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Association Between Vitamin D Levels During Pregnancy and Postpartum Depression

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Abstract

Objective: To evaluate evidence regarding 25-hydroxyvitamin D (25(OD)D) levels during pregnancy and its association with postpartum depression (PPD). **Data Sources:** Primary literature was accessed through MEDLINE, Google Scholar, and International Pharmaceutical Abstracts searches through January 2015. Data from published trials were retrieved for analysis using the following search terms: vitamin D, 25-hydroxyvitamin D, 25(OH)D, postpartum, pregnancy, and depression. **Data Extraction:** Inclusion criteria were human subjects, English language, vitamin D as the sole micronutrient under study, and measurement of vitamin D level during pregnancy. Studies measuring vitamin D levels after delivery were excluded. Also any antenatal or prepartum depression was excluded. **Data Synthesis:** Although a variety factors may contribute to the likelihood and severity of PPD, there are 3 published prospective cohort studies specifically evaluating the relationship between vitamin D and PPD. The results are conflicting: 2 of these studies found a significant correlation between patients with low vitamin D level and PPD, but the third found that high vitamin D levels are associated with a greater incidence of PPD. **Conclusion:** Available evidence suggests a possible correlation between vitamin D levels at midpregnancy and PPD. Women with risk factors for PPD should be educated on this potential association and ways to maintain normal vitamin D levels. Further study is needed to determine the benefit of vitamin D supplementation in preventing PPD.

Keywords

vitamin D, pregnancy, postpartum depression

Background

Several studies have found that low levels of serum 25-hydroxyvitamin D (25(OH)D) are linked to many diseases and disorders such as premenstrual syndrome, nonspecific mood disorder, major depressive disorder, cancer, autoimmune disorders, bone diseases, cardiovascular diseases, preeclampsia, seasonal affective disorder, and post-partum depression (PPD).[1-4] It is suggested that vitamin D is a potential neurosteroid and that it is found in high concentrations in the amygdala, thalamus, hypothalamus, dorsal raphae nucleus, and in the motor neurons, which supports possible effects on the sensory pathway, as well as on endocrine, autonomic, and motor systems. Thus, deficiency in vitamin D could be related to many of the symptoms of depression such as fatigue, mood disturbance, and motor function.[5,6]

Vitamin D is a cholesterol-derivative steroid hormone that can be synthesized in the human body after the cutaneous exposure to ultraviolet B radiation. It may also be obtained from dietary sources such as fish and egg yolk. Pregnant women often do not get sufficient vitamin D due to the liberal application of sunscreen, related to fear of skin cancer as well as decreased fish in the diet, due to fear of mercury content.[7,8] Vitamin D deficiency in the general population is more prevalent than many realize, especially during pregnancy. Studies have found that pregnant women are more likely to have low serum 25(OH)D than nonpregnant women and that the level of 25(OH)D seems to vary among trimesters with the first and third trimesters being lower than second trimester in 25(OH)D concentration.[9,10]

Routine screening for vitamin D deficiency during pregnancy is not considered to be cost-effective, and the World Health Organization and the American College of

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Table 1. Summary of Literature Evaluating Vitamin D Levels During Pregnancy and the Development of PPD.

Reference	No. of Patients	Timing of Vitamin D Measurements	Results	Limitations
Robinson et al[14]	696	18 weeks gestation	OR 2.19 for EPDS 6 or more depressive symptoms	Compared lowest vitamin D quartile (<19 ng/mL) to highest (>28 ng/mL) rather than to normal values (20-50 ng/mL)
Gur et al[15]	208	24-28 weeks gestation	Negative correlation between levels of vitamin D and EPDS score in (1 week $P = .02$, $r = -.2$; 6 weeks $P = .01$, $r = -.2$; 6 months $P < .01$, $r = -.3$)	Samples collected during summer months
Nielsen et al[16]	605 women filling antidepressant medications with 875 controls	Weeks 10-12 and 25 of gestation	Risk with vitamin D ≥32 ng/mL and higher (OR = 1.62); low levels not significant	No direct measurements for depression; data based on antidepressant medication fill data; poorly matched case controls

Abbreviations: OR = odds ratio; EPDS = Edinburgh Postnatal Depression Scale.

Obstetricians and Gynecologists do not recommend routine vitamin D supplementation during pregnancy. However, other international health organizations, including the Turkish Ministry of Health, recommend supplementation of 1200 IU daily of vitamin D starting at week 12 of pregnancy.[11]

PPD is a serious medical condition that not only affects the women themselves but can also affect their infants and their families. PPD may manifest itself in a similar way to major depressive disorder, including symptoms such as sadness, lethargy, loss of interest in formerly pleasurable activities, and even suicidal thoughts or ideation. In PPD, symptoms may also manifest as neglect, inappropriate treatment, or even rejection of their newborns.

A possible association between serum vitamin D levels and depression has been studied in the general population and in women specifically.[11-13] A study completed by Kwasky and Groh[11] examined the correlation between vitamin D and depression in young women but did not find any association. Milaneschi et al[12] observed an association between the low-level serum vitamin D and depression in men and women and found a correlation between low levels of vitamin D and depression in the female population. Shipowick et al[13] conducted a randomized trial suggesting that supplemental vitamin D_3 reduces depressive symptoms in women.

Data Sources and Extraction

Given the possibility of an association between low vitamin D levels and depression, including PPD, an evaluation of the literature is warranted to help guide clinicians in the appropriate treatment of their pregnant patients. Primary literature was searched for the purpose of this review article. Search was done through MEDLINE, Google Scholar, and International Pharmaceutical Abstracts searches through January 2015. The search terms used to build the resulted studies were as follows: vitamin D, 25-hydroxyvitamin D, 25(OH)D, postpartum, pregnancy, and depression. Inclusion criteria were human subjects, English language, and vitamin D as the sole micronutrient under study. We excluded any study without vitamin D measurements during pregnancy. Currently, there are 3 published studies assessing the relationship between low serum 25(OH)D and PPD. The objective of this review is to evaluate this association using the available data.[14-16]

Data Synthesis

Three different studies have been published assessing the correlation between levels of vitamin D and PPD (see Table 1).[14-16]

Robinson et al[14] performed a prospective cohort study in Perth, Australia, analyzing serum samples taken from 696 randomly selected women at midpregnancy (18 weeks gestational age). Only Caucasian women were included in the study. After measuring the level of 25(OH)D in each sample, they were divided into 4 different quartiles based on their vitamin D concentrations: <19 ng/mL, <19 to 23 ng/mL, 24 to 28 ng/mL, and >28 ng/mL. This classification was designed to test possible effects due to deficiencies or insufficiencies based on accepted normal levels of vitamin D, which are considered to be 20 to 50 ng/mL.[17] Women included in the study were followed for 3 days after delivery, and mood disturbances were measured using an index of 6 symptoms derived from the Edinburgh Postnatal Depression Scale (EPDS), including anxiety, sadness, mood fluctuation, teariness, appetite change, and sleep disturbance. Each item

was scored on 4-point scale with the highest total points reflecting poorer mood. For the purposes of the study, a score of 6 or greater was deemed as a possible mood disturbance.

The age of study participants was 20 to 29.9 years, and more than 73% of participants had a body mass index (BMI) within a healthy weight. This study found a statistically significant correlation between lower level of vitamin D at midpregnancy and increased PPD symptoms as measured by total symptom scores. Only 16.5% of participants in the highest quartile experienced PPD with 6+ symptom scores as compared with the 26.9% of the participants in the lowest quartile (P = .017). Several potential cofounders were adjusted for, such as maternal age and BMI, education, season of delivery, smoking, and alcohol use. Women in the lowest 25(OH)D quartile were significantly more likely to have endorsed 6 or more depressive symptoms compared with women in the highest quartile (odds ratio [OR] =2.19, 95% confidence interval [CI] = 1.26-3.78). Women who were in the lowest quartile for 25(OH)D were more likely to endorse between 1 and 5 depressive symptoms than women who were in the highest quartile (OR = 1.43, 95% CI = 0.85-2.40), although this difference was not significant. The authors concluded that there is a correlation between low levels of vitamin D at midpregnancy and increased symptoms of PPD. A possible weakness is that this study used the EPDS scoring tool to assess PPD for only 3 days postpartum. Clinically, PPD symptoms can start any time within the first 4 weeks postpartum and continue up to 1 year.[18,19] It should also be noted that analyzing one blood sample at midpregnancy may be insufficient and that having an additional sample toward the end of the pregnancy could have been more informative.[9,10]

Another prospective cohort study was performed in Turkey and published by Gur and colleagues.[15] They screened 678 pregnant women between 24 and 28 gestational weeks. Women could be included in the study if they were married and planned/desired pregnancy, had a BMI between 20 and 30 kg/m^2, were parity ≤3, had an educational level of at least 8 years, an annual income ≥$4500, and were 18 to 40 years of age. Women with risk factors for PPD were excluded, including a history of depression, prenatal depression and anxiety, stressful life events, poor marital relationship and lack of social support, low socioeconomic status, unplanned/unwanted pregnancy, obesity, smoking, alcohol use, or multiple pregnancy. Participants were also excluded after delivery if they had intrauterine fetal death, neonatal baby death, newborn with anomaly, newborn taken to the neonatal intensive care unit, and complicated delivery.

After study exclusions, blood samples were taken from 208 pregnant women between 24 and 28 weeks gestation. Vitamin D levels were classified as follows: <10 ng/mL (severe deficiency), <20 ng/mL (mild deficiency), and >20 ng/mL (normal). An EPDS scoring system was used to evaluate PPD 1 week after delivery, then again at 6 weeks after delivery and at 6 months after delivery. A patient was considered to have PPD if her score was ≥12 points using the EPDS scoring system. A Pearson correlation was used to measure the strength of the association between EPDS scores and vitamin D levels for each of the 3 time periods (1 week, 6 weeks, and 5 months following delivery).

The mean age of study participants was 28.5 years, and the mean BMI was 26.5. The mean vitamin D level of the participants was 22.4 ng/mL, with 11% of the subjects having a severe deficiency and 40% having a mild deficiency. Approximately 21% of the subjects met the criteria for PPD in the first week postpartum, 23% had PPD by week 6, and almost 24% had PPD by 6 months. The mean vitamin D level was significantly different between women with PPD (EPDS score > 12) and without PPD (EPDS score < 12) in 3 time periods. During the sixth month postpartum 50% of women in the severely deficient group (vitamin D < 10 ng/mL) experienced PPD compared with the control group (>20 ng/mL) in which 11% of women experienced PPD during the sixth month postpartum (P < .001). Findings from first to sixth week postpartum was consistent with that from the sixth month (P = .003 and .004, respectively). There was also a significant negative correlation between levels of vitamin D and EPDS score in the 3 time periods (P = .02, r = −.2; P = .01, r = −.2; P < .01, r = −.3, respectively). The authors concluded that low level of vitamin D during midpregnancy is associated with PPD. A limitation of this study is the timing of vitamin D level blood sampling. They were collected in summer and autumn and so were likely higher than would have been expected at other times of the year.

A third prospective cohort study performed by Nielson and colleagues also analyzed a possible correlation between vitamin D levels and PPD.[16] In this study, participants were recruited from the Danish National Birth Cohort. A total of 605 women were recruited based on filling antidepressant medication prescriptions within 1 year after delivery. The included women were matched to 875 female controls who did not fill any antidepressant prescription within 1 year of delivery. Blood samples were drawn during weeks 10 to 12 and 25 of pregnancy. Vitamin D concentration were categorized into 6 levels (<6 ng/mL, 6-9.5 ng/mL, 10-19.5 ng/mL, 20-31.5 ng/mL, 32-39.5 ng/mL, ≥40 ng/mL) with 20 to 31.5 ng/mL serving as the reference value. The results of this study showed a potential J-shaped relationship where both high and low levels of vitamin D were associated with PPD. In this study, an association between postpartum antidepressant use and vitamin D levels during pregnancy were not significant in the fully adjusted model. However, in a separate analysis examining samples of 32 ng/mL and higher, a significant risk of antidepressant use was found (OR = 1.62, 95% CI = 1.15-2.30). The authors concluded that there is no statistical significant correlation between low level of vitamin D and the risk of PPD. Limitations of the study included

a lack of a reliable scoring tool to measure PPD such as EPDS. Also, inclusion in the study was based on filling antidepressant medications in which case participants with various forms of depression and/or other psychiatric conditions could have been mistakenly placed into the case group. Measuring total vitamin D instead of free vitamin D is one of the weakness of this study, especially considering that only free $25(OH)D_3$ is the biologically active form. Protein level increases during pregnancy and with no adjustment for socioeconomic status, there could be a significant nutrition differences between groups. Also, the samples analyzed were not consistent in their gestational weeks. While the study was designed to have 2 samples, one during 10 to 12 gestational weeks and the second in 25 gestational week, the data presented came from a variety of gestational weeks. A final weakness for the study was that case and control groups were poorly matched in that the case group included more smokers, as well as more patients of lower socioeconomic status and with more prior childbirths.

Discussion

In addition to lower prenatal vitamin D levels and the risk of PPD, there has also been documentation of an association between low vitamin D levels measured shortly after delivery and subsequent development of PPD. A 2010 exploratory study found a correlation between high EPDS scores and low vitamin D levels up to 7 months postpartum.[20] A cohort study by Fu et al[21] examined also vitamin D levels 24 hours after delivery and PPD for 3 months postpartum. They found a significant association between vitamin D levels less than 10.2 ng/mL and PPD as measured by EPDS (OR = 7.17, 95% CI = 3.81-12.94; $P < .0001$). This study stands as one of the evidence supporting the correlation between low vitamin D level and PPD.

Vitamin D supplementation is a relatively inexpensive and safe measure for ensuring a healthy pregnancy. The cost of widespread vitamin D level screenings for the prevention of PPD in pregnant women is not justified at this time. However, due to conflicting data on the effect of high vitamin D levels and PPD, it is important that clinicians do not over-supplement pregnant patients to vitamin D levels beyond 32 ng/mL.

Conclusion

According to the current evidence, there is a potential correlation between low vitamin D levels during pregnancy and the development of PPD, but the data from available cohort studies are inconsistent and complicated with methodological flaws. Ideally, pregnant women's vitamin D levels should be >20 ng/mL. Further studies are needed to determine the benefit of vitamin D supplementation during pregnancy and whether reaching specific target level through supplementations is beneficial in preventing PPD.

Declaration of Conflicting Interests

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