NA) | -U.S.A<br>- 32.1 years (33.0±6.29)<br>- Women who give birth before 37 full weeks of pregnancy (GA) | The mother's rural residence (perhaps due to pesticide exposure), IL-2 levels, and hypomethylation of IL-2 gene site 1 were predictive indicators for preterm delivery. When IL-2 levels are high, the risk of preterm delivery increases by 0.48 times. |
| **Tahsin et al., 2023**[11] | **Observational (Case-Control)** n = 930 (2014-2018) | -Bangladesh<br>-<30 years (n=816); ≥30 years (n=114)<br>- Women with delivery occurring at < 37 weeks of gestation (GA) | Serum 25(OH)D ranged from 30.18 to 48.52 (nmol/L), with a median of 38.0 nmol/L. Once variables were taken into account, there was a significant correlation between VDD and PTB. Furthermore, women who were shorter, primiparous, passive smokers, or took iron supplements during pregnancy were more likely to have PTB. Vitamin D deficiency (VDD) increases the risk of preterm birth in pregnant women. |
| **Woo J et al., 2023**[12] | **Observational (Case-Control)** n = 175 (2017-2020) | -U.S.A<br>-18-35 years<br>- Women who give birth before 37 weeks of pregnancy | Following correction for depressed symptoms and hypertensive disorders of pregnancy, vitamin D deficiency raised the risks of preterm birth (PTB) by 3.34 times. As a prophylactic step against PTB, vitamin D testing and supplementation may be beneficial for pregnant Black women. According to the findings, the odds of a PTB were 2.80 times higher for women with vitamin D insufficiency than for those with adequate levels. |
| **Chen et al., 2023**[13] | **Observational (Prospective cohort)** n = 3923 (2011-2022) | -China<br>-29.31 ± 3.88 years<br>- Women with delivery occurring at < 37 weeks of gestation | The risk of PTB was 2.69 times greater for vaginal births in pregnant women with vitamin D deficiency (VDD) compared to those without VDD. An analysis of the relationship between PTB in pregnant women and 25(OH)D concentrations across the three trimesters revealed no association between vitamin D levels and the risk of disease. Restricted to pregnant women who gave birth vaginally, however, those with VDD in the third trimester of pregnancy were at higher risk for PTB. |
| **Alifu et al., 2023**[14] | **Observational (Cohort and case-control)** n = 6381 (2011-2022) | -China<br>-29.31 ± 4.01 years<br>- Women who give birth before 37 weeks of pregnancy | There were 6381 pregnant women in the cohort trial. There was a lower risk of TPROM and a higher risk of PTB without PROM when there was a VD deficiency in Trimester 3 (PTB without prelabor rupture of membranes (PROM), Term PROM (TPROM), and a smaller change of 25(OH)D between T1 and T3 (PTB without PROM. |
| **Zhang et al., 2019**[15] | **Observational (retrospective cohort)** n = 23.396 **(2015-2016)** | -China<br>-25-35 years<br>- Preterm neonates with age at delivery < 34 weeks | In the early stages of pregnancy, significant vitamin D inadequacy was associated with placental inflammation. The risk of placental inflammation was considerably higher for women with very low vitamin D levels than for those with the highest quartile of vitamin D levels. Placental inflammation is more likely to occur in high-risk pregnancies when there is a significant vitamin D deficiency in the first trimester. |

**Table 2. The role of cytokines in preterm birth**

| Cytokines | Mechanism | Result effect |
|---|---|---|
| TNF-α, IL-8, IL-1, and IL-6 | Collagen degradation | Cervical thinning |
| TNF-α and IL-1 | Matrix metalloproteinase induction | Membrane rupture |
| TNF-α, IL-2, IL-1, and IL-6 | Raises PGF2-α and PGE2 levels. | Uterine contractions |

women who were vitamin D deficient had a 50% increased risk of preterm birth (aOR 1.53, 95% CI: 1.10–2.12) in comparison to women who were not.[11] According to Woo et al., pregnant women who are vitamin D deficient are more likely to experience preterm birth (PTB), low birth weight, and preeclampsia, among other negative pregnancy outcomes. Preterm birth is also influenced by depression symptoms brought on by a vitamin D deficit.[12]

According to Chen et al., there are differences in the relationship between vitamin D levels and PTB between trimesters. In women giving birth vaginally, the only vitamin D shortage that was substantially linked to PTB was in the third trimester. Inconsistent results were caused by variations in the timing of vitamin D level measurements between trials.[13] Alifu et al. found that the term, PTB without PROM, TPROM, and PPROM groups differed significantly ($p < 0.05$) in their 25(OH)D levels, gestational age at vitamin D detection, and vitamin D status in Trimester 3. There were no notable variations between Trimesters 1 and 2.[14]

Zhang et al. found that the group with placental inflammation had a greater frequency of extremely early preterm birth (delivery before 31 weeks) than the group without it (1.3% vs. 3.1%, $p < 0.01$). The placental inflammation-positive group had a decreased preterm birth rate at 34–36 weeks (16.6% vs. 6.6%, $p < 0.01$). There is conflicting research on vitamin D and PTB.[15] According to McDonnell et al., PTB risk was 62% lower at vitamin D values >40 ng/mL.[16] Similarly, a meta-analysis of 10,098 women found that those with vitamin D levels below 20 ng/mL had a greater risk of PTB (OR 1.29, 95% CI: 1.16–1.45).[17] Some research, meanwhile, including a retrospective study conducted in southern China and Wang et al., showed no correlation.[18,19]

Randomized controlled trials (RCTs) yielded inconclusive results. Rostami et al. showed a 40% reduction in PTB rates with vitamin D supplementation[20], while trials by Hossain et al. and Mojibian et al. found no significant differences.[21,22] These discrepancies likely result from variations in study designs, population characteristics, vitamin D measurement timing, and sample sizes. Future large-scale RCTs in vitamin D-deficient populations are necessary to confirm the role of supplementation in reducing PTB rates.

## Pathogenesis of Preterm Birth

There is still much to learn about the etiopathogenesis of preterm birth, including whether it is caused by pathogenic causes or an idiopathic stimulation of normal labor processes. A hypothesis suggests that preterm and term labor share similarities in the preparation for normal physiological labor, particularly at gestational ages above 32 weeks. Below 32 weeks, however, it is believed that a greater pathological stimulus is required to initiate the labor process.[23]

The fundamental difference between term and preterm birth lies in the activation of the labor pathways. In terms of labor, there is simultaneous physiological activation of all pathway components. In contrast, preterm birth involves the activation of one or more pathway components triggered by pathological processes. Preterm birth is caused by several processes, such as decidual hemorrhage, infection and inflammation, uterine stretching, and stimulation of the maternal-fetal hypothalamus-pituitary-adrenal axis.[23]

The role of infections in the pathogenesis of labor is significant but not yet fully elucidated. It is estimated that 50% of preterm birth cases can be attributed to infections. The process may begin with the activation of phospholipase A2, releasing arachidonic acid from the fetal amniotic membrane, thereby increasing prostaglandin synthesis. Endotoxins in the amniotic fluid stimulate decidual cells to produce cytokines and prostaglandins, which can initiate labor. Various cytokines, including TNF, IL-5, and IL-1, are secretory products associated with preterm birth. Platelet Activating Factor (PAF) in amniotic fluid also synergistically activates the cytokine network.[24]

Microbial invasion of the amniotic cavity (MIAC) can lead to an inflammatory response within the amniotic cavity, presenting as intraamniotic inflammation, inflammation of the chorioamnion membrane, and chorioamnionitis. These conditions can be identified histologically and may or may not be accompanied by clinical signs of infection. The normal flora and microbial presence in the vagina or cervix changes during Stage I of an intrauterine infection; microorganisms migrate between the amnion and chorion during Stage II; the intraamniotic cavity invades and enters during Stage III; and fetal tissues, most often the skin and respiratory tract, invade during Stage IV.[25]

Studies indicate that 25% to 40% of preterm births are associated with infectious conditions. MIAC occurs in approximately 12.8% of women with preterm birth and intact membranes, 32% of women with preterm birth and ruptured membranes, and 51% of women with cervical incompetence. Compared to women without MIAC, those with MIAC are more likely to experience chorioamnionitis, spontaneous membrane rupture, and premature birth. Although transplacental infection can potentially cause MIAC, the most frequent source of microbial invasion into the amniotic cavity is the urogenital tract.[25]

Urinary tract and birth canal infections are closely associated with preterm birth. These infections, which are frequently bacterial and originate in the lower urogenital tract, can cause amnion infections, premature membrane rupture, and preterm birth, especially when the pH of the vagina surpasses 5.0.[8] Lactobacillus species, which make up the majority of the typical genital flora, create lactic acid to keep the vaginal pH below 4.5 and

prevent the formation of harmful bacteria. Lactobacillus species multiply tenfold during pregnancy, anaerobic organisms decline, and aerobic organisms stay mostly unchanged, protecting the fetus after birth. Subclinical intrauterine infections are a major contributing factor and are closely linked to maternal and newborn morbidity.[25]

## Diagnosis

Establishing a preterm birth diagnosis involves anamnesis, physical examination, and supporting investigations. Anamnesis should thoroughly explore gestational age, current medical history, obstetric history, surgical history, social history, and family history. Additionally, patient symptoms that may suggest a threat of preterm birth include:[24]

- Contractions that repeat two to three times in ten minutes or at least once every seven to eight minutes.
- Lower back pain, also known as low back ache.
- Vaginal spotting, bleeding, or mucous combined with blood.A sensation of pressure in the cervical area.
- Rupture of amniotic membranes.

A physical examination includes evaluating vital signs, general status, Leopold I-IV maneuvers, uterine contractions (HIS), fetal heart rate (DJJ), inspection, and vaginal touch (VT). A litmus paper test may be added if premature rupture of membranes is suspected. Cervical examination via VT assesses dilation, effacement, fetal presentation, and membrane integrity as follows: cervical dilation of at least 2 cm, effacement of 50–80%, low fetal presentation reaching the ischial spine, and ruptured amniotic membranes. Indicators that may predict preterm birth include laboratory and biochemical markers. Laboratory findings suggesting maternal or intrauterine infection include:

- Leukocytes in amniotic fluid (>20/mL).
- Levels of C-reactive protein (CRP) more than 0.7 mg/mL.
- Leukocytes in maternal serum (>13,000/mL).

Biochemical indicators include:[24]

- Fetal fibronectin: Increased levels in the vagina, cervix, or amniotic fluid indicate chorion-decidua disturbance. At 24 weeks gestation, levels ≥50 ng/mL indicate a risk of preterm delivery.
- Corticotropin-releasing hormone (CRH): An early increase is a strong preterm birth predictor.
- Inflammatory cytokines: Preterm labor is linked to elevated levels of TNF-α, IL-10, IL-6, and IL-8.
- Placental isoferitin: Normally at 10 U/mL in non-pregnant states, isoferitin peaks in the final trimester at 54.8 ± 53 U/mL. A decrease increases preterm birth risk.
- Ferritin: Low levels indicate iron deficiency, linked to inflammatory conditions and preterm birth risk.

## Correlation Between IL-2 and Preterm Birth

Research by Margarita et al. supports the hypothesis that subclinical infections contribute to premature labor. Recent findings indicate a clear association between preterm birth and intrauterine or systemic infections. Idiopathic preterm labor has been strongly associated with subclinical intrauterine infections, as evidenced by positive amniotic fluid cultures. The function of immunomodulatory cytokines is still unclear, even though interleukins 1, 6, and 8 have been thoroughly investigated. This is the first study to concentrate exclusively on IL-2 while concurrently addressing five interleukins.[6]

Interleukins that promote and inhibit inflammation coexist throughout pregnancy. All samples had detectable levels of the IL-2 receptor (IL-2R), which reflects the unique immunological circumstances of the prenatal environment. Idiopathic uterine activity is a result of premature IL-2R activation. A changed inflammatory or immunological status that is not apparent in the clinical history should be taken into consideration when other interleukins are present in controls. Because of its ability to bind to receptors and maintain a prostaglandin equilibrium that is still poorly understood, IL-2 levels in amniotic fluid were found to be extremely low.[6]

Preterm labor was associated with elevated IL-2R concentrations. The immune system and IL-2R seem to be involved in idiopathic preterm labor as well as intrauterine infectious diseases. An elevation in IL-2R, a marker of activated immune cells in peripheral blood, is a good indicator of premature labor in both clinical and subclinical infections. It has demonstrated a 75% positive predictive value for delivery within 48 hours and a 73% positive predictive value for delivery before 34 weeks of gestation.[6]

Given that the majority of human nucleated cells are capable of producing interleukins, our results imply that the interleukins tested might not have come from the decidua. However, because there is no placental transfer, the literature concurs that maternal interleukins do not combine with fetal-produced interleukins. Depending on their concentrations, interleukins can either have a favorable or harmful impact on pregnancy, according to current and previous research. Preterm labor patients with no clinical chorioamnionitis had maternal serum IL-2R levels that were noticeably higher. Therefore, without a clinical infection, maternal blood IL, especially IL-2R, can be used as a diagnostic for the pathophysiology of premature labor.[6]

## Correlation Between Vitamin D and Preterm Birth

Vitamin D, a fat-soluble vitamin, is essential. Within the vitamin D family, the two primary members are cholecalciferol (Vitamin $D_3$) and ergocalciferol (Vitamin $D_2$). Until chylomicrons or vitamin D-binding proteins activate them in the liver, 25-hydroxylase catalyzes catalytic processes that change them into $1\alpha,24,25(OH)D_2$ and $[24,25(OH)D_2]$ in the kidney, neither of them has biological activity. $[25(OH)D_2]$ is frequently used as an indicator to assess vitamin D levels since it is the most important metabolite. Worldwide, prevalence rates of vitamin D insufficiency range from 26% to 78.5%.[26]

Pregnancy-induced diabetes, pre-rupture of fetal membranes, hypertension, and a higher risk of bacterial vaginitis with low serum $[25(OH)D_3]$ levels are all potential reasons for vitamin D deficiency-induced premature labor.[27] There were no statistically significant variations in the levels of $[25(OH)D_2]$, $[25(OH)D]$, and $[25(OH)D_3]$ in all stages of pregnancy,

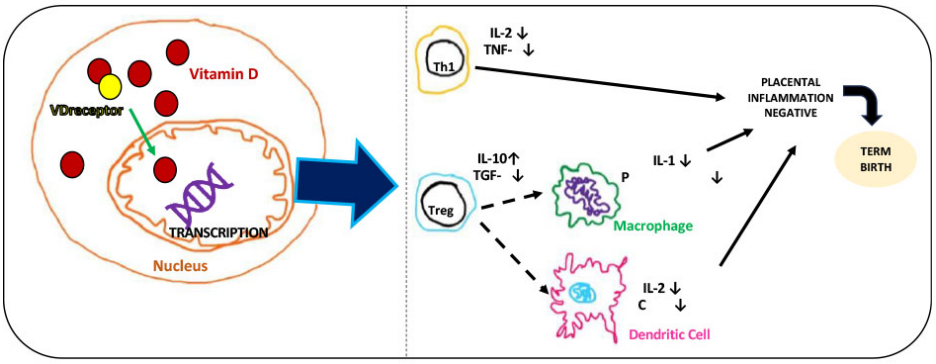


**Figure 2.** Potential mechanism of correlation of vitamin D, IL-2, and term birth (arrow: direct action; dotted arrow: indirect action).

according to Yang et al. Furthermore, pregnant women with [25(OH)D] levels below 20 ng/mL did not exhibit a significantly higher risk of preterm delivery than those with higher levels. Lower than 10 ng/mL, 10–20 ng/mL, or 20–30 ng/mL levels did not substantially raise the risk of early labor.[28]

[25(OH)D] levels were considerably lower in the preterm delivery group than in the full-term group, according to a study done on Japanese mothers.[29] Similarly, pregnant women with [25(OH)D] levels >75 nmol/L had a decreased incidence of preterm labor, according to a US-twin-research.[30] Preterm labor risk can be considerably decreased by taking vitamin D supplements during pregnancy. However, according to prospective Chinese research, women who had serum [25(OH)D] >30 ng/mL between weeks 16 and 20 had a 3.8% increased risk of preterm delivery.[31] This observational data is consistent with a meta-analysis that found no link between vitamin D replenishment and a lower incidence of premature labor.[32] [25(OH)D] levels <20 ng/mL did not significantly alter the risk of preterm birth in Spanish women.[33] Low birth weight and hypertension are two negative pregnancy outcomes linked to vitamin D insufficiency. It is unknown, therefore, whether it plays a direct or indirect role in controlling hormonal variables during pregnancy. Additionally, there is seasonal variation in vitamin D levels, with higher synthesis in the summer due to increased solar exposure. This makes interstudy comparisons difficult and can lead to conflicting results.

Immune modulation is significantly influenced by vitamin D. Immune cells can control their local calcitriol concentrations because they express 1-alpha-hydroxylase. Reduced pro-inflammatory cytokines (IL-2, IL-6, and IL-1) and elevated anti-inflammatory cytokines (IL-10 and IL-4) are linked to adequate serum 25(OH) D levels. On the other hand, a pro-inflammatory cytokine profile and chronic inflammation are associated with vitamin D insufficiency.[31]

### Correlation Between IL-2, Vitamin D, and Preterm Birth

Premature birth rates in the US increased a little from 9.85% in 2016 to 9.93%. Preterm births are significantly more common among African American women, a group that is more likely to suffer from vitamin D insufficiency.[34] The primary mechanism linking vitamin D to the prevention of preterm birth is its role in the innate immune response. Vitamin D receptors (VDR) are expressed by immune cells that recognize microbial substances, such as dendritic cells and macrophages. When activated, these immune cells can produce antimicrobial peptides, which may be crucial in preventing prenatal infections associated with premature birth. Additionally, $1,25(OH)_2D$ suppresses inflammatory cytokines such as interleukin (IL)-2, interferon, and tumor necrosis factor (TNF). The varied immunomodulatory effects of this secosteroid hormone may account for the association between maternal vitamin D insufficiency and an increased risk of preterm delivery.[35]

Woo et al. (2019) conducted a comprehensive assessment of eight meta-analyses on the connection between preterm birth and maternal vitamin D insufficiency. Five of the meta-analyses indicated a substantial correlation between maternal vitamin D deficiency and an increased risk of preterm birth, whereas three found no association at all. The significance of vitamin D in lowering the risk of preterm delivery was highlighted by the meta-analysis with the greatest sample size, which showed a clear positive connection. The interpretation of data is complicated by the heterogeneity across research, which includes differences in test procedures, gestational age at blood samples, and vitamin D supplementation dosages.[36]

### Complication

Preterm labor can lead to a range of complications affecting the mother, fetus, and neonatal development. In Western countries, prematurity accounts for up to 80% of neonatal deaths, and approximately 10% of surviving infants experience long-term health problems. Maternal complications include an increased risk of morbidity and mortality, particularly in the years following delivery; however, further research is required to clarify these risks.[37]

The immaturity of organ systems causes fetal difficulties, including cerebral palsy, movement deficiencies, vision and hearing issues, and cognitive disabilities. Preterm birth has also been associated with behavioral problems, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, depression, and anxiety.[37] During the neonatal period, complications may include growth and developmental delays, bronchopulmonary dysplasia, and retinopathy of prematurity, among others. These risks emphasize the importance of delivering preterm babies in facilities equipped to provide specialized care, thereby reducing the likelihood of adverse outcomes.[37]

## CONCLUSION

Although a high level of IL-2 and vitamin D deficiency is linked to the pathophysiology of preterm birth outcomes and vitamin D and its analogs have shown immunomodulatory effects, the effects of vitamin D supplementation in the prevention and treatment of pregnancy disorders remain unclear.

Vitamin D supplementation may help manage the immune system, lower inflammation, and protect the health of the mother and the fetus, according to a small and uncontrolled body of research on humans.

## DISCLOSURE

### Ethical Statement

The authors declare that all the research and manuscript preparation was conducted with adherence to ethical standards and professional guidelines. The study does not involve direct intervention on human subjects, and all systematic review processes complied with PRISMA recommendations.


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No specific funding was received for conducting this study. The authors carried out this work as part of their academic and professional commitments.


### Conflict of Interest

Regarding the research, writing, and publication of this work, the authors declare that they have no conflicts of interest.

### Authors Contribution

All authors contributed significantly to the development of this manuscript. I Nyoman Hariyasa Sanjaya and Ryan Saktika Mulyana were responsible for conceptualizing the study and designing the research methodology. I Gusti Ngurah Agung Trisnu Kamajaya and Ryan Saktika Mulyana conducted the literature search, data acquisition, and statistical analyses. I Nyoman Hariyasa Sanjaya and I Gusti Ngurah Agung Trisnu Kamajaya contributed to the definition of intellectual content and performed clinical and experimental studies. Manuscript preparation was led by Ryan Saktika Mulyana, with editing and review conducted by I Nyoman Hariyasa Sanjaya and I Gusti Ngurah Agung Trisnu Kamajaya. Each author agreed to take responsibility for the accuracy and integrity of the work after critically evaluating and approving the final article.

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