



Literature review: Vitamin D Levels and Perinatal Depression Association

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ABSTRACT

Background: Vitamin D levels have been linked to psychological symptoms such as anxiety, depression, and impaired cognitive performance. It is found that lower vitamin D levels in early pregnancy are associated with depressive symptoms in perinatal. This study examines the association between vitamin D levels and perinatal depression. This article based on literature source from Pubmed/MEDLINE and Science Direct with keywords: vitamin D levels including 25(OH)D levels or vitamin D deficiency, prenatal, antenatal, and postpartum depression. The discussion of this study will assist readers and health professionals analyze how vitamin D levels in the body affect the incidence of antepartum depression.

Results: these are five filtered literature, the journal discusses the relationship between vitamin D levels and antepartum depression. This literature review shows that pregnant women with less than 20 ng/mL vitamin D levels are 3.3 times more at risk than pregnant women with more than 20 ng/mL. Vitamin D plays a role in the process of increasing serotonin synthesis and increasing anti-inflammatory so that it can suppress the increase in pro-inflammatory cytokines that play a role in the incidence of depression.

Conclusion: There is a correlation between vitamin D levels and the occurrence of depression during the perinatal period. It can be suggested that pregnant women check their vitamin D levels regularly.

Introduction

Depression, or major depressive disorder (MDD), is currently one of the most common illnesses in psychiatry, affecting around 121 million people worldwide (WHO, 2018). Depression comes in many forms, such as loss of interest, constant sadness, worthlessness, hopelessness, and, worst of all, a feeling that there is no value in life anymore (NIMH, 2018).

Mood disturbances often occur during pregnancy and the postpartum period, which can lead to depression. Researchers have focused a great deal of attention on this issue in recent decades and found that childbirth-related mental disorders can cause significant difficulties for the mother, fetus, baby, and family. This situation can potentially negatively impact the infant's growth and lead to long-lasting challenges in their behavior, cognition, social

interactions, and even emotional well-being (Vaziri et al., 2016).

A study conducted by Wijaya (2016) on pregnant women with high risk in Bandung, West Java, showed a higher prevalence of depressive symptoms as much as 34,7% (Wijaya, 2016). In 2018, Riset Kesehatan Dasar or Riskesdas reported that the Special Region of Yogyakarta (DIY) had the second highest prevalence of severe mental disorders in Indonesia (Perwitasari & Wulandari, 2022). Other study that was made from 196 pregnant women as its samples in East Jakarta and Central Jakarta also showed that 59.7% of them were found to be showing signs of depression. Antenatal depression was shown to be significantly more likely to occur in pregnant women with a history of depression (95% CI, $P_v = 0.001$) (Misrawati & Afiyanti, 2020).

It is common for women to experience depression throughout pregnancy and up to a year after giving birth in low- and middle-income countries, and this situation urgently calls for action to enhance maternal and newborn health outcomes (Roddy Mitchell et al., 2023).

The answer may rely on vitamin D, where previous studies have shown that vitamin D levels influence depression in the body. In vitro, vitamin D functions in maintaining extracellular serotonin concentrations in the brain, which acts as a

neurotransmitter center that is responsible for cases of depression (Sabir et al., 2018) ((Dregan et al., 2019) (Raison & Miller, 2011). The vitamin D receptor (VDR) mediates the biological activity of vitamin D. The binding complex between VDR and VDRE on the promoter of a gene will initiate a transcription process associated with the production of brain serotonin, namely TPH2. When the enzyme TPH2 is activated, it promotes tryptophan metabolism, leading to the synthesis of serotonin. However, an imbalance in vitamin D levels can disrupt serotonin levels and their functioning in the brain. This disruption can subsequently affect behavior and the executive functions of the brain (Patrick and Ames, 2015; Pratiwi and Sukmawati, 2020). The primary components of executive function encompass various cognitive abilities. These include inhibition, which involves self-control and the ability to resist impulses; interference control, which relates to selective attention and cognitive inhibition; working memory, which involves holding and manipulating information in mind; and cognitive flexibility, which encompasses creative thinking, adopting new perspectives, and adapting effectively to changing circumstances. Together, these components form the core of executive function (Diamond, 2013).

Low vitamin D levels in early pregnancy have a higher risk of experiencing perinatal depression. Vitamin D can be active in the body with the help of sunlight in the form of absorption of UVB by 7-dehydrocholesterol in the skin and then converted into vitamin D₃ (the most natural form of vitamin D), which can be isomerized into Vitamin D₃, which will later form biological products that play a role in in the brain (Vaziri et al., 2016; Wacker & Holick, 2013). There are few literature studies on perinatal depression related to vitamin D deficiency. Therefore, further analysis is needed to determine whether there is a relationship between vitamin D levels and perinatal depression.

Method

The data collection and analysis in this systematic review adhered to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. These guidelines were employed as a standardized and transparent framework to collect and report information consistently throughout the entire review process. Studies were obtained from two databases: Pubmed/MEDLINE and Science Direct, with keywords: vitamin D levels including 25(OH)D levels or vitamin D deficiency, prenatal, antenatal, and postpartum depression, published between 2000 and 2022. This review included

randomized controlled trials, case series, controls case, cross-sectional, crossover, cohort, prospective, and retrospective studies. After obtaining eligible studies, the articles were evaluated using the Joanna Briggs Institute scoring tool to assess the study's methodology and determine how well it was subject to bias, conduct, and analysis.

Results

The results of the search in PUBMED are a total number of 83 studies, with the keyword being “Vitamin D Level” and “Perinatal”, or “Postnatal” or “Antenatal” or “Prenatal” or “Postpartum” and “Depression”. The year of the study are chosen from 2000-2023 which leave 78 studies. There are 10 studies out of 78 remaining after selecting the studies with only clinical trials and RCTs methods that are available for free access. Then we delete the duplicates with Mendeley Reference Manager resulting 3 studies left.

The results of the search in ScienceDirect are a total number of 20,763 studies, with the keyword being “Vitamin D Level” and “Perinatal”, or “Postnatal” or “Antenatal” or “Prenatal” or “Postpartum” and “Depression”. The year of the study are chosen from 2000-2023 which leave 14,826 studies. There are 852 studies remaining after selecting the design of the studies with only research and case report that have free

access. Due to plenty unsuitable titles, the studies are filtered down resulting in final result of 3 studies.

The total of 6 studies from both search engines are then assessed for its quality through Joanna Briggs' Institute Critical Appraisal. Based on the results of the review, the following results were obtained:

Table 1. Data from a review of 6 articles on the relationship between vitamin D levels and antepartum, antenatal, and postpartum depression

Author (year)	Title	Study design type	Assessment	Patient's vitamin d level	Outcome	Confounding factors (bias risk)	Conclusion
Williams J., Romero V., Clinton C. Et al. (2016)	Vitamin D levels and perinatal depressive symptoms in women at risk: a secondary analysis of the mothers, omega-3, and mental health study	Secondary analysis of a randomized trial	Beck Depression Inventory (BDI) and MINI International Neuropsychiatric Interview	Selected a vitamin D level ≥ 20 ng/ml (N=98) for our reference group and < 20 ng/ml (N=19) for our "low vitamin D" group for sub-analysis.	This study provides evidence indicating a significant association between low vitamin D levels during early pregnancy (between 12-20 weeks) and elevated depression symptom scores in early and late pregnancy among women at risk for depression.	It is still possible that the intervention, or even the participation in a clinical trial itself, led to inappropriate conclusions	In women at risk for depression, early pregnancy low vitamin D levels are associated with higher depressive symptom scores in early and late pregnancy.
Abedi P., Bovayri M., Fakhri A., et al (2018)	The Relationship Between Vitamin D and Postpartum Depression in Reproductive-Aged Iranian Women	Case-control study	Beck Depression Scale	25(OH)D < 10 ng/ml and $10-20$ ng/ml were considered as severe deficiency and moderate insufficiency respectively, $20-30$ ng/ml as mild insufficiency and > 30 ng/ml was considered normal	Women of experiencing postpartum depression was 3.30 times higher among women with vitamin D levels below 20 ng/ml compared to those with vitamin D levels above 20 ng/ml.	Taking supplements and sunlight exposure may be affected by recall bias. Data collection and vitamin D measurements have been done in the two seasons (winter and spring) which may	Women with postpartum depression had a lower mean of 25-OH-D. Also, the number of women with moderate insufficiency and severe deficiency was significantly higher in the

						affect the level of vitamin D	postpartum depression group compared to normal women
Accort E., Schetter C., Peters R., et al. (2016)	Lower Prenatal Vitamin D Status and Postpartum Depressive Symptomatology in African American Women: Preliminary Evidence for Moderation by Inflammatory Cytokines	Cohort study	The Edinburgh Postnatal Depression Scale (EPDS)	The sample's average level of 25(OH)D (a form of vitamin D) from January to March was 13.2 ng/ml. This value falls below the standard cutoff criteria for vitamin D inadequacy, indicating that the participants had insufficient vitamin D levels during that period.	Among women with higher levels of inflammatory markers, lower prenatal log 25(OH)D was associated with significantly higher PPD symptoms (p <0.05).	Maternal age, marital status, prenatal depressive symptoms (CES-D), and season of vitamin D measurement.	These preliminary results are intriguing because if replicable, simple translational opportunities, such as increasing vitamin D status in pregnant women with elevated pro-inflammatory cytokines, may reduce PPD symptoms
Accort E., Arora C., Miroha J., et al. (2021)	Low Prenatal Vitamin D Metabolite Ratio and Subsequent Postpartum Depression Risk	Analytical Cross-Sectional Studies	BDI (Beck's Depression Inventory) and 21-item CES-D (Center for Epidemiologic Studies Depression) Scale		A total of 89 women had complete depression, biomarker and demographic data and 34% were at risk for PPD (CES-D \geq 16). Stepwise multiple logistic regression models for PPD risk were carried out with eight predictors.	BMI, maternal age, smoking, and BDI (risk for prenatal depression)	Vitamin D insufficiency as measured by the VMR is associated with higher risk for PPD.

Ogiji J., Rich W. (2022)	An exploratory study of vitamin D levels during pregnancy and its association with postpartum depression, Australia	Retrospective observational study, used 161 sample	Blood samples were collected from women during their first trimester of pregnancy and were analyzed at the local pathology lab for 25(OH)-vitamin D serum concentration and Edinburgh Postnatal Depression Scale (EPDS) was used to screen for PND	Vitamin D level 25-50 nmol/L (N:22), 51-74 nmol/L (N: 39), 75-99 nmol/L (N: 29) and ≥ 100 nmol/L (N:2). low vitamin d levels if ≤ 50 nmol/L	Women with PPD had significantly lower levels of vitamin-D antenatally ($p < 0.01$) compared to women without PPD. PPD was significantly negatively correlated with antenatal vitamin D levels ($p < 0.01$)	Previous psychiatric history, smoking and unplanned pregnancies were also positively correlated with PPD which suggests that overall healthcare and nutritional status are likely to have an impact on developing PPD and may therefore confound results.	Low vitamin-D levels during pregnancy are associated with developing PPD.
Wang Y., et al. (2023)	Perinatal depression and serum vitamin D status: A cross-sectional study in urban China	cross-sectional study, used 1773 sample	Edinburgh Postnatal Depression Scale (EPDS) was used to screen for PND and Serum 25-hydroxyvitamin D concentrations were assessed with high-performance liquid chromatography	Vitamin D level < 20 ng/mL (N:349), 20-30 ng/mL (N:228) and > 30 ng/mL (N:289), low vitamin d levels if < 30 ng/ml	There is a relationship between vitamin D deficiency with a higher prevalence of PPD (OR = 1.71, 95%CI: 1.01–2.88, $p = 0.044$).	confounding factors that have not been considered, such as a family history of depression and nutrition.	In conclusion, this study suggested a significant association between vitamin D status and PPD

From the studies obtained, all patients first need to be assessed with BDI (Beck depression inventory) and EPDS (Edinburgh post-natal depression scale) assessment to determine symptoms of perinatal depression. The assessment is done during gestational weeks. After assessment, blood samples were then taken to measure each of the patient's vitamin D levels.

In the assessment of perinatal depression, BDI and EPDS were used in all of the studies obtained. The EPDS is the most used instrument for detecting depression associated with childbirth. This instrument contains ten items that provide ranks from 0 to 3 that reflect the patient's experience over the past week. This instrument has received considerable validation for usage both throughout pregnancy and after delivery.

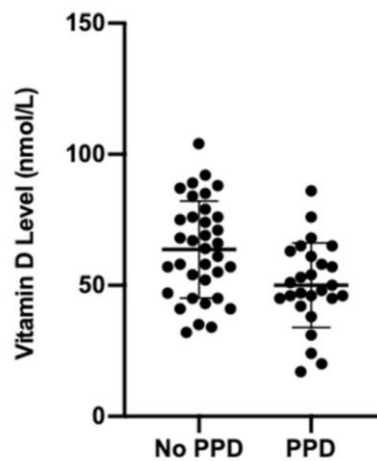


Figure 1. Scatter plot comparing vitamin D levels in women with postpartum depression (PPD) vs the control group (No PPD). (Ogiji J., & Rich W., 2022)

An acceptable cut-point for identifying women at risk for severe depression in clinical settings is an EPDS score of ≥ 13 . The Research Diagnostic interview detected a major or minor depression in 86% of postpartum women with an EPDS score ≥ 13 (specificity=78%, positive predictive=73%). According to a screening of a community sample of women

4–6 weeks postpartum (n=400), 6% of screened patients had PPD verified by the SCID. The optimal time to screen for EPDS is 4–6 weeks after delivery. (Sit, D. K., & Wisner, K. L., 2009).

A study identified more instruments with good psychometric qualities to measure perinatal symptoms in a thorough study. These instruments include the

General Health Questionnaire (GHQ), the Beck Depression Inventory (BDI I or II), and the Inventory of Depressive Symptomatology. These tests all had enough evidence to show their reliability among women who spoke various languages. High scores on either instrument may indicate a risk for anxiety disorders. The EPDS and BDI have a strong correlation with anxiety measures. (Sit, D. K., & Wisner, K. L., 2009).

From the result, all studies show associations between vitamin D and perinatal depression, especially in circumstances where there is a presentation of perinatal depression in individuals with lower vitamin D levels. A study done by (Accort E. et al., 2016) found that low prenatal 25(OH)D and high prenatal inflammation might predict future postpartum depressive symptomatology in African-American women and potentially in other subgroups of the population as well. It is also stated that pro- and anti-inflammatory cytokines (e.g., IL-6 and IL-10, respectively) would moderate the association between prenatal 25(OH)D and PPD symptomatology. Lower prenatal vitamin D levels are also associated with higher PPD symptoms.

In another study by (Accort E. et al., 2021), Vitamin D insufficiency measured by VMR is proven to be associated with a higher risk of PPD. It also states that women

with darker skin generally have a lower total of 25(OH)D suggesting that the total serum 25(OH)D may be misleading by falsifying vitamin D status in various ethnic groups without evidence of vitamin D insufficiency.

A study from (Abedi P. et al. 1.) also showed evidence that women with Vitamin D <20ng/ml have a higher risk of having postpartum depression, as much as 3.30 times that of those with Vitamin D >20ng/ml. It suggests a significant relationship between age, economic situation, and the desire for pregnancy connected with postpartum depression. Their results showed that undesired pregnancy, age, and poor economic situations could be included as risk factors for postpartum depression.

According to (Ogiji J., & Rich W., 2022), it is stated that lower antenatal vitamin D levels were greatly associated with postpartum depression in women with PPD (Postpartum Depression). This study also demonstrated favorable correlations between PPD and prior psychiatric history, smoking, and unplanned deliveries. This shows that overall health care and nutritional status are likely to have an impact on the development of PPD. The research suggests the most effective way to prevent PPD during pregnancy is to make sure vitamin D levels are at adequate levels.

A study from (Wang Y., et al., 2023) reported results that breastfeeding woman with vitamin D insufficiency had a greater risk of PDD compared to those who had sufficient vitamin D. Pregnant women, however, did not show a similar correlation between vitamin D levels and antenatal depression. Additionally, it was discovered that there was no significant correlation between serum 25(OH)D and PSQI (Pittsburgh Sleep Quality Index) scores, although there was a significant correlation between serum 25(OH)D and PPD. Therefore, sleep was not an influential variable in the 25(OH)D and PPD mediation study.

It is stated in a secondary analysis of a randomized trial study done by (Williams J., Romero V., Clinton C., et al., 2016) that depressive symptoms were prevented by prenatal omega-3 fatty acid supplementation. Despite the fact that vitamin D levels had no relation to diagnoses of major depressive disorder or generalized anxiety disorder, low vitamin D levels in early pregnancy are associated with greater depressive symptom scores in both the early and late stages of pregnancy in women at risk for depression.

Discussion

Vitamin D has been demonstrated to promote the Th2 or humoral immunity pathway while down-regulating

the Th1 or cellular immunity route (McCann and Ames, 2007). By presumably enhancing anti-bacterial and anti-inflammatory responses in both the maternal and fetal components of the placenta, vitamin D also regulates placental development and function and encourages fetal tolerance (Arora and Hobel 2010). The production of pro-inflammatory cytokines is decreased, while the production of anti-inflammatory cytokines is increased, which helps to achieve these regulatory changes (McCann and Ames, 2007). The circumventricular organs, specific regions of the brain outside the blood-brain barrier (BBB), or vagal afferents are additional pathways that allow cytokine signals from the periphery to be transmitted to the brain. These pathways may alter maternal neurotransmission and later depression symptomatology (Webb A., Kazantzidis A., Kift R., et al., 2018).

A few studies stated that each race and the variety of colors have varied needs for vitamin D levels. According to a 2013 study by O'Connor et al., Africans living in tropical areas should create a lot of vitamin D3 internally due to their considerable UVB exposure (O'Connor et al., 2013). However, 7-dehydrocholesterol and epidermal melanin compete for UVB absorption. Therefore, longer sun exposure is required to generate vitamin D3. Stated from (Harris, 2006), most young and healthy African

Americans (blacks) in North America never achieve the recommended 25-hydroxyvitamin D [25(OH)D] 48 concentrations. This is because African Americans (blacks) are more likely than other Americans to be vitamin D deficient.

A number of studies carried out in South and Southeast Asian countries have demonstrated that vitamin D deficiency and insufficiency are extremely prevalent. Epidemiologic research from several regions of India revealed that vitamin D deficiency [25(OH)D 50nmol/L] was more frequent than 70% of the time in all age groups, including infants, children, pregnant women, their newborns, and adult males, even where there is enough sunlight all year long. In Singapore, local residents are found to be in the same situation. Singapore has a significantly higher risk of vitamin D deficiency than Thailand even though it is closer to the equator. This is in part due to Singapore's higher level of industrialization (Nimitphong & Holick, 2013).

Specific type of clothing is an additional factor that could affect vitamin D levels. According to (Mohamed et al., 2021), the issues of vitamin D insufficiency may be increased by the style of clothing worn, particularly fully covering garments like the headscarf or hijab. It was found that women who wear concealing apparel have

a 2.28 times higher risk of having vitamin D deficiency than those who do not.

The hypothalamus-pituitary-adrenaline or HPA axis is linked to serotonin and oxytocin as two primary contributors. It is also likely that the HPA axis play a role in the development of depression. Based on certain studies, oxytocin may play a number of roles in the regulation of mood, behavior, social interaction, and brain development. Numerous mental disorders, including depression have been linked to its absence. The necessity of steroid hormones, including vitamin D for the synthesis and release of the nano-peptide oxytocin is becoming acknowledged progressively. The same study, however, revealed that vitamin D supplementation was unable to significantly alter the levels of platelet serotonin and serum oxytocin in the intervention group. Therefore, it is still unproven that the antidepressive effects of vitamin D treatment was produced by the changes in the measured neurotransmitters (Kaviani et al., 2020).

This study's limitation lies on the fact that some populations or races (such South East Asians) were left out of the research that were conducted. The conclusion that there is a link between vitamin D levels and prenatal depression cannot, therefore, be generalized to all communities or races. Additionally, it was not able to determine

how the levels of vitamin D were associated to some of the risk factors in this study, including socioeconomic status and pregnancy uncertainty.

Conclusion

This study suggests that there is strong association between Vitamin D levels with perinatal depression. The association is an indirect relationship through reducing serotonin synthesis and increasing interleukin levels, which initially have gone up due to the natural inflammation process of pregnant women.

From the results of this systematic review, it can be suggested that pregnant women check their vitamin D levels regularly. In patients with a vitamin D deficiency, supplements can be given to reduce the risk factors for perinatal depression.

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