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Do abnormally low concentrations of Vitamin D during pregnancy contribute to postpartum depression?

Anita R. Cintron-Rivera

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Abstract

Background: Vitamin D has been linked with poor mood and depression, as well as cognitive delay. During pregnancy, with the demands placed on the body by the fetus, there is increased risk for vitamin D deficiency. Postpartum depression is a common disorder that has been shown to have significant effects on both mother and child. Postpartum depression has also been implicated in lower cognition and mood disorders in children of mothers that suffered from postpartum depression. The aim of this systematic review is to determine if low levels of vitamin D during pregnancy contribute to postpartum depression.

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL and Web of Science using the keywords: postpartum depression and vitamin D levels. The search was then narrowed to include only English language articles. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating vitamin D levels during pregnancy with subsequent diagnosis of postpartum depression were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).[20] A search on the National Institute of Health (NIH) clinical trials site revealed no currently registered trials, at any phase, relating to vitamin D levels during pregnancy and postpartum depression.

Results: A total of three articles met inclusion criteria and were included in this systematic review. A prospective cohort study conducted in Turkey with 689 participants demonstrated a significant relationship between low 25(OH)D3 levels in mid-pregnancy and postpartum depression by using the Edinburgh Postpartum Depression Scale (EDPS). A case-control study that included 1480 Danish women concluded that low 25(OH)D3 levels measured during pregnancy were not related to postpartum depression. A second case-control study that included 706 Australian women concluded that low 25(OH)D3 is a risk factor for postpartum depression.

Conclusion: There is confounding evidence to support the hypothesis that low serum vitamin D levels measured during pregnancy are indicative of risk of postpartum depression. Nonetheless, some studies do demonstrate a relationship. As such, low vitamin D levels during pregnancy should be addressed if not for risk of postpartum depression then for the evidence suggesting that vitamin D has other deleterious effects including negative cognitive effects in children as well as associations with poor mood. More research is needed to solidify a relationship between low serum vitamin D during pregnancy and postpartum depression.

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Do abnormally low concentrations of Vitamin D during pregnancy contribute to postpartum depression?

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Biography

Anita Cintron-Rivera is a native Oregonian. She received a Bachelor of Science degree from Oregon State University in Corvallis, Oregon, in 2007, with a major in Biology. She spent the next several years working in the healthcare field. Prior to attending PA school she worked as a Spanish Medical Interpreter for a public health primary care clinic in Oregon and also as Patient Care Coordinator at Pacific University's Interprofessional Diabetes Clinic. She has a significant background in working with underserved Spanish speaking Latinos in healthcare. During PA school, she was a Pacific University Rural Health Scholar. She also accepted the Primary Health Care Loan Forgiveness award and as such will be spending her first year in practice at a rural, underserved Primary Health Clinic in Oregon.

Abstract

Background: Vitamin D has been linked with poor mood and depression, as well as cognitive delay. During pregnancy, with the demands placed on the body by the fetus, there is increased risk for vitamin D deficiency. Postpartum depression is a common disorder that has been shown to have significant effects on both mother and child. Postpartum depression has also been implicated in lower cognition and mood disorders in children of mothers that suffered from postpartum depression. The aim of this systematic review is to determine if low levels of vitamin D during pregnancy contribute to postpartum depression.

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Keywords: Vitamin D, postpartum depression

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List of Abbreviations

DNBC ..... Danish National Birth Cohort
EPDS ..... Edinburgh Postpartum Depression Scale
GRADE ..... Grading of Recommendations, Assessment, Development and Evaluations
NIH ..... National Institute of Health
PPD ..... Postpartum Depression

25(OH)D3 ..... Vitamin D

The Contribution of Abnormally Low Concentrations of Vitamin D During Pregnancy to Postpartum Depression

BACKGROUND

Postpartum depression is a common health occurrence with significant implications for both mother and baby. The disorder is characterized by labile emotions, tearfulness, changes in appetite, problems with sleep, poor focus and memory, fatigue, irritability, feelings of guilt, inadequacy and inability to take care of the infant.[17] It can lead to thoughts of suicide and rejection of the baby.

Additionally, postpartum depression has been linked with significant negative impacts on development of the child. Infants of mothers who suffered from postpartum depression have been shown to exhibit behavioral and emotional problems in early childhood.[4] Studies have also shown that children of mothers who were depressed postpartum also have attention and cognitive problems.[3]

The etiology of postpartum depression is not well understood due to many complicated factors that contribute to risk of experiencing depressive symptoms postpartum. However, some risk factors have been identified. Significant predictors of postpartum depression include experiencing depression or anxiety symptoms during pregnancy, past history of psychiatric illness, stressful life events including a difficult pregnancy or a stressful birthing experience and lack of adequate social support during pregnancy.[20] Additionally, deficiency in certain micro-nutrients have been identified as a risk factor.[21]

One such micro-nutrient that has been investigated as a risk factor for postpartum depression is vitamin D. During pregnancy, women are at increased risk of vitamin D deficiency.[7] Most of the vitamin D used by the body is obtained from sun exposure, but small amounts are also gleaned from dietary sources including fish, eggs and liver. Pregnant women may be particularly susceptible to vitamin D deficiency due to dietary and lifestyle changes but also increasing demands on the body created by the developing fetus.

Previous studies have shown that low levels of vitamin D are associated with mood disorders

and depression in the general population.[8] This systematic review is aimed at examining the possible link between low vitamin D levels during pregnancy and postpartum depression.

METHODS

An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL and Web of Science using the keywords: postpartum depression and vitamin D levels. The search was then narrowed to include only English language articles. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating vitamin D levels during pregnancy with subsequent diagnosis of postpartum depression were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).[19] A search on the National Institute of Health (NIH) clinical trials site revealed no currently registered trials, at any phase, relating to vitamin D levels during pregnancy and postpartum depression.

RESULTS

The initial result of the search yielded 33 articles for review. After screening relevant articles for primary data and human studies, a total of three articles met inclusion criteria. Two of these articles were case-control studies[14,16] and the third was a prospective cohort study.[9]

Gur et al

This prospective cohort study[9] originated from a community based study that was performed in Sifa University Bornova Health Research and Application Hospital in Izmir, Turkey. Blood samples were drawn and questionnaires were administered to 687 pregnant women, between 24 and 28 weeks pregnant, evaluating physical and socio-demographics; medical, psychiatric, gynecological and obstetric history; and lifestyle, diet and medication. The study group was created by eliminating women

that had risk factors for postpartum depression and by excluding unhealthy newborns as well as complicated labor and deliveries. Characteristics of the study group were: married, planned/desired pregnancy, body mass index (BMI) 20-30 kg/m^2, parity ≤3, educational level ≥8 years, annual income ≥US 4500, Caucasian ethnicity, 18-40 years of age, non-employed, non-smoker and non-alcohol drinker, unknown medical disease, unknown psychiatric disease, with a singular pregnancy and a native Turkish speaker. After exclusion criteria was applied 189 women were screened for postpartum depression one week after delivery, 184 women at six weeks and 179 at six months.[9]

Blood sample analysis was performed in a single laboratory, and 25(OH)D3 levels were analyzed by ELISA (EUROIMMUN, D-23,560 Lübeck, Seekamp 31, Germany). Serum 25(OH)D3 levels #20ng/mL (50nmol/L) were classified as vitamin D deficient. Vitamin D deficiencies were classified as follows: (a) Mild vitamin D deficiency: serum 25(OH)D3 concentration between 10 and 20 ng/mL (25–50 nmol/L) (b) Severe vitamin D deficiency: serum 25(OH)D3 concentration 10 ng/mL (25 nmol/L).[9]

Postpartum depression was screened for using a Turkish version of the Edinburgh Postpartum Depression Scale. The EPDS is a ten question screening tool used to measure the depressive symptoms of the mother during the last seven days. Scores range from 0-30 with the cut-off value of ≥12 used in primary care settings.[5] The EPDS was administered by a physician assistant.[9]

Of the 208 pregnant women included in the study, 11% were found to have severe vitamin D deficiency, 40.3% with mild deficiency, and 48.5% with normal vitamin D levels. There were 21.1% of the participants that were accepted as having PPD in the 1st week postpartum, 23.2% had PPD in the 6th week postpartum, and 23.7% had PPD in the 6th month postpartum.[9] Mean vitamin D levels were found to be significantly different between women with PPD and women without PPD at 1 week postpartum, 6 weeks postpartum, and 6 months postpartum ($p = 0.003, 0.004, <0.001$, respectively). Additionally, a significant correlation was found when comparing mean EPDS scores between women with low and

women with normal vitamin D levels at 1 week, 6 weeks, and 6 months postpartum ($p = 0.002$, <0.001, 0.001, respectively). Higher levels of postpartum depression symptoms at 1 week, 6 weeks, and 6 months postpartum were associated with lower maternal vitamin D levels in the second trimester of pregnancy.[9]

The authors found that one limitations of this study was a small sample size. Additionally, the authors discussed the need to evaluate vitamin D status throughout pregnancy to determine exactly when changes in the micro-nutrient status occur because seasonal change can effect amount of sun exposure in turn affecting vitamin D levels. Finally, the authors recognize the need for research on vitamin D supplementation and it's effect on PPD.[9]

Robinson et al

This case control study[16] included 2900 pregnant women that had been enrolled in the Western Australian Pregnancy Cohort (Raine) Study between May 1989 and November 1991 at King Edward Memorial Hospital in Western Australia. Exclusion criteria included: maternal body mass index (BMI), cigarette smoking and alcohol use, maternal age, education status, total family income as measured at 18 weeks gestation, hypertensive diseases of pregnancy, gender of the child, admission to the Special Care Nursery, proportion of optimal birth weight and season of birth. All women that participated were required to be Caucasian to eliminate any potential confounding due to the rate of vitamin D absorption.[16]

The blood samples that were used for analysis had been drawn when participants were at 18 weeks pregnancy during the period of the study and then stored. Samples were analyzed for 25(OH)-vitamin D levels in June 2011 using an enzyme immunoassay kit. Vitamin D levels were then stratified into quartiles. These quartiles were used to rank degree of deficiency, if any. The quartiles were: quartile 1 <47 nmol/L, quartile 2 47–58 nmol/L, quartile 3 59–70 nmol/L, and quartile 4 >70 nmol/L. Quartile 1 indicated vitamin D deficiency while quartiles 2-4 indicated normal or above normal vitamin

D levels.[16]

Postpartum depression was evaluated three days postpartum in 706 women using a six question version of the EPDS. The missing data resulted from women that had left the hospital prior to the 3 days postpartum when the questionnaire was administered. The authors indicate that on the full 10 point EPDS a score of >10 indicates postpartum depression. As such, the authors drew a correlation to the 6 question EPDS and assigned a value of >6 as indicating symptoms of PPD.[16]

A significant relationship was observed between increased experience of postnatal depressive symptoms and lower 25(OH)-vitamin D status (p=0.017) (see Table 2), with those who scored in the range to indicate possible postnatal mood disturbance more likely to be in the lowest quartile for 25(OH)-vitamin D. Women with the lowest vitamin D levels were more likely to report six or more depressive symptoms on the EPDS compared with women with the highest vitamin D levels (OR=2.19, 95 % CI=1.26, 3.78). Additionally, when compared with women with normal vitamin D levels, women in the lowest quartile were more likely to endorse symptoms of PPD (odds ratio (OR)=2.19, 95 % CI=1.26, 3.78).[16]

The authors of this study discussed limitations as being the lack of a physician to address symptoms of postpartum depression and also the use of the abbreviated EPDS. The authors also acknowledge that they did not have access to antenatal mental health information which can be a contributor to postpartum depressive symptoms. Information regarding sedentary lifestyle was not included in this study as it was not available. Sedentary lifestyle may also play a role in limiting ones absorption of vitamin D. Finally, the authors address that vitamin D levels were measured only at 18 weeks gestation. It is uncertain if vitamin D levels fluctuate during pregnancy. More studies are required to evaluate how vitamin D levels change during pregnancy and what effect it may have on PPD.[16]

Nielsen et al

This case-control study[14] compared serum OH(25)D3 vitamin D in both 605 women with PPD and 875 controls. The women had been previously enrolled in the Danish National Birth Cohort during the period of 1996-2002. To be eligible for inclusion in this study, the DNBC participant had to have 1)been born in Denmark; 2) had a singleton pregnancy; 3) delivered a living child; and 4) had blood collected late in pregnancy (ca. Week 25).[16] Women with anti-depressant use registered in the Danish Register of Medicinal Product Statistics in the year before delivery and women registered in the Central Psychiatric Register with mental illnesses prior to their DNBC pregnancy were excluded from the study.[14] Season and gestational week in which the vitamin D sample was taken, as well as maternal parity, smoking during pregnancy, socioeconomic status, pre-pregnancy BMI, physical activity during pregnancy, social support and multivitamin supplement use during pregnancy was factored into the final results.[16]

Blood samples were drawn between 10-12 weeks and at 25 weeks of pregnancy during routine prenatal care. It was then shipped at ambient temperature to Statens Serum Institut (Copenhagen, Denmark) where it was stored d at -80uC for 9-15 years before being thawed and analyzed for 25(OH)D3 and 25(OH)D2 by liquid chromatography-tandem mass spectrometry.[16]

Postpartum depression was defined as women who filled prescriptions for anti-depressive medications within one year after delivery but were not hospitalized for PPD. Women defined as not having PPD were women who neither filled prescriptions for anti-depressive medications in the year after delivery nor were hospitalized for PPD. Controls were randomly selected in such a way that the resulting pool of controls had the same distribution of maternal ages and delivery years as the group of women with PPD.[16]

Two models were utilized for statistical analysis. The first model adjusted only for maternal age and year of delivery. In this model, increased risks of PPD were observed for both low (ORs of 1.70 [95% confidence interval {CI}: 0.91; 3.16], 1.05 [95% CI: 0.70; 1.58] and 1.26 [95% CI: 0.98; 1.61]

for vitamin D concentrations < 15 nmol/L, 15–24 nmol/L and 25–49 nmol/L, respectively and high (ORs of 1.30 [95% CI: 0.93; 1.82] and 1.77 [95% CI: 1.07; 2.93] for vitamin D concentrations 80-99 nmol/L and ≥100 nmol/L, respectively) concentrations of vitamin D; however, overall, the effect of vitamin D concentration was not statistically significant (p=0.014).[14]

The second model adjusted for the effect on vitamin D by smoking, BMI and multivitamin supplementation. After adjusting for these potential confounders, (ORs of 1.35 [95% CI: 0.64; 2.85], 0.83 [95% CI: 0.50; 1.39] and 1.13 [95% CI: 0.84; 1.51] for low vitamin D concentrations, < 15 nmol/L, 15–24 nmol/L and 25–49 nmol/L, respectively, and ORs of 1.53 [95% CI: 1.04; 2.26] and 1.89 [95% CI: 1.06; 3.37] for high vitamin D concentrations, 80-99 nmol/L and ≥100 nmol/L, respectively). The overall effect of vitamin D level remained non-significant (p=0.08).[14]

Similar analysis was completed using the four categories of vitamin D that are customarily used (<25, 25–49, 50–79 and ≥80 nmol/L). After fully adjusting for the effect on vitamin D by smoking, BMI and multivitamin supplementation, ORs were 0.96 (95% CI: 0.61; 1.50), 1.13 (95% CI: 0.84; 1.51) and 1.62 (1.15; 2.30) for vitamin D levels < 25 nmol/L, 25-49 nmol/L and ≥ 80 nmol/L, respectively, compared with reference levels (50-79 nmol/L). The P-value for overall association was 0.04, substantiating the finding of higher vitamin D levels being associated with increased PPD risk.[14]

Based on these findings, the authors then further compared the risk of PPD between the women from the two highest categories of vitamin D concentrations (80-99 and ≥ 100 nmol/L) with women with normal vitamin D concentrations (50-79 nmol/L). They found that the risks of PPD were significantly different, regardless of the adjustment variables included (<15nmol/L p=0.04, 15-24nmol/L p=0.01, 25-49nmol/L p=0.02 and 50-79nmol/L p=0.02), suggesting that a dose-response relationship between vitamin D concentration and PPD risk exists within normal and high vitamin D concentrations.[14]

Discussion

While abnormally low vitamin D levels have been demonstrated to have an effect on general depressive symptoms, few studies have analyzed the link between low vitamin D status during pregnancy and subsequent postpartum depression symptoms.[6,10-13,15] The studies that have attempted have many limitations. Postpartum depression is a serious health concern with significant impact on both mother and baby.[7-8] Certain risk factors for postpartum depression are already well established, such as, previous history of behavioral disorders, abnormal BMI and cigarette use.[7,17]

This systematic review examined three studies,[9,14,16] that investigated a relationship between low serum vitamin D levels during pregnancy and postpartum depression. Two of these studies [9,16] demonstrated that low vitamin D levels during pregnancy correlated with postpartum depression. A third study found the opposite to be true, that in fact high vitamin D levels during pregnancy correlated with postpartum depression while low vitamin D levels during pregnancy demonstrated no correlation with postpartum depression. The studies were evaluated using the GRADE method and results can be seen in Table 1.

While the results of the study done by Nielsen et al[14] yielded contradictory findings compared to the studies done by Gur et al[9] and Robinson et al[16] there are several possible explanations for the inconsistencies. First of all, all three studies analyzed vitamin D levels collected at different time-points during pregnancy. Nielsen et al[14] sampled blood from 10-12 weeks pregnancy and also at 25 weeks. Gur et al[9] analyzed samples taken between 24-28 weeks and Robinson et al[16] analyzed samples taken at approximately 18 weeks. In neglecting to assess vitamin D levels throughout pregnancy, these studies assumed that vitamin D levels remained constant during pregnancy until the outcome of postpartum depressive symptoms was measured after birth.

Although the results of the Gur et al[9] study correlated with Robinson et al,[16] the Gur et al[9] study was limited by small sample size. Although p values were found to be significant between women with PPD and women without PPD at 1 week postpartum, 6 weeks postpartum, and 6 months postpartum (p

= 0.003, 0.004, <0.001, respectively), it is uncertain that these results would be replicable in a larger study population.[9]

A limitation of the Robinson et al[16] study is that the EPDS was measured at three days postpartum which assumes both that symptoms of PPD are evident at three days after birth and that no further outcomes could be measured beyond three days postpartum. While PPD symptoms generally first appear within six weeks postpartum[20] it is possible that at 3 days postpartum the symptoms the women were describing were perhaps more consistent with postpartum blues. Postpartum blues has very similar symptoms to PPD but onset is within a few days of childbirth and the duration of symptoms is much shorter.[20] Diagnostic criteria of PPD is that symptoms must be present for at least two weeks and interfere with daily functioning.[20] Nonetheless, it is likely that Robinson et al[16] in fact measured the potential for development of PPD because of the use of the EPDS but in order to be diagnostic of PPD, EPDS would need to be administered at multiple time-points after birth. Furthermore, Robinson et al[16] neglected to account for antenatal depressive symptoms which could confound results.

A significant limitation to the study by Nielsen et al[14] is that postpartum depression was defined as women who filled a prescription for anti-depressive medications within one year after delivery but were not hospitalized for PPD. Women defined as not having PPD were women who neither filled prescriptions for anti-depressive medications in the year after delivery nor were hospitalized for PPD. However, Gur et al[9] observed that the women who had an EPDS score greater than 12 did not apply for professional health support, and none of them used antidepressant drugs.[9] Additionally, since Nielsen et al[14] used no objective criteria, such as EPDS scores, they did not show a relationship between vitamin D levels and the severity of PPD.

Despite the limitations of these studies,[9,14,16] the question of PPD and vitamin D deficiency is still viable. It is already well established that vitamin D deficiency correlates with general

depression.[6,10-13,15] Vitamin D levels are easily measured with a serum sample. Vitamin D replacement is cost-effective and well tolerated by patients. Furthermore, the implications of postpartum depression are tremendous making it all the more worthwhile to further investigate and clarify the relationship of vitamin D and PPD.

Further study would need to be done on this topic in order to truly evaluate the effects of low vitamin D levels during pregnancy on postpartum depression. There are still several areas that could be improved on with further study. A larger, randomized control trial, that evaluated vitamin D levels throughout pregnancy and perhaps include antenatal, multiple perinatal and postnatal vitamin D levels for comparison would eliminate the limitation caused by lack of information regarding how vitamin D levels change during pregnancy and how that affects PPD risk. Additionally, the study would need to evaluate PPD using an objective tool such as the EPDS with follow-up throughout the first year postpartum. Finally, to further support the findings of the previously mentioned study, an additional study comparing the effects of vitamin D supplementation during pregnancy with incidence of postpartum depression could lead to more solid results.

Conclusion

The effects of low vitamin D levels on postpartum depression are unclear. The studies evaluated in this systematic review did not yield a definitive answer as to whether or not low vitamin D levels contribute to postpartum depression. Nonetheless, they did indicate a complex mechanism for the interplay of vitamin D levels during pregnancy and risk of postpartum depression. The implications that postpartum depression for the mother and baby are significant. Vitamin D has already been identified as a key factor in general depression. Vitamin D is easily measured, cost-effective and well tolerated. If such a simple explanation for PPD exists, further investigation of this topic is warranted.

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Table 1

Study	Design	Limitations	Inconsistencies	Indirectness	Imprecision	Publication Bias Likely	Quality
Gur et al[9]	Prospective Cohort Study	Not Serious	Not Serious	Not Serious	Serious[a]	No bias likely	Very low
Robinson et al[16]	Case-Control study	Serious[b]	Not Serious	Not Serious	Not Serious	No bias likely	Very low
Nielsen et al[14]	Case-Control study	Not Serious	Not Serious	Serious[c]	Not Serious	No bias likely	Very low

[a]Sample size was small consisting of only 209 participants
[b]No data regarding prior behavioral health history was considered when selecting participant and PPD was evaluated at 3 days postpartum
[c]PPD was assumed based on if participant filled a prescription for anti-depressants within one year of giving birth as opposed to using an evidence-based approach such as EPDS

Table 2 Robinson et al[16] Adjusted general linear model analysis showing effect of maternal serum 25(OH)-vitamin D levels on risk for postnatal depression symptoms

	Quartile 1 Regression coefficient b (95 % CI)	Quartile 2 Regression coefficient b (95 % CI)	Quartile 3 Regression coefficient b (95 % CI)	Quartile 4 Regression coefficient b (95 % CI)
Postnatal depressive symptoms (increasing symptoms)	0.93* (0.27, 1.58) 0.005	0.12 (-0.53, 0.77) 0.721	0.38 (-0.26, 1.03) 0.245	0.00 (ref)

Adjusted for pre-pregnancy body mass index, maternal age, maternal education, total family income, maternal smoking, maternal alcohol intake, hypertensive diseases of pregnancy, proportion of optimal birth weight, child gender, SCN admission and season of birth; Perth, Western Australia 1989-1992
CI 95 % confidence intervals
*$p<0.05$, significant