

Depression Related to Pregnancy, Could Vitamin D Correction Make a Difference? A Systematic Review

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ABSTRACT

Background: Vitamin D deficiency is linked to multiple medical conditions and is associated with some psychiatric disorders. It has been proposed that adjusting vitamin D levels using vitamin D and calcium supplementation can reduce the risk of these disorders, especially during pregnancy.

Objective: The goal of this investigation is to examine the medical literature to evaluate the correlation between vitamin D levels and the incidence and severity of antenatal and postpartum depression.

Method: A search of the literature spanning 2010–2020 was conducted using the following databases: Medline, PubMed, Embase, and Ovid. The search terms included combinations of the following words: “Association” AND “vitamin D correction” AND “antenatal and postpartum depression” AND “deficiency”, and their synonyms. Following this, the results were screened. Only original research articles exploring the correlation vitamin D levels and the incidence of antenatal and postpartum depression were included. The selected trials mentioned the type of depression under investigation.

Result: Overall, 1,876 articles were retrieved. Once animal studies were excluded and only studies describing human trials were included, 39 studies were found. In total, there were eleven eligible articles. These studies covered a total of 20,590 pregnant females with either antenatal or postpartum

depression. All included literature described prospective cohort studies, except four studies, two of them were: case–control studies, one randomized controlled trial, and a retrospective study.

Conclusion: Although the present data support the fact that vitamin D and calcium supplements can have a positive effect on the incidence of postpartum depression, data correlating vitamin D levels with the incidence of postpartum depression is conflicting. Further, randomized controlled studies are needed to determine the association between vitamin D deficiency and postpartum and antenatal depression.

Keywords: Vitamin D, Postpartum, Antenatal, Depression.

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INTRODUCTION AND BACKGROUND

The onset of pregnancy-related depression is a significant disability-causing condition in mothers.¹ The incidence of antenatal and postpartum depression has increased globally over the past few years, reaching up to 20%.²

Some reports have recently correlated pregnancy-related depression with adverse outcomes on both mothers and babies.³ Pregnancy-related depression has even been associated with delayed cognitive abilities, as well as behavioral and physical disturbances in infants.⁴

Many trials in the medical literature have examined the concepts of antenatal and postpartum depression.⁵ However, it is still unclear how depression begins during pregnancy⁶, although it has been postulated that this could be a multifactorial process.⁷ Moreover, some studies assumed that the incidence of depression during pregnancy could be related to some dietary habits.⁸ Vitamin D is one of the top supplements used during pregnancy.⁹

It is also correlated with a reduced incidence of depression in the adult population more generally.¹⁰ Furthermore, some physiological studies have shown that there are multiple vitamin D receptors on the neurons of the brain. Hence, a deficiency of this vitamin could lead to depression, particularly when considering the neurohormonal role of this vitamin.¹¹

Vitamin D concentrations may regulate calcium ions levels and can thus play a significant role in terms of vitamin D deficiency symptom onset.¹² It appears to have an impact on mood changes due to various neurological mechanisms.¹³

Some reports have also shown the positive influence of vitamin D and calcium supplementation during pregnancy, even in females with normal vitamin D levels. It has been shown that these supplements can reduce both the incidence and severity of postpartum depression and its associated symptoms.¹³ Despite the available data that has evaluated the impact of vitamin D

levels during pregnancy, the correlation between correcting vitamin D levels and the incidence and severity of depression in pregnant females is still controversial. Therefore, this systematic review aims to explore the relationship between vitamin D levels and the incidence and severity of antenatal and postpartum depression, as identified in the literature.

METHODOLOGY

This systematic review was aligned with the guidelines presented in the PRISMA checklist for systematic reviews and meta-analyses.⁵ Various electronic databases were searched as part of this systematic review to search for and identify eligible studies investigating the relationship between vitamin D levels and antenatal and postpartum depression. All eligible studies published until April 2020 were retrieved from four databases: Embase, Medline, Ovid, and PubMed.

Search Strategy

The search terms adopted for this systematic review included the following: “Association” AND “vitamin D correction” AND “antenatal and postpartum depression” AND “deficiency”. Synonyms of these keywords were used separately and in

combination using the operator ‘OR’. These keywords included [“Association” OR “Correlation” OR “Relationship” OR “Link” OR “Interrelation” OR “Connection”] AND [“vitamin D” OR “ergocalciferol” OR “cholecalciferol” OR “25-OH vitamin D” OR “25-hydroxy vitamin D”] AND [“deficiency” OR “supplement” OR “correct” OR “insufficient” OR “low” OR “reduced”] AND [“perinatal depression” OR “post-natal depression” OR “postpartum depression” OR “antenatal depression”]. Following this step, duplicates were removed through the database and then in Endnote 9. Each of the resulting titles and abstracts was reviewed to ensure that no pertinent literature had been missed. Each article was then screened for eligibility. For this systematic review, only original research articles that examined the relationship between vitamin D level correction using vitamin D supplements, calcium, or both, as well as those investigating the incidence and severity of antenatal and postpartum depression were included. Moreover, the included studies specified the type of depression (either postpartum or antenatal) being examined. Studies were eligible for inclusion if they were written in English, irrespective of the country in which the study was conducted. Further, all study types were included in this review.

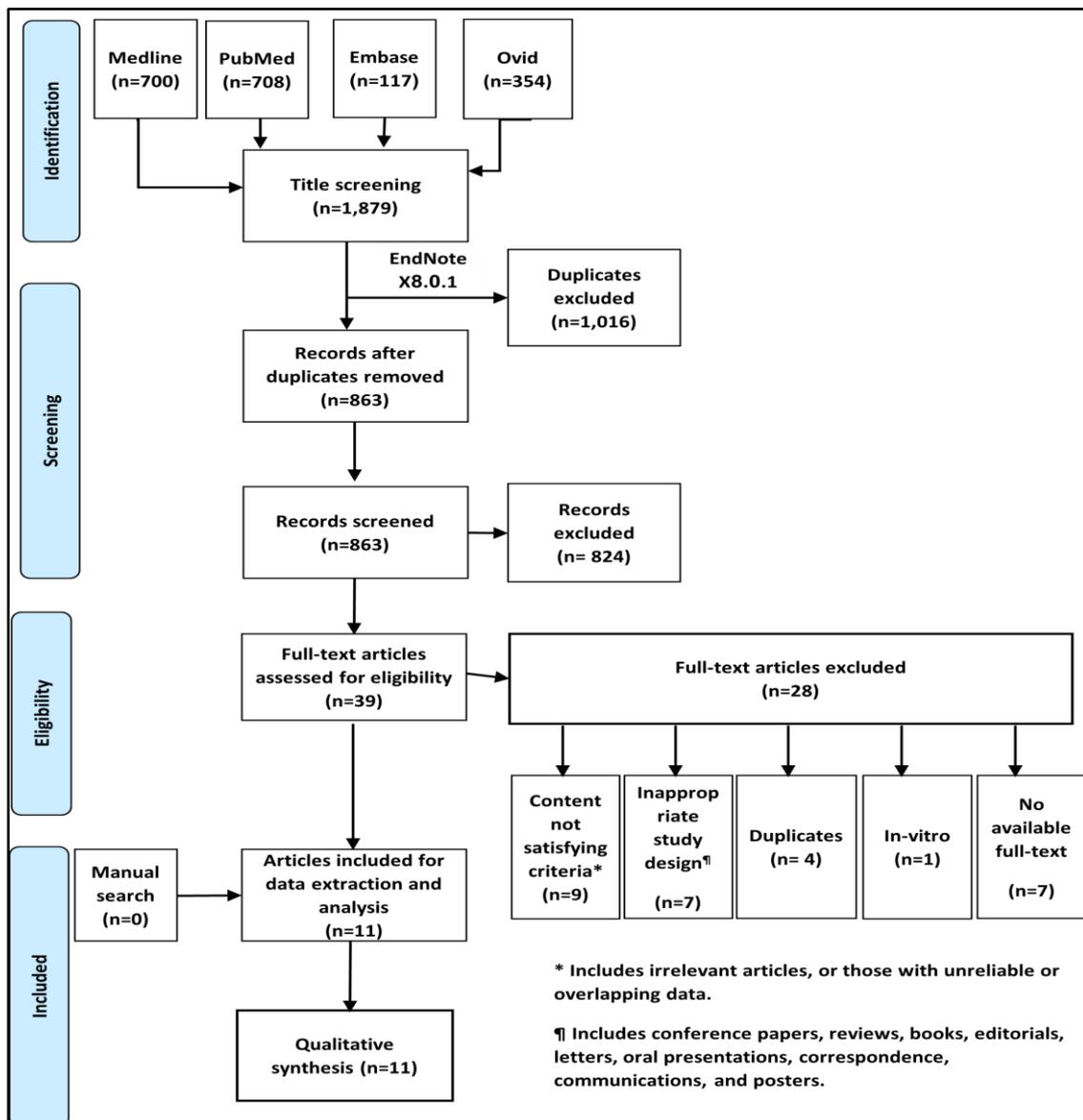


Fig 1: Search strategy

Eligibility Criteria

Once the search and first-pass screening were completed, the inclusion criteria for this review were determined. As a second-pass screening approach, all abstracts were examined by the research team, who determined which were most appropriate for inclusion. Specifically, studies were included in the systematic review if they featured adult pregnant females, and if they specified the type of depression under investigation. In vivo and animal studies were excluded from this review. Also excluded were studies that featured incomplete or overlapping data, or those whose full-text articles could not be retrieved.

After this screening step, the research team examined the reference lists of the included articles to identify additional relevant articles for inclusion. The results from each included study were then documented, compiled, and summarized in a dataset for reporting purposes. The complete search strategy is illustrated in Figure 1.

DATA REVIEW AND ANALYSIS

A preliminary review was conducted, which began with data extraction. In this case, an Excel database was created and used to summarize the data and findings from each study. Any articles that were published a single research group, and which investigated similar variables, were reviewed for duplication. We also used the Cochrane tool to determine the quality of each

included article.⁶ Descriptive statistics were carried out to summarize the data. Specifically, categorical variables included the number of cases and percentages. Numerical variables were described with means, standard deviations, medians, and interquartile ranges. These calculations were carried out with IBM SPSS (version 26; Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) for Microsoft Windows.

RESULTS

Once the abstracts were reviewed and screened against the eligibility criteria, eleven articles¹³⁻²³ were included in the systematic review. These articles were all published between 2010 and 2020 and studied 20,590 pregnant females in total.

Of the eleven included studies, seven^{16-21,23} adopted a prospective cohort design, while only two^{15,22} was case-control studies. One study had a retrospective design¹⁴ and one study was a randomized controlled trial.¹³ Additionally, only two studies included patients with antenatal depression^{14,16}, while several studies focused on postpartum depression.^{13,15,17-23} Additionally, the minimum number of recruited patients was 81,¹³ while the maximum number of recruited patients was 16,528.¹⁴

When examining the extracted data, all studies examined the correlation between vitamin D levels, the correction of vitamin D levels, and the incidence of antenatal and postpartum depression. The final list of included studies is presented in Table 1.

Table 1: Included Studies.

Author(s)	Year	Study design	Sample size	Type of depression	Objective	Result
Amini et al [13]	2020	RCT	81	Postpartum depression	To examine the impacts of calcium and vitamin D supplementation on postpartum depression symptoms	There was a significant reduction in the postpartum depression score after the correction of vitamin D levels ($P=0.008$); however, supplementation did not affect the levels of estradiol or inflammatory markers that have been linked to postpartum depression.
Jani et al [14]	2020	Retrospective	16,528	Perinatal depression	To determine whether a correlation exists between obesity, vitamin D deficiency, and perinatal depression in an Australian population	Obesity was linked to increased perinatal depression risk (AOR 1.421; 95% CI, 1.191, 1.696) and to vitamin D deficiency incidence rates (AOR 1.950; 95% CI; 1.735, 2.191). Patients with a high risk of perinatal depression also had a higher incidence of vitamin D deficiency when compared with those with a low risk of the same (AOR 1.321; 95% CI, 1.105, 1.579). Perinatal depression risk reduced upon vitamin D level correction "(95% CI 1.003, 1.030), $P=0.02$. Path C': B=0.014 (95% CI 1.001, 1.028), $P=0.04$."
Amini et al [15]	2019	Case-control	163	Postpartum depression	To investigate the correlation between dietary supplementation containing vitamin D and calcium on postpartum depression incidence rates	Intake of vitamin D, calcium, and vitamin B complex reduced the incidence of postpartum depression; however, vitamin A and beta-cryptoxanthin can increase the incidence of postpartum depression.
Figueiredo et al [16]	2017	Prospective cohort	179	Antenatal depression	To evaluate the correlation between vitamin D concentrations and correction with a depression diagnosis during pregnancy.	In the first trimester, the prevalence of depression with vitamin D levels of <30, <50, and <75 nmol/L were "69.3%, 14.0% and 1.7%, respectively". With respect to depressive symptoms, their prevalence rates were "20.1%, 14.7%, and 7.8% for the first, second and third trimesters, respectively." During the first trimester, the incidence of both vitamin D deficiency and antenatal depression symptoms are highest. Higher vitamin D levels during this time were correlated with a 2% reduction in antenatal depression onset throughout pregnancy.
Accortt et al [17]	2016	Prospective cohort	91	Postpartum depression	To evaluate if low prenatal vitamin D levels can predict postpartum depression in pregnant African-American women. To also explore whether "high levels of prenatal inflammatory cytokines" was associated with low vitamin D levels, and subsequently, to postpartum depression symptoms.	An inverse correlation between prenatal vitamin D levels and postpartum depression symptoms approached significance ($P=0.058$). Those who had increased concentrations of inflammatory markers and lower vitamin D tended to experience significantly more severe postpartum depression symptoms ($P<0.05$).

Gould et al [18]	2015	Cohort	1,040	Postpartum depression	To evaluate the correlation between vitamin D levels and postpartum depression risk among a cohort of Australian women.	Cord blood samples of vitamin D during delivery and postpartum depression were not found to be correlated at either 6 weeks or 6 months after birth. Vitamin D levels obtained through cord blood of 25–50 nmol/L and >50 nmol/L at delivery was correlated with a decreased risk of postpartum depression 6 weeks after birth. At 6 months, no relationship was apparent between cord blood vitamin D levels (<25 nmol/L) at delivery and postpartum depression.
Fu et al [19]	2015	Cohort	323	Postpartum depression	To evaluate the potential correlation between serum vitamin D concentrations and postpartum depression in Chinese women.	12.2% of patients were diagnosed with postpartum depression. Serum vitamin D levels were higher in patients without depression than those with it ($P<0.0001$). The incidence of postpartum depression was more likely to be related to serum vitamin D levels " ≤ 10.2 ng/mL (OR 7.17, 95%CI 3.81–12.94; $P<0.0001$)", which was significantly reduced following correction using vitamin D and calcium supplementation. Lower serum vitamin D concentrations were correlated with postpartum depression onset, independent of other factors.
Gur et al [20]	2014	Prospective cohort	687	Postpartum depression	To examine a possible correlation between postpartum depression and serum vitamin D concentration during mid-pregnancy.	11% and 40.3% of patients had a severe or mild vitamin D deficiency, respectively, during pregnancy. The associated frequency of post-partum depression was 21.6% during week 1, 23.2% week 6, and 23.7% at 6 months. Correction of vitamin D levels using high doses of vitamin D (1200 IU/day) and calcium supplements improved the symptoms of post-partum depression in week 1 ($P=0.001$) and week 6 ($P=0.002$), as determined using logistic regression analysis.
Robinson et al [21]	2014	Prospective cohort	796	Postpartum depressive	To understand whether low concentrations of serum vitamin D levels during pregnancy are correlated with the incidence of postpartum depression symptoms.	The study subjects reportedly experienced symptoms of postnatal depression 3 days after delivery. Those who tended to report greater postnatal depression symptoms had vitamin D levels in the lowest quartile versus those in the highest ($P=0.017$). This held true independent of potential confounding factors, including "season of birth, body mass index and sociodemographic factors."
Nielsen et al [22]	2013	Case-control	605	Postpartum depression	To evaluate whether low vitamin D levels in pregnancy were associated with postpartum depression.	Vitamin D levels and postpartum depression risk did not appear to be linked ($P=0.08$). Rather, women who had the highest vitamin D levels were more likely to experience postpartum depression. The adjusted odds ratios for postpartum depression were as follows: "1.35 (95% CI: 0.64; 2.85), 0.83 (CI: 0.50; 1.39)", as well as "1.13 (CI: 0.84; 1.51) for vitamin D [levels] 15 nmol/L, 15–24 nmol/L, and 25–49 nmol/L, respectively." In contrast, the adjusted odds ratios were "1.53 (CI: 1.04; 2.26) and 1.89 (CI: 1.06; 3.37)" for vitamin D levels "80–99 nmol/L and ≥ 100 nmol/L, respectively."
Murphy et al [23]	2010	Prospective cohort	97	Postpartum depression	To examine the potential association between and predictive ability of vitamin D levels and postpartum depression symptoms.	A statistically significant relationship was evident between low vitamin D levels and postpartum depression incidence rates ($P=0.02$). The authors note how future studies should investigate this relationship among a larger number of patients to bolster these findings.

DISCUSSION

Postpartum depression is a common condition that can be life-threatening in severe cases, according to reports from the World Health Organization.⁸ Many studies have investigated the etiology of antenatal and postpartum depression.² Additionally, dietary habits were shown to influence postpartum depression incidence rates.¹⁴ However, the relationship between vitamin D levels, their correction, and the incidence and severity of postpartum and antenatal depression is still under investigation.¹⁸

The present review investigated the correlation between vitamin D levels and their correction on the severity and incidence of postpartum depression and antenatal depression symptoms. By reviewing the medical literature published in the past decade, there seems to be a conflicting opinion on the correlation between vitamin D deficiency and the occurrence of antenatal and

postpartum depression. However, it was noted that correcting vitamin D levels using vitamin D or calcium supplementation can reduce the severity and incidence of depression related to pregnancy.¹³⁻²³

Some studies have supported the correlation between vitamin D deficiency and the occurrence of antenatal and postpartum depression. Figueiredo et al.¹⁶ evaluated the association between vitamin D levels measured during the first trimester and the incidence of antenatal depression. Figueiredo et al.¹⁶ showed that females with high vitamin D levels during the first trimester were found to have a lower incidence of antenatal depression by almost 2%, whereas depression prevalence rates of 69.3%, 14.0%, and 1.7% were observed for vitamin D levels of <30 nmol/L, <50 nmol/L, and <75 nmol/L, respectively.

Further, Jani et al.¹⁴, in a retrospective study on 16,528 patients, showed that obese females face a greater risk of vitamin D deficiency and subsequent perinatal depression (adjusted odd ratio: 1.321; 95% CI, 1.105, 1.579). and that correcting vitamin D levels can reduce the incidence of perinatal depression (95% CI, 1.003, 1.030; $P=0.02$).¹⁴

Also, Accorrt et al.¹⁷ examined the relationship between vitamin D levels in African- American, pregnant women, to determine if this marker can be used to predict symptoms of depression after delivery ($P<0.05$). Accorrt et al.¹⁷ found an inverse association between vitamin D levels during pregnancy and the severity of depression symptoms postpartum.¹⁷

Fu et al.¹⁹ showed similar results among pregnant females from China. In this case, a vitamin D deficiency appeared to be an independent risk factor for postpartum depression, with an incidence of 12.2%. Similarly, Gur et al.²⁰, Robinson et al.²¹, and Murphy et al.²³ had supportive results for the inverse relationship between vitamin D levels and their correction with the severity and incidence of postpartum depression symptoms.

Amini et al., in both a randomized controlled trial¹³ and a case-control study¹⁵, revealed a significant reduction in postpartum depression symptoms and severity among patients who received vitamin D supplementation and calcium during pregnancy ($P=0.008$); this did not affect estradiol levels.^{13,15}

In the most extensive study identified to date on this subject, Gould et al.¹⁸ evaluated the relationship between vitamin D levels and postpartum depression. The authors demonstrated that the vitamin D levels in cord blood (25–50 and >50 nmol/L) during delivery were not associated with the occurrence of postpartum depression from 6 weeks to 6 months after delivery, recommending further investigations to confirm these findings.

Another critical finding was identified by Nielsen et al.²² These authors recruited 605 patients in a case-control study to investigate whether low levels of vitamin D during pregnancy are correlated with postpartum depression. The authors showed that there was no significant difference between those with high versus low vitamin D levels, with an adjusted odds ratio for postpartum depression of 1.35 (95% CI: 0.64; 2.85) and 0.83 (CI: 0.50; 1.39), respectively. More importantly, these authors demonstrated that women with high vitamin D levels showed an increased risk of postpartum depression, despite the non- significant difference. Nevertheless, Nielsen et al.²² recommended further randomized and multicenter studies to confirm these findings.

While this systematic review provides an overview of the critical studies identified to date that have examined the potential link between vitamin D levels and antenatal or postpartum depression, there are some limitations that should be considered. Specifically, it is important to note that most of the studies were performed at a single center. This may have affected the validity of the observed results. Further, only two studies explored antenatal depression in depth. As such, it is recommended that additional studies be conducted to address these limitations to determine whether they affect the outcomes reported herein.

Finally, this study sheds light on an important relationship in pregnancy: the onset and management of pregnancy-related depression in association with vitamin D and calcium supplementation. The results of this review should guide clinicians as they provide care for pregnant females to improve the associated outcomes for both mothers and infants.

CONCLUSION

The relationship between vitamin D deficiency and antenatal and postpartum depression is still not established. However, vitamin supplementation should generally be encouraged in pregnant females. The results of this review suggest that future studies on antenatal depression are needed to confirm whether any correlations exist between vitamin D deficiency and depression in pregnant females.

These findings should alert health authorities to increase their awareness of the various risk factors and hazards associated with vitamin D deficiency that can ultimately affect pregnant females and their infants.

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