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Updates on Vitamin D deficiency and antenatal and postpartum depression: A systematic review

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Abstract
Objectives: To comprehensively evaluate and synthesize existing research on the association between vitamin D deficiency and antenatal depression (AD) and post-partum depression (PPD).
Methods: A total of 513 pertinent publications were found after a comprehensive search across four databases. 46 full-text publications were examined after duplicates were eliminated using Rayyan QCRI and relevance was checked; eight studies finally satisfied the requirements for inclusion.
Results: We included eight studies with a total of 5370 pregnant and postpartum women. The prevalence of AD ranged from 4.8% to 90% and the prevalence of PPD ranged from 8.1% to 85.4%. Some studies suggest that higher vitamin D levels, alongside iron, are linked to reduced third-trimester depressive symptoms, indicating a possible protective role of supplementation. However, others found no correlation between vitamin D levels and depression during pregnancy, suggesting that this relationship may be influenced by additional factors. Elevated IL-6 levels have been associated with third-trimester depression, while vitamin D shows an indirect role. Low postpartum vitamin D levels have been connected to an increased risk of postpartum depression, pointing to a potential risk factor. Regional analyses highlight a stronger association of vitamin D deficiency with postpartum than antenatal depression.
Conclusion: The link between vitamin D levels and perinatal depression remains unclear, with mixed evidence suggesting that vitamin D might reduce depressive symptoms, particularly postpartum, though some studies show no association. While vitamin D supplementation in maternal care has potential, further research is needed to understand its impact on mental health fully. Future studies should focus on clarifying the timing, dosage, and mechanisms of vitamin D's role in preventing perinatal depression.

Keywords: Vitamin d deficiency, antenatal depression, postpartum depression, maternal mental health, systematic review

Introduction

About 10% to 15% of women experience AD [1], while PPD affects 5% to 20% of women globally, with a range of 12% to 25% in Brazil [2]. Both postpartum and gestational depression can cause symptoms ranging from suicidal thoughts to appetite loss [1, 2].

In addition to a higher likelihood of preeclampsia and cesarean section [3], depression throughout the gestational and postpartum instances is linked to increased morbidity, maternal-infant impairment, and adverse outcomes like low birth weight, premature delivery, and restricted intrauterine growth [4, 5].

The name "vitamin D" refers to a family of secosteroid hormones that are created in animal tissue (cholecalciferol; vitamin D3) and fungi (ergocalciferol; vitamin D2) following exposure to sunshine (i.e., UVB radiation). Human skin naturally produces cholecalciferol after being exposed to UVB rays, particularly in the summer. Given the restricted availability of ergocalciferol and cholecalciferol from food sources, sunshine is therefore essential for vitamin D status [6]. The main form of vitamin D in the blood, 25-hydroxyvitamin D (25(OH)D), is produced in the liver through the metabolism of ergocalciferol and cholecalciferol [7]. Apart from its significance for bone health (see Miller and Peters9), 25(OH)D may also play a role in immune system promotion [8] and reproduction [9, 10].

Vitamin D is important in many physiological functions that involve immunomodulation, cell growth, and importantly, even brain health. There is an accumulation of evidence in the literature showing a link between deficiencies in vitamin D and disorders in mental health, with particular attention to depression. Pregnancy and postpartum are periods when a woman goes through extensive physiological, hormonal, and psychological changes, making her more vulnerable to any kind of mental disturbance, such as depression. Because AD and PPD affect a significant portion of women, the condition has dire implications for maternal and infant health. Importantly, pregnant and postpartum women are at increased risk of vitamin D deficiency due to their increased nutritional demand, limited sun exposure, and dietary constraints.

Understanding the possible association of vitamin D deficiency with APD may provide insights into prevention and intervention strategies. By addressing one easily modifiable factor, that is, vitamin D levels, healthcare providers may be in a better position to improve mental health outcomes not only for mothers but possibly also improve the developmental outcomes for their children. A systematic review will help develop a better understanding of this relationship and consolidate current evidence that could guide future research and clinical practices involving maternal mental health.

This systematic review aims to comprehensively evaluate and synthesize existing research on the association between vitamin D deficiency and AD and PPD.

Methods

Search strategy

The PRISMA and GATHER criteria were adhered to in the systematic review. To locate pertinent research on the

association between vitamin D deficiency and AD and PPD, a comprehensive search was carried out. Four electronic databases were searched by the reviewers: SCOPUS, Web of Science, Cochrane, and PubMed. We eliminated any duplicates and uploaded all of the abstracts and titles that we could find using electronic searches into Rayyan including studies within the last 5 years (2019-2024). After that, all of the study texts that met the requirements for inclusion based on the abstract or title were gathered for a thorough examination. Two reviewers independently assessed the extracted papers' suitability and discussed any discrepancies.

Study population—selection

The PEO (Population, Exposure, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Pregnant women or in postpartum period, (ii) Exposure: Vitamin D deficiency, (iii) Outcome: AD and/or PPD.

Data extraction

Data from studies that satisfied the inclusion requirements were extracted by two objective reviewers using a predetermined and uniform methodology. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Country, (v) Sample size, (vi) Age, (vii) Gender, (viii) Depression diagnostic tool, (ix) Prevalence of AD, (x) Prevalence of PPD, (xi) Main outcomes.

Quality review

Since bias resulting from omitted factors is frequent in studies in this field, we used the ROBINS-I technique to assess the likelihood of bias since it enables a thorough examination of confounding. The ROBINS-I tool can be used for cohort designs where individuals exposed to different staffing levels are tracked over time and is designed to assess non-randomized studies. Each paper's risk of bias was evaluated independently by two reviewers, and any differences were settled by group discussion [11].

Results

The specified search strategy yielded 513 publications (Figure 1). After removing duplicates (n =266), 247 trials were evaluated based on title and abstract. Of these, 201 failed to satisfy eligibility criteria, leaving just 46 full-text articles for comprehensive review. A total of 8 satisfied the requirements for eligibility with evidence synthesis for analysis.

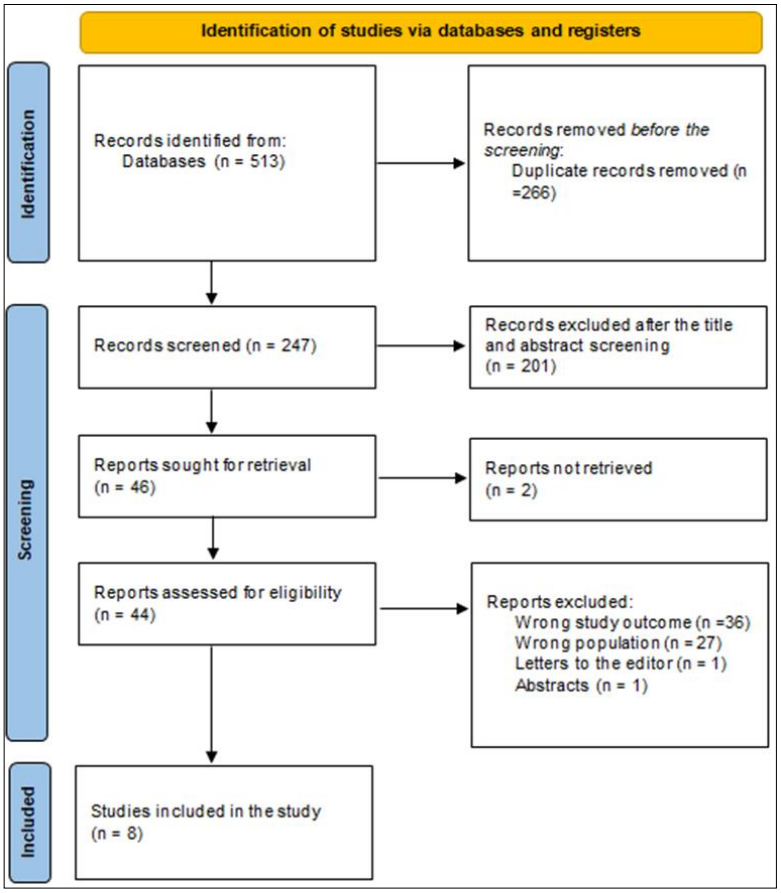

Fig 1: PRISMA flowchart [12].

Sociodemographic and clinical outcomes

We included eight studies with a total of 5370 pregnant and postpartum women. Regarding study designs, three studies were cross-sectionals [16, 17, 19], two were prospective cohorts [13, 14], one was a prospective observational study [15], one was a retrospective observational study [20], and one was a case-control [18].

Five studies used the 10-item Edinburgh Postnatal Depression Scale (EPDS) [13, 15-18], one used the center for Epidemiologic Studies Depression Scale (CES-D) [14], one used the Mini International Neuropsychiatric Interview [19], and one depended on retrospective medical records [20]. The prevalence of AD ranged from 4.8% [17] to 90% [13] and the prevalence of PPD ranged from 8.1% [17] to 85.4% [13].

Increasing levels of vitamin D, alongside iron, are associated with reduced depressive symptoms in the third trimester; therefore, supplementation with such nutrients might convey some protective effects on maternal mental health [13]. Another study investigated the association of levels of vitamin D with symptoms of depression during the course of pregnancy and did not find one, which can suggest that this relationship is not so straightforward and may be influenced by other factors [14]. Some of the studies found that IL-6 level, as an inflammatory marker, had a significant association with third-trimester depressive symptoms, though vitamin D and CRP levels did not show any direct relationship with perinatal depression, hence suggesting that although immune response markers are associated with mood changes, the role of vitamin D could be indirect [15].

Moreover, low serum vitamin D levels, especially during the postpartum period, have been associated with an increased risk of postpartum depression [16].

In some regions, through the use of cross-sectional analyses, findings have shown the strong association of vitamin D deficiency with postpartum depression, though there is no direct linkage between the levels of Vitamin D and antenatal depression [17].

Further case-control studies have evidenced that though low vitamin D levels are a common feature in maternal blood and breast milk, such deficiencies failed to correspond with an increased risk of postpartum depression [18]. The lack of association here may point to exploring other pathways through which vitamin D could influence mood disorders [19]. In contrast, other studies indicate that major depressive disorders during pregnancy may be associated with the insufficiency of vitamin D, which might signal a significant role of vitamin D in pregnancy for maintaining good mental health [20].

Table 1: Outcome measures of the included studies

Study ID	Study design	Country	Sociodemographic	Depression diagnostic tool	AD prevalence	PPD prevalence	Main outcomes
Evanchuk *et al*., 2024 [13]	Prospective cohort	Canada	N= 2134	EPDS	1920 (90%)	1822 (85.4%)	Reduced mother depression symptoms in the third trimester were predicted by increased mid-pregnancy maternal iron and vitamin D status, either separately or in combination.
Seppälä *et al*., 2024 [14]	Prospective cohort	Finland	N= 307	CES-D	NM	NM	Pregnant women's 25(OH)D levels and depression symptoms did not correlate over the course of the pregnancy.
Nassr *et al*., 2022 [15]	Prospective observational study	Iraq	N= 80 Mean age: 27	EPDS	NM	NM	The results of the study indicate that IL-6 concentration and third trimester depression symptoms are significantly correlated, however that vitamin D and CRP levels are not correlated with perinatal depression symptoms.
Pillai *et al*., 2021 [16]	Cross-sectional	India	N= 660 Age range: 23-29	EPDS	NM	330 (50%)	Postpartum depression symptoms were linked to reduced serum levels of 25(OH)D, both total and free. A risk factor for postpartum depression could be postpartum hypovitaminosis D.
Wang *et al*., 2023 [17]	Cross-sectional	China	N= 1773 Mean age: 29	EPDS	85 (4.8%)	144 (8.1%)	The results of this study indicated that there was a strong correlation between vitamin D deficiency and PPD, but not between vitamin D status and AD.
Yuvaci *et al*., 2020 [18]	Case-control	Turkey	N= 75 Mean age: 30.1	EPDS	NM	NM	While vitamin D was found to be low in both maternal blood and breast milk, there was no discernible relationship between PPD and the levels of vitamin D in either.
Dos Santos *et al*., 2024 [19]	Cross-sectional	Brazil	N= 180 Mean age: 20.1	The Mini International Neuropsychiatric Interview	50 (27.8%)	NM	Major depressive disorder during pregnancy may be related to vitamin D insufficiency.
Ogiji *et al*., 2022 [20]	Retrospective observational study	Australia	N= 161 Mean age: 30.1	Medical records	NM	26 (16.1%)	Pregnancy-related low vitamin D levels are linked to PPD development.

Table 2: Risk of bias assessment using ROBINS-I

Study ID	Bias due to confounding	Bias in the selection of participants into	Bias in the classification of interventions	Bias due to deviations from the intended interval	Bias due to missing data	Bias in the measurement of outcomes	Bias in the selection of reported result	Overall bias
Evanchuk *et al*., 2024 [13]	Mod	Mod	Low	Low	Low	Low	Low	Low
Seppälä *et al*., 2024 [14]	Low	Low	Low	Low	Low	Mod	Low	Low
Nassr *et al*., 2022 [15]	Low	Low	Low	Low	Low	Mod	Low	Low
Pillai *et al*., 2021 [16]	Mod	Low	Mod	Mod	Low	Low	Low	Moderate
Wang *et al*., 2023 [17]	Low	Mod	Mod	Low	Low	Mod	Low	Moderate
Yuvaci *et al*., 2020 [18]	Low	Low	Mod	Mod	Low	Low	Mod	Moderate
Dos Santos *et al*., 2024 [19]	Mod	Mod	Low	Low	Low	Mod	Mod	Moderate
Ogiji *et al*., 2022 [20]	Mod	Low	Mod	Mod	Low	Low	Low	Moderate

Discussion

This review provides an overview of the conflicting evidence regarding the association between vitamin D levels and symptoms of depression during the antenatal and postpartum period. Some indicate that higher levels of vitamin D equate to lower depressive symptoms, particularly in the third trimester, suggesting a possible protective effect of supplementation. In contrast, other studies do not find such an association and point to a more complex relationship between vitamin D and maternal depression, possibly moderated by other biological, environmental, or lifestyle factors. For example, the levels of certain inflammatory markers correlate more strongly with depressive symptoms, indicating greater relevance in perinatal mood variations from immune or inflammation processes than vitamin D alone. The review thus points out a need to investigate with more detail the mechanisms whereby vitamin D may influence mental health during and after pregnancy.

Ribamar *et al.* also concluded a potential link between VDD and an increased risk of developing depression during pregnancy and after giving birth. Furthermore, it was conceivable to note that vitamin D supplementation has been suggested as a viable method of lowering the likelihood of depressed symptoms during these biological times [21]. Another narrative review by Bateineh & Atoum found that PPD is substantially linked to pregnant mothers with vitamin D deficiency. Studies with longitudinal follow-up are required to assess the relationship between vitamin D deficiency and PPD [22].

A recent Cochrane study expressed worry about the potential negative consequences of over-supplementation and did not advocate routine screening for 25(OH)D in pregnant women [23]. On the other hand, because of the increased metabolic demand during pregnancy and lactation, as well as to prevent pre-eclampsia and the need for a cesarean delivery, the Endocrine Society advises regular cholecalciferol supplementation [24].

Although the origin of PPD is uncertain, articles demonstrated that it may be related with a psycho-neuro-immune component [25], and three hypotheses have been proposed: The first is that PPD has been associated with a reduction in the brain's synthesis of monoamine neurotransmitters, such as serotonin [26]. The placenta releases the biological estrogens estradiol and estriol, which rise throughout pregnancy. Estradiol increases serotonin function and is strongly associated with mood disorders. Estradiol levels rise sharply during pregnancy and then sharply reduce after birth; this rapid reduction in estradiol levels may contribute to complex PPD [27]. Second, stress causes the hypothalamus to release Corticotrophin-Releasing Hormone (CRH), which in turn causes the pituitary to release corticotrophins and produce cortisol. The rise in cortisol levels during pregnancy and the consequent sharp drop after delivery are just two of the many irregularities that contribute to PPD, which is characterized by a malfunction in the hypothalamic-pituitary-adrenal alignment [28]. The third is the link between certain cytokines, such as tumor necrosis factor and interleukin-6, and the onset of PPD [28].

These findings indicate that screening for and treating vitamin D deficiency among pregnant and postpartum women might be one of the most critical components of maternal mental health care. Given the potential link between a lack of this fat-soluble vitamin and postpartum depression, healthcare professionals may want to monitor vitamin D levels in routine prenatal and postnatal care, especially among those with a high risk of deficiency. If confirmed by further research, vitamin D supplementation might offer a simple and inexpensive intervention to prevent postpartum depression. However, because of this inconsistent evidence, practitioners should also review other inflammation markers and nutritional status in general during the assessment of the risk for depression among pregnant and postpartum patients. Vitamin D supplementation may be more effective as part of a general multi-nutrient approach to maternal mental health rather than being given in isolation.

Strengths and limitations

It constitutes a detailed review of studies conducted across diverse geographical regions, populations, and study designs that enable a broader understanding of the applicability of vitamin D levels on maternal mental health worldwide. Both the prospective cohort studies and cross-sectional analyses are synthesized in this review to capture wide insights-ranging from possible prevention by vitamin D to its association with inflammation. This attention to specific periods, namely the antenatal and postpartum periods, enables the clearer timing of the potential effect of vitamin D on depressive symptoms, an under-explored aspect in previous reviews.

Limitations to these findings include several issues that have to be taken into consideration in considering such findings. Firstly, studies are very diverse regarding methodology, sample size, and population, which could also form a basis of the inconsistent results observed. Many of the studies relied on self-reported measures of depression, which may introduce some bias or inaccuracies. Also, very few studies have controlled for potential confounders like sun exposure, dietary factors, and socioeconomic status, all of which greatly influence the levels of vitamin D and the outcomes in mental health. Another weakness is that some of these studies are cross-sectional in nature; no causal link can be established between a deficiency in vitamin D and depressive symptoms. Longitudinal designs of future studies should be more intensive, using standardized diagnostic tools that in the future might further elucidate the causal relationship between vitamin D and maternal depression, defining the role of timing in this association.

Conclusion

In summary, evidence regarding the association of vitamin D level with depressive symptoms during the antenatal and postpartum periods is still not conclusive. Although several studies suggest a protective effect of higher levels of vitamin D in decreasing the risk of depressive symptoms, especially those of postpartum origin, others find no convincing association-a situation which, once again, makes the relationship complex and multifactorial. Supplementing Vitamin D is a promising but relatively unexplored area of prevention regarding perinatal depression. Screening for vitamin D and supplementing it in maternal care could contribute to better mental health outcomes; this needs to take place in the context of an overall multifactorial approach that takes nutrition and physiology into account on many levels. Longitudinal and controlled studies in the future will be required to establish a clearer understanding

of the mechanisms by which vitamin D might influence maternal mental health and to clarify the optimal timing and dosage for any potential intervention.

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