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A Review of the Association Between Vitamin D and Postpartum Depression

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Abstract:

Vitamin D (specifically vitamin D3) is a lipid soluble essential nutrient. It is found in few foods naturally but can be synthesized upon skin exposure to sunlight. Its intermediate structure in the blood is serum 25-hydroxyvitamin D, also called calcidiol, and is formed in the liver. Vitamin D receptors have been found in numerous areas of the brain that are involved in mood-related hormone production. It has also been found to be protective against the brain degradation of Alzheimer's. Numerous studies have found a significant relationship between vitamin D and major depressive disorder. This review summarizes research on the connection between vitamin D and postpartum depression. Research indicates that vitamin D is likely to be an influential factor in the development and/or severity of postpartum depression. However, more studies are needed to confirm the findings. Preventative screening for deficiencies and encouraging prenatal supplementation could be simple and effective ways to possibly protect from postpartum depression.

Introduction:

A number of studies have investigated the role and mechanism of various nutrients in the development of neurological diseases[1]. More recently, in an attempt to understand the complexity of mood disorders in postpartum women, studies have begun to research the role of diet in their development[2]. Specifically, regarding postpartum depression, some key risky exposures that have been identified include BMI, and personal history of pre-pregnancy and antenatal depression. According to the CDC, postpartum depression affects 1 in 9 mothers in the United States[3].

Vitamin D deficiencies have been found to be significantly correlated with depression, however there is little research regarding the biochemical mechanism[4]. Some studies have noted that vitamin D receptors are found in the areas of the brain that also produce key hormones and related enzymes important to neuroimmunomodulation, neurodevelopment, and overall brain function[4]. Other studies have found that vitamin D is protective against Alzheimer's disease and other neurodegenerative diseases[1]. The exact mechanism is still a significant area of research in the future.

Numerous other studies have found significant vitamin D deficiencies in pregnant women compared to nonpregnant women. [5]One possible reason for vitamin D deficiencies in pregnancy is proposed by Gur et al[6]: because the fetus gains its own vitamin D from the mother, umbilical cord blood vitamin D levels have been found to correlate well with maternal vitamin D. Also, Narchi et al[7] found in their longitudinal study on maternal vitamin D status that throughout pregnancy and lactation (postpartum) there is a steady decrease in serum vitamin D levels. In order to elucidate the complex mechanism of postpartum depression, this relationship has been investigated in recent years[8]. Because of the multifactorial nature of this disorder, numerous

demographic variables are considered potential confounders in the following studies. In this review, I aimed to include the most relevant methods and data points for analysis. Complete methodology and data analysis can be found in the cited sources.

Natural sources of vitamin D include exposure to sunshine and some foods, including fatty fish. Vitamin D from these sources must then be metabolized into calcidiol (25-OH-D) in the liver then to its active form, calcitriol, by the kidneys. The form of vitamin D referred to in this paper and all the following studies is specifically vitamin D3. According to the NIH, the recommended daily allowance (RDA) for vitamin D for women of childbearing-age (19-50 years) is 600IU/day. For pregnant and lactating women, it is also 600IU/day. Papers were included in this review if there was at least one measurement of depression post-delivery as well as a vitamin D measurement or supplemental intervention at any point during or after pregnancy. Papers were also limited to those available in English. A total of 15 studies were identified that fulfilled these requirements.

Although perinatal depression studies are included, in this review, the objective will be analyzing depression data taken after delivery.

Literature Review:

Abedi and colleauges[9] performed a cross-sectional study in Izeh, Iran, a city in the northeastern part of the country to analyze differences in 25-dihydroxy vitamin D (25-OH-D) serum levels in 120 postpartum women. Eligible participants were 18-35 years old and 6-8 weeks postpartum. 60 women with postpartum depression and 60 women without postpartum depression were selected. Participants were also matched to account for age and vitamin D supplementation. Depression was measured using the Beck Depression Scale[10], which included 21 questions and quantified results on a scale from 0 (no depression) to 3 (severe depression). Various demographics and patient histories were taken including breastfeeding, number of pregnancies, and mode of delivery. Venous blood was drawn for determining levels of 25-OH-D, and participants were then classified into groups according to serum levels. Normal was classified as 25-OH-D>30ng/ml, mild deficiency as 20-30ng/ml, moderate deficiency as 10-20ng/ml and severe deficiencies as <10ng/ml.

Participants with postpartum depression had a higher body mass index (BMI) than women without depression, though not significantly. No significant difference was found regarding mode of delivery, breastfeeding, abortion history, and number of pregnancies. A nonsignificant difference was found between sunlight exposure between the two groups: women with postpartum depression had less exposure (9 ± 13.01min/week) compared to women without depression (10.53 ± 13.86min/week). There was a significant difference in vitamin D levels between women with and without depression: women with depression had a mean vitamin D level of 16.89 ± 7.05ng/ml whereas women without depression had levels of 21.28 ± 7.13 (P=.001). The majority (53.3%) of women with postpartum depression were found to have a moderate vitamin D deficiency while the majority of women without postpartum depression

(50%) were found to have a mild deficiency. After odds ratio (OR) analysis, it was found that women with 25-OH-D<20ng/ml were 3.30 times more likely to report depression than women with D>20ng/ml. Women in good economic situations and whose last pregnancy was desired were less likely to be depressed (P= 0.054 and P=0.02, respectively).

A weakness of the study includes lack of longitudinal data for the participants. No data was gathered regarding the serum vitamin D levels or depression symptoms during pregnancy. The authors noted in their discussion that vitamin D deficiency has been found to be more prevalent in Iranian women. Based on their data, the authors concluded that women with a severe vitamin D deficiency were twice as likely to have postpartum depression within 6-8 weeks of giving birth. They recommend that testing vitamin D levels in pregnant women be a standard test in order to proactively prevent consequential postpartum depression.

In 2015 a prospective study was published by Accort et al[11] to determine whether prenatal serum 25-OH-D status was related to postpartum depression and if inflammatory cytokines during the prenatal period were involved in the development of postpartum depression. Secondary data were used from previous investigations by Cassidy-Bushrow et al[12,13] published in 2012. Eligible participants were 18-44 years old and in their second trimester of pregnancy. Participants with very morbid obesity were excluded (BMI>60kg/m^2)[14]. African American women were recruited from health centers in Detroit, Michigan who had had serum 25-OH-D levels measured in their first trimester. Serum vitamin D data were collected from patients' medical records. Inflammatory cytokines were measured from a blood draw during the second trimester. The inflammatory biomarkers assessed were high-sensitivity C-reactive protein (hs-CRP) as well as various interleukins: IL-1β, IL-6, IL-10, and TNF-α. Because levels for IL-1β and TNF-α were below the Limit of Detection (0.1mg/ml) in greater than 20% of the sample,

results for these two markers were not reported. CES-D (Center for Epidemiological Studies-Depression)[15] scores were gathered by Cassidy-Bushrow and colleagues during the antenatal period, and this data was used in the Accort et al study as a continuous variable for regression analyses. Various demographic characteristics were also measured. For postpartum depression scores, only participants who had a postpartum checkup in which depression screening occurred were included in the investigation by Accort et al Postpartum depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS)[16]. 91 African American women fit the eligibility criteria and were included in the analysis by Accort et al.

Participants' average age was 26 years old. The average BMI was 29.2, and the majority of women were overweight or obese (N=58). Histories of depression, hypertension, and preterm birth were low (7%, 9%, and 9%, respectively). The majority of participants were unmarried (75%), had a high school diploma (58%), and were currently employed (63%). Preterm birth (<37 weeks' gestation) occurred for 6 of the 91 women. A total of 85 women had been excluded because of a lack of postpartum EPDS scores. Their data was compared to the 91 women who were included in the study to assess differences in maternal age, 2nd trimester CES-D scores, preterm birth, vitamin D levels, and inflammatory cytokine levels. No significant differences were found in any of these measures (P>0.05). Regression analyses were performed in order to determine any relationships among vitamin D levels, inflammatory markers, and postpartum depression. In regression analyses adjusted for covariates, the log 25-OH-D levels were associated marginally with EPDS scores (P=0.058). However, in unadjusted analyses there was no significant association (P=0.172). There was no significant association found between any one inflammatory marker and postpartum depression. However, it was found that IL-6 and the IL-6/IL-10 ratio both significantly interacted with serum 25-OH-D levels and its association with

postpartum depression (P=0.025 and P=0.016, respectively). It was also found that in participants with higher Il-6/IL-10 ratios, more depression symptoms were reported. The authors also noted that their findings remained after controlling for prenatal depression from the CES-D scores. Although, only a marginally significant association was found between serum vitamin D levels and postpartum EPDS scores (P=0.058), the authors concluded that women with higher inflammatory cytokine levels (IL-6 and IL-6/IL-10 ratio) as well as low vitamin D levels reported greater postpartum depression symptomology. The authors suggest that the higher cytokine levels could be penetrating areas of the brain affecting neurotransmitters in mom and leading to depressive symptoms in the future. One strength of the study was the analysis of women both prenatal and postpartum. However, the authors note that in general, African Americans have been found to have higher risk of vitamin D deficiency and inflammation, limiting the applicability of the findings. The authors suggest similar studies specifically analyzing synergistic interactions among vitamin D, inflammatory markers and postpartum depression in a larger sample.

Fu et al[17] conducted a study in China that analyzed correlations between postpartum serum 25-OH-D levels and prevalence of postpartum depression in 213 Chinese women. The duration of the study was from August of 2013 to November 2013 in a hospital in Beijing, China. Eligible participants were women who had given birth at full term (≥37 weeks' gestation), to a single, live-born infant. Participants were excluded if they had any history of psychiatric care during pregnancy, confidential personal information, or whose infant was admitted to the neonatal intensive care unit directly after delivery. Fasting blood samples were collected from the mothers before they left the hospital but after some recovery time: 24-48 hours after birth.

Three months later, the women returned for a postpartum check-up which included a Chinese version of the EPDS. Various baseline characteristics were also collected at enrollment.

The median age of the sample was 31 years. The majority of participants were considered middle class (55.9%). Women were not excluded based on mode of delivery – 60.6% of participants had a vaginal delivery. Depression occurred before or during pregnancy for 5.6% of the participants. The ethnicity of 91.1 percent of the participants was Han Chinese. Other data collected included breastfeeding rate, stressful life events, whether the pregnancy was planned, and partner support. It was found that 82.6% of the participants were vitamin D deficient, categorized as <20ng/ml. The median serum 25-OH-D level was 13.8ng/ml and no significant difference was found in samples taken in different months. A weak negative correlation was found between serum vitamin D levels and postpartum symptomology ($r=-0.293$, $P<0.0001$). After adjusting for confounding variables such as breastfeeding, stress, partner support and others, the association using linear regression was still significant. Of these, depression before or during pregnancy, stressful life events, and decreased partner support were found to be predictors of postpartum depression. 25-OH-D levels showed a strong association with EPDS scores with an unadjusted odds ratio of 0.74. An increased risk of postpartum depression symptomology was associated with vitamin D levels ≤10.2ng/ml in multivariate analysis after adjusting for all confounders. One noted weakness of this study included the single blood sample for vitamin D analysis. The authors stated it would be helpful to observe changes in vitamin D levels from prenatal to a few months postpartum.

Another postpartum blood and depression study was performed by Gould et al[18] and published in 2015. For this study cord blood 25-OH-D levels were analyzed immediately postpartum for possible association with postpartum depression. The data for this study was

collected from a previous randomized control trial in 2010 studying the effects of omega-3 fatty acid DHA supplementation on postpartum depression by Makrides et al[19] Eligible participants were recruited at less than 21 weeks' gestation for singleton pregnancies. Exclusion criteria included not having a cord blood vitamin D analysis done, giving birth at <20 weeks' gestation, already taking DHA supplementation or participating in another fatty acid study, and having previous history of drug or alcohol abuse. Women were randomly assigned to the treatment or placebo group. Those in the treatment group were told to take three 500mg/day DHA-rich fish-oil supplements. The control group was told to take three 500mg/day capsules of vegetable oil. The authors stated that there was no vitamin D in the fish-oil or vegetable oil capsules.[18] Supplementation was done from day of entry until day of delivery. On the day of delivery, cord blood samples were taken and analyzed for levels of serum vitamin D. Depression screening was performed through administration of the EPDS at two time points: six weeks and six months postpartum.

Demographics were collected as well as possible confounders including maternal age, race, parity, BMI, history of depression, and supplement use during pregnancy. Cord blood samples were collected from 1040 women. The majority of both the DHA treatment group and control group had 25-OH-D levels of >50nmol/L. Other levels of vitamin D were <25nmol/L and 25-50nmol/L. The authors stated that these could not be used to determine maternal vitamin D sufficiency or insufficiency due to the fact that cord blood vitamin D is generally lower than maternal blood. Demographic and lifestyle characteristics were taken from all of the participants so there remain significant holes in the collected data. At least 24.5% of women were taking dietary supplements at baseline. Seasonal changes in potential vitamin D exposure were accounted for before analysis. Overall, there was no significant association between cord blood

vitamin D and postpartum depression at six weeks or six months (P=0.11 and P=0.41, respectively). Treatment group did not affect these findings. However, women in the control group at six weeks postpartum were less likely to report depression symptoms if their serum vitamin D levels at delivery were >50nmol/L compared to control participants with vitamin D<25nmol/L (P<0.001). The authors concluded that evidence was inconsistent concerning the mediation of postpartum depression by vitamin D levels at delivery. One weakness of the study is the lack of control on external dietary supplementation by the participants. Because this study was a secondary analysis, that data was not available, and the possibility of alternative vitamin D supplementation before, during, or after delivery remains a confounder. Another weakness is the incomplete demographic and lifestyle data gathered at baseline. One major strength of this study, however, is the large sample size.

Gur and colleagues[6] published a study out of Sifa University in Turkey investigating the association between vitamin D levels during mid-pregnancy and postpartum depression. Participants were pregnant women at 24-28 weeks' gestation from a hospital in Izmi, Turkey. Inclusion criteria were relatively strict. Eligible participants were married, Caucasian women of 18-40 years old with a desired or planned singleton pregnancy. They also were of BMI 20-30kg/m^2, had 8 or more years of education, of parity of ≤3, receiving an annual income of ≥$4500 USD, nonsmokers, nondrinkers, without an unknown psychiatric or medical disease, and a native Turkish speaker. The purpose of these criteria were to exclude participants prone to postpartum as established by previous investigations [20-21]. 208 women were enrolled in the study, and blood samples were collected, and serum 25-OH-D levels were determined. After giving birth, 19 women were excluded from the study due to various complications with the delivery.

179 women completed the study through final data collection. To measure depression symptomology, participants completed the EPDS at 1 week, 6 weeks and 6 months postpartum.

Demographic statistics were calculated from the 208 enrolled women. The mean age was 28.5 years and the mean BMI was 26.5 for this group. The mean gestation age of vitamin D sampling was 25.2 weeks. The majority of participants were taking vitamin D supplements of 400IU/day (84.6%) and 7.6% of participants were taking 1200IU/day regularly (≥3 times per week). The remaining 7.6% did not report taking any vitamin D supplements. It was found that 11% of the women had a severe vitamin D deficiency (≤10ng/ml), 40.3% had a mild deficiency (10-20ng/ml), and 48.5% showed normal levels of serum vitamin D (≥20ng/ml). One week after delivery, 21.1% of women were defined as EPDS ≥12. At six weeks' postpartum 23.2% had postpartum depression, and at 6 months 23.7% had postpartum depression. At each of the three EPDS screening time points, a significant negative correlation was found between serum 25-OH-D levels and EPDS scores (r= -0.2, -0.2, -0.3, respectively). There was also a significant difference found in mean vitamin D levels between women with and without postpartum depression at all time points (P=0.003, 0.004, <0.001, respectively). The difference in mean EPDS scores between women with normal vitamin D levels and severe or mild deficiencies was also significant at all time points (P=0.002, <0.001, 0.001, respectively). The authors concluded that low maternal vitamin D status at mid-pregnancy was associated with prevalence of postpartum depression at 1 week, 6 weeks and 6 months postpartum in this study. Secondary conclusions included determining that vitamin D deficiencies were prevalent in a large portion of the sampled population, even as analyses were performed during summer and autumn. It was also noted that some significant weaknesses of the study include its small sample size, lack of vitamin D level analyses throughout pregnancy, and lack of moderation of results due to serum

sampling during the summer and autumn seasons. Upon review of this study, I had wished to see a baseline depression score taken antenatal. Though this would have added more complexity to the data, it would have given insight into its association with postpartum depression. Although women with psychiatric diseases were excluded, depression is considered a disorder, not a disease.[22] Moderating for this affect would effectively manage this possible confounder.

Lamb and colleagues[23] conducted a cohort study on the association between vitamin D deficiency and depression in the perinatal period. Similar to the study by Gould et al [18], blood 25-OH-D levels were determined from samples of cord blood. However, maternal blood vitamin D levels were also collected in order to analyze relationships between these two blood sources and maternal depression. Participants were recruited from a hospital in California where they were receiving prenatal care. Eligible participants were pregnant women at <25 weeks' gestation and at least 18 years old. Exclusion criteria were defined by the following: 1) parathyroid disease, 2) uncontrolled thyroid disease, and 3) severe mental illness other than depression. 125 of enrolled women completed the study through data collection. Data was collected at three time points. In early pregnancy (mean=14 weeks estimated gestational age (EGA)), women self-reported demographic information, took the EPDS, and provided a blood sample for serum vitamin D analysis. Delivery was timepoint 2 (T2); women took the EPDS, gave maternal blood, and had a cord blood sample taken. Timepoint 3 was on average 10 weeks postpartum. Women took the EPDS again and gave another maternal blood sample. Along with demographics, women reported if their pregnancy was planned and any current medications or supplements.

Depression was defined as an EPDS score of ≥15 and blood 25-OH-D deficiency was defined as <20ng/ml. Mean age of participants was 33.2 years and mean BMI was 26.6kg/m^2. 21.6% of women had vitamin D deficiencies at baseline, and the majority were married or living

with a partner (95.2%). 73.6% of their pregnancies were planned, and the mean EGA at time of birth was 37.7 weeks. Family history of depression was reported by 20% of participants and personal history of depression of the mother was reported by 8.8%. Vitamin D supplementation was taken by 9.6% of participants and their mean dosage was 508.3IU/day; there was an increase (7.4ng/ml) in serum vitamin D levels between T1 and T2 in these women compared to the whole sample. Differences in EPDS scores among all time points were not significant (P=0.19). Serum vitamin D levels at T1 and EPDS at T3 (postpartum) were correlated with a coefficient of -0.23 (P<0.05). There was no significant correlation between EPDS T3 and vitamin D at T2. Vitamin D T3 and EPDS T3 were significantly correlated with a coefficient of -0.22 (P<0.05). Lamb et al concluded from their investigation that vitamin D demonstrates a significant inverse relationship with antenatal and postnatal depression. However, they were not able to draw conclusions on the direction of the association. One weakness in the data was the lack of control for family depression history and personal depression history as a confounder for postpartum depression scoring. The authors did control for family depression history only for the relationship between baseline EPDS and baseline vitamin D.

In 2013, Leung et al published a study out if the University of Calgary studying the association between micronutrient supplementation and postpartum depression. This cohort study collected information on the current supplementation habits of 600 pregnant women. These participants then took the EPDS at least twice during pregnancy and 12 weeks postpartum. Participants were taken as a sample from the APrON (Alberta Pregnancy Outcomes and Nutrition) study which was going on concurrently. Eligible women were at least 16 years old at ≤27 weeks' gestation. Women were excluded if they did not speak English, were a known drug or alcohol abuser, or were planning to move to a difference region within 6 months of screening.

At enrollment, women completed demographic and lifestyle characteristics. Women provided information on their current supplementation habits (frequency and dose) 2-3 times during pregnancy.

The supplements analyzed were limited to vitamins, minerals, and fatty acids; data was taken on a broader category which included herbal products, amino acids, homeopathic remedies, and traditional medicines, overall referred to as natural health products (NHP). Data was taken on 475 women who completed all data collection points. Depression was determined as an EPDS score of ≥10. Demographic characteristics were associated with the EPDS scores of <10 or ≥10 at their postpartum screening. The mean age of women with EPDS<10 was 31.2 and for those with EPDS≥10, mean BMI was 31.6 with no significant difference between the groups. Mean BMI for women with and without postpartum depression were 24.1 and 24.2, respectively with no significant difference. The mean vitamin D supplementation taken by women without postpartum depression was 618IU/day and the mean for women with postpartum depression was 567IU/day (P=0.48). Of women who were taking below the Recommended Dietary Allowance of vitamin D, 12.3% had postpartum depression. RDA values were taken from the Institute of Medicine[24]. Vitamin D levels were not found to be a predictor for postpartum depression (OR=1.00, P=0.92). The authors concluded that patients consuming vitamin D at less than the RDA were more likely to have EPDS≥10 postpartum. However, it was not found to be a significant predictor of postpartum depression. One limitation was reliance on recall and self-reporting of supplement use by the participants. Another major limitation identified in the study was the lack of serum concentration data for any of the nutrients studied. Therefore, the authors were unable to relate supplementation to biological vitamin D levels. Overall, the data does not show that vitamin D supplementation is a predictor of postpartum depression.

Another study investigating nutritional status and postpartum depression symptoms was performed by Lin and colleagues[25], specifically on its association with postpartum nutritional status. Participants were women at a Taiwanese hospital who returned for a postpartum checkup from 6-8 after delivery. Recruitment occurred from January of 2016 to September 2017. Women were excluded for smoking, drinking alcohol, preterm delivery, mental disorder diagnosis (including depression), acute infection, congenital diseases, parity greater than 1, and if the infant born had any diseases. At the postpartum checkup, participants took the Chinese version of the EPDS. Scores ≥10 were defined as present postpartum depression. Various demographic and lifestyle characteristics were also taken at this timepoint. These included traditional postpartum confinement and breastfeeding status. Nutritional levels were determined form a venous blood sample taken at the postpartum checkup.

A total of 120 participants completed all data collection. Postpartum depression was present in 80.8% of the sample. The mean age of this group was 32.6 and the mean BMI postpartum was 23.4. For the group without confirmed postpartum depression, the mean age was 31.6 and mean BMI was 21.5. There were no significant differences in any of these variables between the two groups. Significant differences were found between these two groups regarding lack of family support, lack of husband support, financial stability, psychological stress, and postpartum care satisfaction. Nutritional biomarkers analyzed included hemoglobin, ferritin, vitamin D (25-OH-D), and riboflavin. Mean vitamin D levels in the non-postpartum depression group was 24.0ng/ml and for the postpartum depression 26.3ng/ml. There was no significant difference in vitamin D between these two groups (0.197). Correlations between nutritional metrics and EPDS scores were also done with and without adjustment for covariates. Covariates included postpartum confinement, psychological stress, and postpartum care satisfaction. There

were no significant relationships found between prevalence of postpartum depression symptomology and serum 25-OH-D levels without or with adjustment (P=0.198 and P=0.352, respectively). Though the authors found that there was a high prevalence of vitamin D insufficiency and deficiency in their sample, there was no evidence of an association with postpartum depression. Some key weaknesses identified by the authors was the lack of longitudinal data, specifically on vitamin D levels and small sample size.

Murphy et al[26] performed a prospective cohort study analyzing the correlation between serum 25-OH-D levels and concurrent postpartum depression symptomology in women who were a part of a larger cohort study involving vitamin D supplementation. Women completed demographic questionnaires, the EPDS, and gave a sample of venous blood once a month for the first seven months after delivery. Eligible women were 18-45 years old and participating in a concurrent study at Medical University of South Carolina. They delivered at least 35 weeks' gestation and were 4-6 weeks postpartum at first visit. Women were excluded if their deliver was not a singleton, had existing diabetes, hypertension, parathyroid or uncontrolled thyroid diseases. EPDS scores of <9 defined an absence of postpartum depression. A score of ≥9 was used to define postpartum depression. Demographic information included infant feeding method, season of the visit, and marital status. Vitamin D status was defined as deficiency, insufficiency, and sufficiency (<20ng/ml, 20-32ng/ml, and >32ng/ml, respectively).

Data was collected on 97 participants, all of whom were found to be taking vitamin D supplements of at least 800IU/day. Statistical analysis was adjusted for demographic and clinical characteristics that could be confounders. Women with sufficient vitamin D were more often married, more educated and had a planned pregnancy that those with insufficient vitamin D levels at baseline. Adjusted EPDS scores were significantly lower for the group with sufficient

vitamin D levels than those without (P=0.02). Unadjusted EPDS scores maintained this relationship over all seven timepoints. There was also a significant negative relationship between EPDS scores and being unmarried. Significant positive relationships existed between EPDS scores and breast-feeding. The authors concluded that vitamin D deficiency or insufficiency postpartum is a potential risk factor for women developing postpartum depression. The authors noted that routine screening for vitamin D levels could not be recommended until a similar study was performed with a larger sample and yielded similar results. One noted strength of the study is the longitudinal tracking of vitamin D levels and postpartum depression trends over time for mothers. One weakness that I observed in this study was the lack of control for women who had family or personal histories of depression.

In 2013, Nielsen et al[27] published a study on the relationship between vitamin D status during pregnancy and rates of postpartum depression. This was a case-control study nested in the Danish National Birth Cohort study. Serum 25-OH-D levels were measured in late pregnancy and correlated with postpartum depression. Women were recruited between 1996 and 2002. Eligible participants were Denmark-born, had a singleton, live birth, and had given a blood sample in late pregnancy (~25 weeks' gestation). Women in the case group had filled a prescription for anti-depressant medication within one year of delivery but were never hospitalized for postpartum depression. Eligible women for the control group were selected randomly from this same sample in such a way as to represent the maternal age and delivery year distribution of the case group. Women were excluded if they had ever been diagnosed and recorded has having any mental illness before pregnancy or using antidepressants within a year before delivery. Confounders that were identified included BMI, social support, smoking, multivitamin use during pregnancy, and socioeconomic status (SES). Vitamin D levels were

identified in six levels of nmol/L: <15, 15-24, 25-49, 50-79, 80-99, and >100. Odds ratios were calculated for differences in the number of women with a particular vitamin D concentration between cases and controls.

Data was collected from 605 women in the case group and 875 women in the control group. Odds ratios between confounding variables were calculated in order to discover any significant differences in these factors between the 2 groups. There were significant differences found regarding social support, parity, SES, and smoking status during pregnancy. The median vitamin D status for the whole sample was found to be 55.62nmol/L. This is within the sufficient range according to the Danish National Board of Health (50-79nmol/L). Odds ratios were calculated with various adjustments for confounders. When only adjusted for maternal age and year of delivery, no significant difference was found between the two groups. However, when adjusted for further variables (+season, gestation week, parity; +smoking, SES, BMI, physical activity, social support; +multivitamin supplementation) significant differences were found (P=0.03, 0.08, and 0.08, respectively). The authors noted that vitamin D binding protein may have played a role in these results as it affects the availability of serum 25-OH-D. Controlling for this variable is noted as a point of further study. A main strength in the procedures of this study identified by the authors was the biological measurement of vitamin D levels as opposed to recording supplementation, in which it is difficult to control for food intake. Another strength is the large sample. However, the lack of a controlled determination of depression is a limitation because of potential for inaccurate diagnoses. Also, women could have experienced postpartum depression but never sought a medical consultation or filled in a prescription.

Paoletti and colleagues [28] performed a study in Italy that administered supplements for postpartum women in a randomized controlled trial. The goal of this study was to determine the

efficacy of the supplement Elevit® on mood in postpartum women. Postpartum women who recently had their first full-term delivery (within 3 days) were eligible to participate. Eligible women were 20-40 years old, BMI between 22-26kg/m^2, had a spontaneous delivery at 37-41 weeks' gestation to a healthy baby (determined as an Apgar score 9-10 within 5 minutes). Low hemoglobin levels, delivery by Cesarean section, and personal or familial history of or current psychiatric or mental illness were some exclusion criteria. At the first visit (3 days after delivery), women were enrolled, completed the EPDS, gave a venous blood sample, and were randomly assigned to a treatment group. The first group (defined as group A) was given a treatment regimen of daily oral tablets of Elevit®, the second group (group B) received a tablet of Orotre®, a vitamin D and calcium supplementation of 400IU and 500mg, respectively. The second visit was approximately 15 days after delivery and the final visit was 30 days after delivery. At each follow-up visit, a blood sample was taken, and women completed the EPDS. An EPDS score of greater than 12 indicated significant depressive symptoms. The blood samples were analyzed for hemoglobin, iron, and ferritin levels.

Five hundred and fifty-two women completed the study through the third follow-up visit: 274 in group A and 278 in group B. The mean BMI for group A and group B at baseline were 23.9 and 24.0, respectively. At baseline, 85.7% of participants had EPDS scores<12. There was no significant difference in EPDS scores between the two groups at this first timepoint. There was a significant decrease in EPDS scores in both groups (regardless of baseline EPDS score) for both groups. However, the decrease was significantly larger for group A ($P<0.05$). Elevit®, administered to group A, contains vitamins A, B1, B2, B6, B12, C, D (500IU), and E as well as biotin, folic acid, and various minerals. Compared to Orotre®, Elevit® contains 100IU more in each dose. One weakness of the study is the lack to data on serum vitamin levels to determine the

biological effects each supplement. With this data, a correlation between vitamin levels and EPDS scores could be calculated. This study is still valuable as it is one of the few randomized control trials to include vitamin D interventions and postpartum depression measurements.

Robinson and colleagues [29] performed a correlational study in Australia with a subset of women enrolled in the Western Australian Pregnancy Cohort (Raine) Study[30]. Venous sera measurements of 25-OH-D were taken antenatal (around 18 weeks' gestation) and demographic characteristics were recorded. At three days post-delivery, participants took a variation of the EPDS. Eligible women were at 18 weeks' gestation and Caucasian. Full enrollment details were not cited in the study by Robinson et al[29], they can be found in the work by Newman et al[31] (1993). An EPDS score of ≥10 was determined to indicate possible mood disturbances.

Sera were collected from 796 women, and postpartum depression symptomology data also collected for 706 women. No specific demographic data is given in the study for the sample. However, the authors did adjust analyses for a number of characteristics including BMI, smoking, alcohol use, season of birth, and maternal age. There was a significant relationship found between postpartum depression symptoms and low vitamin D levels (P=0.017). Smoking during pregnancy was also found to be correlated with low vitamin D levels (no P-value given). Women with a vitamin D concentration of <47nmol/L were significantly more likely to develop postpartum depression symptoms than women with vitamin D >70nmol/L (OR=2.19). One weakness of this study is the lack of reporting on demographic characteristics. This prevents the possibility of secondary analysis on the given confounding variables. Another weakness is the single assessment of postpartum depression as opposed to multiple measurements over a longer period of time. However, the adjustment of the many confounding variables strengthens the

findings. Although requiring participants to be Caucasian controlled for melanin and vitamin D skin absorption, it also made the findings less generalizable.

Rouhi et al published a double-blind, randomized, controlled clinical trial in 2018 that analyzes the effect of vitamin D supplementation on postpartum depression in Iranian women. Participants were recruited at approximately 4 months' postpartum. Some inclusion criteria were vaginal birth, no history of psychiatric disorders, and breastfeeding. Women then took the EPDS and Fatigue Identification Form (FIF). Participants were randomly assigned to a treatment or placebo group if they had EPDS≥13 and FIF≥20. The treatment group received pills of 1000IU vitamin D and the control group was given similar placebo pills. All participants were assigned to take one pill daily for the next 6 months. Participants were also told not to take any outside supplements during this time period. Six months later (10 months' postpartum), participants took the EPDS again.

Eighty women completed the study through final assessments. There were no significant differences in demographic characteristics between the two groups at baseline (age, rate of vaginal delivery, unplanned or complicated pregnancy, marital problems, and obesity). The mean age was 24.7. There was also no significant difference in EPDS scores between the two groups at baseline ($P=0.484$). The treatment group showed significant decreases in depression compared to the placebo group ($P<0.001$). Some other predictive factors that were not addressed include family and social support, lifestyle, and parity. One weakness of the study is the lack of blood sampling for vitamin D deficiency measurements. It was also a relatively small trial. The participants were also selected by convenience sample at certain health centers. Although no significant differences were found in demographic characteristics, these values were not reported in the study.

Vaziri and colleagues [32] performed a single-blind randomized clinical trial in Iran to assess the effect of vitamin D supplementation on perinatal depression. Eligible participants were pregnant women 18 years' or older with no history of mental illness. They were also 26-28 weeks' gestation and scored 0-13 on a baseline EPDS assessment. After enrollment, participants were randomly assigned to either the treatment or placebo group. Each group received pills to take daily until childbirth. The treatment group received supplements of 2000IU/day of vitamin D. Serum 25-OH-D levels were measured at two timepoints: baseline and childbirth. Depression was assessed with the EPDS at baseline, 38-40 weeks' gestation, and 4-8 week's postpartum. 136 women completed the study through final timepoints.

There was no significant difference between the two groups at baseline in age, education, parity, or sun exposure. However, there was a significant difference at baseline in use of other supplement and whether the pregnancy was planned. (P=0.017, and 0.01, respectively). The mean baseline vitamin D levels was 12.35ng/ml. Vitamin D deficiency was defined as <20ng/ml and was found in 87.6% of participants at baseline. There was no significant difference in vitamin D levels between the two groups at baseline. The difference in mean depression scores was not significant different between participants with vitamin D <20ng/ml and those with vitamin D≥20ng/ml. A significant difference was found between those with vitamin D deficiency and sufficiency in sun exposure at baseline (P=<0.001). At delivery, a significant difference in vitamin D levels was found (P=0.001). At 38-40 weeks' gestation there was a significant difference of P=0.01 found between the treatment and control group in depression scores. Depression scores were also significantly different between the two groups at 4 weeks and 8 weeks postpartum (P=<0.001 for both). No correlation was found between change in vitamin D concentrations and change in depression scores at 380 40 week's gestation or 4 and 8 weeks

postpartum. Overall, this is a valuable clinical trial because of the controlled nature. It is also strong because of the simultaneous intervention as well as measuring blood vitamin D levels at multiple timepoints including antenatal. The major weakness of the study is the small sample size.

Williams et al[33] performed a secondary analysis of a randomized clinical trial (Mozurkewich, 2011[34]) that assessed the effect of omega-3 and fatty acids on depression in pregnant women. Participants were recruited from October 2008 to May 2011 in Michigan. Eligible women were pregnant and at risk for depression (past history of depression, postpartum depression or EPDS score 9-19). Participants were also ≤18 years old, in a singleton pregnancy of 12-20 EGA. Participants were excluded for reasons including current major depressive disorder, bipolar disorder, and taking antidepressant medication. Enrolled women were randomly assigned to either one of two fish oil supplement groups or a placebo group. The Beck Depression Inventory (BDI) was used along with Mini International Neuropsychiatric Interview (MINI)[35] to assess depression at baseline, 26-28 weeks EGA, 34-36 weeks EGA, and 6-8 weeks postpartum. Vitamin D levels in the blood were also taken at baseline and 34-36 weeks' gestation. In the relevant study by Williams et al, vitamin D levels and BDI scores were analyzed to find correlations. Low vitamin D was defined as <20ng/ml. For the secondary analysis, the sample was separated into those with low vitamin D (<20ng/ml) and the rest of the group.

One hundred and five participants completed the whole study of the 126 that were enrolled. Full demographic information is located in the parent study.[34] The sample was 81.3% white and the mean vitamin D level at baseline was 28.17ng/ml. There was a significant correlation between vitamin D levels at 12-20 weeks' and 34-36 weeks' gestation (Pearson's $p=0.60$, $P<0.001$). Those with low vitamin D were significantly younger ($P=0.03$). There was no

other significant difference found between these two groups at baseline. Vitamin D at 12-20 weeks was significantly predictive of BDI scores at 12-20 weeks' and 34-36 weeks' gestation ($P<0.05$). Vitamin D levels at 34-36 week's gestation did not predict participants' BDI at the same time point. However, there was no association between low vitamin D and postpartum BDI in regression analyses and adjusting for confounding factors such as age, antidepressant use, and BMI did not affect those results. Major depressive disorder was not associated with vitamin D levels at any time point. Overall, the authors concluded that low vitamin D in early pregnancy is predictive of more depressive symptomology in pregnancy but not postpartum. The strengths of this study include its design as a prospective, longitudinal design, as well as measurement of vitamin D levels at multiple time points. The other main strength is the diagnosis of depression at all assessments through the MINI. However, the sample size is relatively small and the BDI was used instead of the EPDS which is intended for pregnant and postpartum women. These strengths and limitations are all identified in by the authors.

Discussion:

Significant results pointing to a relationship between vitamin D and postpartum depression are present in nearly all the analyzed studies. One key factor that should be considered in the future is the effect of prenatal depression on postpartum depression. Though there are a few studies that elucidate this relationship, more are needed. IF the relationship remains confirmed, there is a need for future postpartum depression studies to include data on antenatal depressive symptoms. Most of these studies controlled for histories of depression by excluding participants with personal history, familial history, current depression, or even multiple risk factors. This relationship would suggest that vitamin D status be tracked throughout pregnancy and potentially even before pregnancy. Most studies identified the inefficiency of routine screening for vitamin D insufficiency in pregnant women and recommended it be instated[6]. From this review, such an action is supported as a preventative measure for both the mother's and baby's subsequent health.

Depression measures used in these studies were EPDS[16], CES-D[15], BDI[10], and MINI[35]. The majority used EPDS because it pertains specifically to postpartum women. However, the EPDS, CES-D and BDI questionnaires are not diagnostic tests for major depressive disorder as they are only self-reporting. In person interviews with a trained clinician, like the MINI, are required for a formal diagnosis. Only one study in this review included the MINI in its depression assessments (Williams et al, 2016[33]). More studies employing formal diagnostic procedures would strengthen the findings on this relationship. Another limitation of the data from the measures is the differing cutoffs of scores from depression measures. Most studies in this review used the EPDS to identify depressive symptomology, however the cutoff for data analysis differed across studies. The range of cutoffs for the EPDS was from 9-13.

All of the studies measured vitamin D (specifically vitamin D3) in its form 25-OH-D. Most studies controlled or adjusted for the season of pregnancy/birth because of its effect on vitamin D from sun exposure. In other studies, the recruitment period is included. These studies were performed in a wide variety of locations across the globe. Because of this, each of their findings is minimally generalizable to other ethnicities. However, because significant positive results have been found from multiple locations, they confirm each other. More studies are needed that include a diversity of ethnicities, specifically melanin levels, in order to systematically control for its effect on sun-sourced vitamin D while maintaining generalizability of findings. A few studies took place in the Middle East.[9,6,36,32] Most noted that women generally have lower vitamin D levels compared to other regions of the world.[37] One proposed reason is that culture in the Middle East has women's skin covered throughout the year possibly preventing reception of vitamin D from the sun. Studies that specifically investigate the reason for this disparity would be critical for determining effective treatment for this population.

Conclusion:

Fifteen studies were identified that assessed postpartum depression at least once and measured or intervened with vitamin D supplementation. Ten out of these studies found a significant positive result indicating an effect of vitamin D levels or supplementation on postpartum depression symptoms. This was with or without adjustment for confounding factors. All 3 randomized control trials found positive results on the effect of the intervention. From the following studies, it is concluded that vitamin D is a likely factor in the severity and presence of postpartum depression. This review combined a number of different study types in order to include all studies that investigated the relationship between vitamin D and postpartum depression. Before more randomized control trials are performed for potential treatments, more correlational studies with ethnically diverse samples and large sample sizes are needed to confirm this relationship. Studies that use interviews like Williams et al[33] and diagnose the presence of depression are necessary to strengthen the results of assessments.

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