Vitamin D deficiency and depressive symptoms in pregnancy are associated with adverse perinatal outcomes

Eynav Elgavish Accortt, Amy Lamb, James Mirocha & Calvin J. Hobel

Journal of Behavioral Medicine

ISSN 0160-7715

J Behav Med
DOI 10.1007/s10865-018-9924-9

Springer

J Behav Med
https://doi.org/10.1007/s10865-018-9924-9

Vitamin D deficiency and depressive symptoms in pregnancy are associated with adverse perinatal outcomes

Eynav Elgavish Accortt[1] · Amy Lamb[1] · James Mirocha[2] · Calvin J. Hobel[1]

Received: September 29, 2017 / Accepted: April 11, 2018

Abstract Prenatal vitamin D deficiency and prenatal depression are both separately associated with adverse perinatal outcomes; however, to our knowledge no studies have investigated the effects of having both risk factors. Our objective was to determine to what extent vitamin D deficiency predicts adverse perinatal outcomes and whether elevated depressive symptoms in pregnancy places women at additional increased risk. This study was a secondary data analysis of prospective data collected from a cohort of pregnant women (N = 101) in an obstetric clinic of a large medical center. Maternal vitamin D deficiency (serum 25(OH)D $\leq$ 20 ng/ml) and depressive symptoms (Edinburgh Postnatal Depression Scale, EPDS) were assessed in early pregnancy. A composite of four adverse perinatal outcomes (low birth weight, preterm birth, small-for-gestational age, and preeclampsia) were abstracted from medical charts. Nineteen of the 101 women had one or more adverse perinatal outcome and 84% with an adverse outcome (16/19) were not White. Both prenatal and time of delivery vitamin D deficiency were associated with developing an adverse outcome compared to those vitamin D sufficient (prenatal relative risk 3.43; 95% CI 1.60–7.34, $p = 0.004$; delivery time relative risk 5.14, 95% CI 2.68–9.86, $p = 0.004$). These both remained significant after adjusting for BMI. A higher rate of adverse outcome was found when women had both prenatal vitamin D deficiency and elevated depressive symptoms (EPDS $\geq$ 10). Sixty percent with both risk factors had an adverse perinatal outcome versus 17% with only one or neither risk factor (relative risk 3.60; 95% CI 1.55–8.38, $p = 0.045$), worthy of investigation with larger samples. Together, prenatal vitamin D deficiency and elevated depressive symptoms in pregnancy may increase risk for adverse perinatal outcomes, especially in racial minorities. Obstetric providers should consider routine prenatal depression screening. The impact of vitamin D supplementation to reduce risk for adverse perinatal outcomes should be studied in prospective trials. Our results suggest that supplementation early in pregnancy might be especially beneficial for depressed women.

Keywords Vitamin D deficiency · 25(OH)D · Adverse pregnancy outcome · Prenatal · Depression

Introduction

According to the CDC, one of the widest of all racial disparities in women's health is the perinatal mortality rate (Creanga et al., 2012). Using national data sets collected over 11 years, Tucker et al. (2007) reported that Black women were two to three times more likely to die from preeclampsia, eclampsia, placental abruption, placenta previa, and postpartum hemorrhage than white women who

A portion of these findings were presented at the Society for Maternal–Fetal Medicine (SMFM) 2015 Annual Pregnancy Meeting February 2–7, 2015 in San Diego, CA, USA and at the Association for Psychological Science Conference May 25–28, 2017 in Boston, MA, USA.

✉ Eynav Elgavish Accortt
Eynav.accortt@cshs.org

✉ Calvin J. Hobel
Calvin.Hobel@cshs.org

[1] Department of Obstetrics and Gynecology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

[2] Cedars-Sinai Biostatistics Core, Research Institute, Clinical and Translational Science Institute (CTSI), Clinical and Translational Research Center (CTRC), Los Angeles, CA, USA

Published online: 18 April 2018

had the same condition (Tucker et al., 2007). The research literature is teeming with examples of racial/ethnic disparities in both obstetric outcomes and care (Aseltine et al., 2015; Attanasio & Kozhimannil, 2017; de Bocanegra et al., 2017). These health outcomes have multiple and overlapping contributors such as systems biology, genetics, the physical and social environment (i.e. racial discrimination) and health behaviors. An important biological mechanism, vitamin D and the multiple processes it regulates, may underlie these disparities in maternal and infant mortality, and is often overlooked.

Vitamin D plays a critical role in reproductive health and provides a multi-systemic measure of functioning in women (McCullough, 2007). This unique neurosteroid hormone regulates placental development and function, promotes tolerance of the fetus and modulates the immune system (Arora & Hobel, 2010). Therefore, vitamin D deficiency is a risk factor for certain gestational-associated pathologies (Chirumbolo et al., 2017). Indeed, recent research has found that vitamin D deficiency is associated with increased rates of adverse perinatal outcomes such as preeclampsia and preterm birth (Aghajafari et al., 2013; Bodnar et al., 2015). Recent meta-analyses showed positive associations between vitamin D deficiency and adverse pregnancy outcomes (Aghajafari et al., 2013; Amegah et al., 2017; Wei et al., 2013), and an "umbrella review" of meta-analyses on associations of vitamin D with a variety of health outcomes concluded that vitamin D is reliably associated with low birth weight (LBW), small for gestational age (SGA) births and depressive symptoms (Theodoratou et al., 2014). Adverse pregnancy outcomes increase maternal morbidity and infant mortality and cause costly, life-long problems (Creanga et al., 2014). Despite improvements in prenatal care, U.S. rates of adverse perinatal outcomes remain high; rates are 9.6% for preterm birth (PTB) (Martin et al., 2017), down from 13% in 2007, 16 8.1% for LBW (Martin et al., 2017), 2–8% for preeclampsia (Redman & Sargent, 2005; Steegers et al., 2010), and 9–16% for SGA (Ananth et al., 2004).

These multisystem outcomes often overlap and strong evidence suggests that women who experience high levels of stress and depression during pregnancy are more likely to have biological changes that lead to adverse outcomes (Kane et al., 2014; Mancuso et al., 2004). Prenatal depression is quite common with rates ranging between 12 and 22%, twice that as in the general female population (Andersson et al,. 2003; Bennett et al., 2004; Lee et al., 2007; McDonald et al., 2013). Depression during pregnancy has been associated with poor maternal health behaviors (Zuckerman et al., 1989) and risk of postpartum depression (PPD) (Burt & Stein, 2002). Furthermore, prenatal depression and anxiety are associated with increased risk for adverse birth outcomes, including PTB, LBW, and intrauterine growth restriction (Davalos et al., 2012; Ding et al., 2014; Grote et al., 2010; Szegda et al., 2014) although more rigorous research is needed to differentiate specific predictive effects on outcome (Accortt et al., 2015).

Low levels of vitamin D are also associated with risk for both depression and adverse outcomes and may be involved in the underlying physiological mechanisms of both conditions. According to a meta-analysis of 31,424 males and females, vitamin D was inversely associated with depression (Anglin et al., 2013), however, none of the included studies were on pregnancy or the postpartum. Three prospective studies have investigated whether low levels of prenatal vitamin D were associated with later PPD symptoms. In a high quality prospective study of 796 women, a negative association was found between low vitamin D levels at 18 weeks gestation and PPD symptoms (Robinson et al., 2014). Another smaller (N = 179) prospective study reported that lower 25(OH)D3 levels in the second trimester of pregnancy were associated with higher levels of PPD symptoms at 1 week, 6 weeks, and 6 months postpartum (Gur et al., 2014). Nielson and colleagues (2013), however, did not find this result in their study with 605 women with PPD and 875 controls in a case control study nested in the Danish National Birth Cohort. The authors used register data on antidepressant use as a measure of PPD, which was not diagnosed, nor were any validated depression screening tools used in this study, a major flaw in their research design (Nielsen et al., 2013).

Cross-sectional studies have also been published in support of these prospective ones. Prenatal depressive symptoms have been associated with low prenatal vitamin D levels in four published studies (Brandenbarg et al., 2012; Cassidy-Bushrow et al., 2012; Huang et al., 2014; Williams et al., 2016). To our knowledge, the largest study was conducted with the Amsterdam Born Children and Their Development cohort. Maternal serum vitamin D (N = 4101) was measured during early pregnancy and maternal depressive symptoms were measured at 16-week gestation. Vitamin D deficiency was significantly associated with high levels of depressive symptoms (odds ratio [OR], 1.48; 95% CI 1.13–1.95), even after adjustment for confounding variables (Brandenbarg et al., 2012). Postpartum depressive symptoms have been associated with low postpartum vitamin D levels in two published studies (Murphy et al., 2010; Fu et al., 2015). Fu et al. (2014) obtained a blood sample 24–48 h after childbirth to test serum levels of 25(OH)D. Three months postpartum, women were screened for depression using the EPDS, with PPD identified as EPDS $\geq$ 12. Of the 213 women who were included, 12.2% met criteria for PPD. Serum 25(OH)D levels in women with no PPD were significantly higher than those in women with PPD

($p < 0.0001$). Multivariate analyses showed an increased risk of PPD associated with 25(OH)D levels $\leq$ 10.2 ng/ml (OR 7.17, 95% CI 3.81–12.94; $p < 0.0001$) after adjusting for possible confounders (Fu et al., 2015). Most recently, a significant inverse relationship between vitamin D levels and depressive symptoms (EPDS) was observed at three time points in the Depression and Vitamin D (DAVID) study. Higher EPDS scores in the third trimester were inversely associated with low cord blood 25(OH)D (Lamb et al., 2015). Thus, the larger literature on low vitamin D levels and depression has been extended into pregnancy and postpartum.

To our knowledge, no studies have investigated the combined effects of low vitamin D status and elevated depressive symptoms in pregnancy on the development of adverse perinatal outcome. The present secondary data analysis sought to determine to what extent prenatal and delivery vitamin D deficiency predicted a composite of four adverse perinatal outcomes and whether prenatal depressive symptoms placed women in the DAVID study at increased risk for an adverse outcome.

Materials and methods

Participants

The study participants were women 18 years of age or older with a confirmed pregnancy at less than 25 weeks gestation. Participant recruitment and data collection occurred from 2013 to 2014 at Cedars-Sinai Medical Center in Los Angeles, California. The recruitment and retention process of study participants in the parent study has been detailed elswhere (Lamb et al., 2015).

Procedures

This secondary data analysis of a subset of data from the Depression and Vitamin D (DAVID) Study included 101 women who completed biomarker collection and depression screening at 2 time points. Data collection for Time 1, including blood sampling and questionnaires, occurred in early pregnancy (Mean estimated gestational age = 14 weeks $\pm$ 5.45). IRB approval for the parent study was received from Cedars-Sinai Medical Center and Vanderbilt University.

Vitamin D

Serum 25(OH)D was used to measure vitamin D levels in maternal blood samples collected at Time 1 (early pregnancy) and Time 2 (delivery) of the DAVID study. Samples were analyzed by LC–MS/MS using a Thermo® ARIA® TX-4 HPLC system with Agilent® 1200SL pumps and a Sciex® API5000 triple quadrupole mass spectrometer. Both 25(OH)D3 and 25(OH)D2 were measured, and the combined total 25(OH)D value is used in this analysis. The standard cutoff of $\leq$ 20 ng/ml was used to define deficiency (Ross et al., 2011).

Depressive symptoms

Symptoms were assessed in the first trimester using the Edinburgh Postnatal Depression Scale (EPDS) as part of the parent (DAVID) study. The EPDS is a 10-item scale that assesses the cognitive and affective components of depressive symptomatology, while excluding somatic symptoms specific to the perinatal period (Cox et al., 1987). Each answer is given a score of 0–3 and the maximum score is 30. The EPDS has been validated for use in pregnant and postpartum women and the sensitivity and specificity was 86 and 78%, respectively (Cox et al., 1987). The EPDS score was used as a dichotomous variable (EPDS $\geq$ 10) in this study to include minor depression and increase sensitivity in line with previously recommended 9/10 ('10 or more') as the cutoff score (Harris et al., 1989; Murray & Carothers, 1990). This cut-off score is recommended as optimum for the properties of sensitivity and specificity for risk of minor depression (Matthey et al., 2006).

Perinatal complications/outcomes

Pregnancy data were abstracted from the medical records, including: diagnosed *preeclampsia; pre-term birth (< 37 weeks gestation);* and *low birthweight (< 2500 grams).* The outcome, *small for gestational age* was calculated as birth weights at or below the tenth percentile for gestational age (Dashe et al., 2000). Data on gestational diabetes (GDM) was collected and several of the women with GDM also had an additional adverse outcome, and were included in the study analyses. The women with only a GDM diagnosis had babies large for gestational age, and likely a different mechanistic pathway was involved. Therefore, we do not include gestational diabetes as a separate diagnosis in analyses. A composite of these four adverse perinatal outcomes was created, and women were dichotomized based on the presence or absence of (1 or more) adverse outcomes and categorized into 2 groups.

Statistical analysis

Numerical variables were summarized by mean and standard deviation or median and range. Categorical variables were summarized by counts and percentages. Numerical variables were compared across groups by the independent

Table 1 Demographic and clinical variables stratified by adverse perinatal outcome for descriptive purposes for N = 101 women from the DAVID study

	No adverse outcome N = 82 (81.2%)	Adverse outcome* N = 19 (18.8%)	*p* value
Age (years)	33.2 ± 4.9	32.8 ± 6.4	0.79
Married	70 (84.3)	18 (69.2)	**0.032**
Employed (full or part-time)	58 (70.7)	16 (84.2)	0.39
Education (years)	16.5 ± 2.6	16.3 ± 2.3	0.78
Race/ethnicity			0.077
White	34 (41.5)	2 (10.5)	
Black	13 (15.9)	5 (26.3)	
Hispanic	18 (22.0)	5 (26.3)	
Asian	10 (12.2)	5 (26.3)	
Indian	2 (2.4)	1 (5.3)	
Mixed	5 (6.1)	1 (5.3)	
Number of pregnancies[1]	2.3 ± 1.4	2.8 ± 1.7)	0.16
BMI	25.8 ± 4.5	27.9 ± 7.1	0.23
Pregnancy Vitamin D ng/ml	28.7 ± 9.0	22.9 ± 9.6	**0.014**
Vitamin D < 20 ng/ml	12 (14.6)	9 (47.4)	**0.004**
Pregnancy EPDS	5.2 ± 3.8	6.7 ± 4.2	0.114
Pregnancy EPDS ≥ 10	12 (14.6)	5 (26.3)	0.30

Data are N (%) or mean ± standard deviation

Comparison was tested with *t* tests or Chi square. Statistically significant *p* values in bold

No adverse outcome: women with no adverse perinatal complications of interest in the study

*Adverse perinatal outcome includes one or more of the following: low birth weight, preterm birth, small for gestational age or preeclampsia

[1]Number of pregnancies available for N = 100

Pregnancy = 1st trimester

EPDS Edinburgh Postnatal Depression Scale

samples *t* test or the Wilcoxon rank sum test. Categorical variables were compared across groups by the Fisher exact test. Multivariable log-binomial regression models were used to estimate adjusted relative risks to assess the association between predictor variables (vitamin D and EPDS) and the adverse perinatal outcome composite. A two-sided 0.05 significance level was used throughout. Statistical calculations were made using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Women in the present study were on average 33 years old (SD = 5.2). Approximately 36% were White, 23% were Hispanic, 18% were Black, 15% were Asian, 3% were Indian and the remaining 6% were mixed race. Approximately 35% were primiparous. The average pregnancy EPDS score for the sample was 5.5 ± 3.9 and 17% (N = 17) were considered at prenatal risk for minor depression by the EPDS cutoff (EPDS ≥ 10) in this study. At time of delivery 15% of the women were still considered at risk for minor depression.

Participant characteristics were stratified for descriptive purposes by having experienced one or more of four adverse perinatal outcomes (Table 1). In line with rates of adverse perinatal outcomes reported previously in the U.S. (Martin et al., 2017), 19% experienced one or more of these 4 outcomes. Eleven percent had preterm birth (PTB), 10% had babies who were small for gestational age (SGA), 8% had babies who were low birth weight (LBW), and approximately 5% had preeclampsia (PE). The only demographic variable that statistically differed between the two groups was marital status; women in the adverse outcome group were significantly less likely to be married than those who had no adverse outcomes (69 vs. 84%, $p = 0.032$). It is important to highlight that 16 of the 19 women with one or more adverse outcome were not White (5 Hispanic, 5 Black, 4 Asian, 1 Indian and 1 identified as mixed race). Nine of these 19 women experienced more

Table 2 Nine women from the DAVID Study had more than one adverse perinatal outcome

Participant	PTB	LBW	SGA	PE	GDM*	GA (wks)	BW (g)	Mean BW percentile (%)**
1	Yes	Yes	Yes	Yes	Yes	35.29	2149	10
2	Yes			Yes	Yes	35.71	2665	27
3	Yes	Yes	Yes			35.14	2050	7
4		Yes	Yes			38.14	2128	1
5	Yes	Yes				33.14	2061	30
6	Yes	Yes	Yes			36.00	2345	10
7	Yes	Yes	Yes		Yes	36.86	2389	5
8	Yes	Yes		Yes		31.29	1350	16
9	Yes	Yes				33.57	2260	27

PTB = preterm birth; LBW = low birth weight; PE = preeclampsia; GDM = gestational diabetes mellitus; SGA = small for gestational age; GA = gestational age; BW = birth weight

*A total of 10 women had GDM. Three of the 10 are shown above. The other 7 only had GDM (no other adverse outcome) and therefore were not included in study analyses

**Percentiles obtained from Table 2 in Oken et al. (2003)

than one outcome (Table 2). Note that the mean birth weight (BW) percentiles listed in Table 2 are all less than the 50th percentile suggesting that these adverse perinatal outcomes are all significantly related to poor fetal growth. All women had pregnancy 25(OH)D status measured during January–March. The mean level of 25(OH)D in the sample at the prenatal time was 27.6 ng/ml (SD = 9.1), and 21% (N = 21) met criteria for 25(OH)D deficiency (vitamin D $\leq$ 20 ng/ml). The adverse outcome group had significantly higher rates of 25(OH)D deficiency than those who had no adverse outcomes (47 vs. 15%, $p = 0.004$).

Table 3 presents log-binomial results. Women with prenatal vitamin D deficiency had 3.43 times the risk of developing an adverse outcome compared to those vitamin D sufficient (relative risk 3.43; 95% CI 1.60–7.34, $p = 0.004$). Women with delivery vitamin D deficiency had 5.14 times the risk of an adverse outcome (relative risk 5.14, 95% CI 2.68–9.86, $p = 0.004$), which remained significant after adjusting for BMI. A higher rate of adverse outcome was found when women had both prenatal vitamin D deficiency and elevated prenatal depressive symptoms. Sixty percent with both risk factors had an adverse perinatal outcome versus 17% with only one or neither risk factor (relative risk 3.60; 95% CI 1.55–8.38, $p = 0.045$), worthy of investigation with larger samples.

Comment

Prenatal vitamin D deficiency increased risk for adverse perinatal outcomes in this sample of 101 pregnant women from the DAVID study. This relative risk increased as the woman reached her delivery, with RR = 3.43 at 14 weeks gestation and RR = 5.14 at the time of delivery. Nineteen percent of the sample was considered at risk for minor depression by the study cutoff of EPDS $\geq$ 10. When women were both above this minor depression cutoff and below the vitamin D deficiency cutoff (25(OH)D $<$ 20 ng/ml) they were more likely to have an adverse perinatal outcome. To our knowledge, this is one of the first studies to include vitamin D deficiency and depression risk in predicting adverse birth outcomes. This finding needs to be replicated in a larger sample and for individual birth outcomes.

Strengths, limitations and future directions

The main strength of the DAVID study was the prospective design. Women in this sample were studied in early pregnancy and at the time of their delivery and collecting medical and psychosocial data enabled control for relevant confounders. Vitamin D samples were assayed with a competitive chemiluminescence immunoassay platform, consistent with other large clinical laboratories. The entire sample had their pregnancy 25(OH)D status measured during January–March, which allowed for consistency and lack of seasonal differences in vitamin D. There is a higher risk of vitamin D deficiency and related complications in cooler climates because in winter the oblique angle of the sun allows for fewer solar UVB photons to reach the earth (Holick, 2007; Bouillon, 2001) even in warmer, sunnier locations like Southern California. Limitations of this secondary data analysis include some missing data on adverse outcome because a portion either terminated their pregnancy, miscarried, or their clinician did not record the outcome in the chart. Furthermore, this study does not involve confirmed cases of PPD and future research should include diagnostic interviews.

Table 3 Associations between vitamin D deficiency, EPDS cutoffs and adverse perinatal outcomes (relative risks for N = 101 women from the DAVID study)

	Unadjusted RR	Adjusted RR*	95% confidence interval	*p* value
Pregnancy vitamin D < 20 ng/mL	3.43		1.60–7.34	**0.004**
		2.67	1.32–5.39	**0.006**
Delivery vitamin D < 20 ng/mL	5.14		2.68–9.86	**0.004**
		2.88	1.16–7.13	**0.022**
Pregnancy EPDS ≥ 10	1.76		0.73–4.25	0.304
		1.50	0.63–3.67	0.350
Double Hit: pregnancy vitamin D < 20 ng/mL and pregnancy EPDS ≥ 10	3.60		1.55–8.38	**0.045**

Adverse perinatal outcomes = Preterm birth, Low birthweight, Small for Gestational Age and/or Preeclampsia

Pregnancy = 1st trimester

*Adjusted for BMI only

Women who did not have an adverse outcome were more likely to be married and have lower BMI than women who had an adverse outcome, findings worthy of further study. Marriage and social support in general are important protective factors against stress and depression (Catov et al., 2015; Christian et al., 2013; Yim et al., 2015), however relationship quality should be considered (Akincigil et al. 2010). Regarding BMI, pre-pregnancy obesity rates and excessive weight-gain during pregnancy have been associated with increased incidence of gestational diabetes, preeclampsia, Cesarean, postpartum hemorrhage, maternal mortality, and childhood obesity (Chung et al., 2012; Gaillard et al., 2013; Marshall & Spong, 2012; Norman & Reynolds, 2011). Therefore, it is possible that the risk of adverse outcomes could be driven by these and other factors that correlate with vitamin D levels, and that vitamin D deficiency in and of itself may not cause the adverse outcomes. While these results are preliminary and do not establish causation, they are novel and important given the prevalence of low 25(OH)D and elevated depressive symptoms in pregnancy, especially in Black women. We hope that they encourage interest in further research on this topic including randomized controlled studies.

Future directions of this research will also explore the anti-inflammatory mechanism of vitamin D in pregnancy. In line with our previous research, we hypothesize that women with low prenatal vitamin D and high prenatal inflammatory markers will be at increased risk for PPD, as well as increased risk for adverse perinatal outcomes (Accortt et al., 2016, 2017). A woman's response to pregnancy may serve as her first physiological and psychological "stress test," and whether she has an adverse perinatal outcome may serve as a window into future maternal CVD risk (Williams, 2003; Minissian et al., 2018). Therefore in future research it is critical to consider cardiovascular risk markers, inflammatory biomarkers and specific forms of vascular dysfunction which may be linked to adverse perinatal outcomes.

It will also be important to focus on racial disparities in future research. Black women, for example, have among the highest rates of PTB in the USA., with rates in the range of 16–18% compared with 5–9% for Whites (Goldenberg et al., 2008). Additionally, the preterm-related infant mortality rate in 2007 was 1.8 for Whites and 6.0 for Blacks (Behrman & Butler, 2007). Black women also have higher rates of prenatal and PPD compared to other racial groups in the USA (Culhane & Goldenberg, 2011; Howell et al., 2006; Orr et al., 2006; Segre et al., 2006). They are at increased risk for vitamin D deficiency (Nassar et al., 2011) because darker skin limits synthesis of vitamin D and due to lower intake of supplemental vitamin D (Bodnar & Simhan, 2010). Furthermore, higher levels of inflammatory markers have been documented in Black men and women (Deverts et al., 2010) and in both non-pregnant and pregnant Black women in a stress reactivity study (2013). Collecting data on stress and anxiety will be important in future research. Black women tended to have marginally higher rates of anxiety compared to White women, and chronic anxiety among Black women may contribute to racial disparities in adverse perinatal outcomes via an impaired inflammatory response (Catov et al., 2015). In the present study, 84% of the women with adverse perinatal outcome were Black, Hispanic, Asian, or Mixed race and had mean birth weights below the 50th percentile. Tamura et al. (1984) were first to report reduced fetal growth prior to preterm birth. Subsequently Wadhwa et al. 1993 found that pregnancy stress was associated with a 55 g decrease in infant birth weight. Thus, the cause of poor fetal growth is likely a combination of factors such as poor implantation of the placenta (Misra et al., 2009), impacted by vitamin D deficiency, maternal stress and depression and other factors related to socioeconomic status.

Clinical implications

Obstetric providers should routinely screen for depression and consider vitamin D supplementation to reduce risk for adverse perinatal outcomes, which might be especially beneficial for depressed women. Our results suggest that screenings be conducted as early as possible in the pregnancy, because the combined risk (vitamin D deficiency and high EPDS scores) was present as early as 14 weeks of pregnancy and was significantly associated with having an adverse perinatal outcome. We considered the possibility that early pregnancy depressive symptoms predicted later vitamin D deficiency however this analysis did not yield statistically significant results and has not been reported. The significant inverse cross sectional associations between vitamin D levels and depressive symptoms (EPDS) observed at three time points has been reported in the parent Depression and Vitamin D (DAVID) study (Lamb et al., 2015). The significant prospective DAVID study finding was between higher EPDS scores in the third trimester which were inversely associated with low cord blood 25(OH)D (Lamb et al., 2015).

Early screening would allow for early intervention which could benefit the pregnant woman, her baby and her entire family (Accortt & Wong, 2017). Best practice would be prenatal testing for blood levels of 25(OH)D both before and after supplementation to ensure that a woman has adequate levels of cirdulating vitamin D, regardless of the season. Vitamin D supplementation is a cost-effective and safe intervention during pregnancy (Hollis & Wagner, 2011) that may benefit the mother's health and that of the developing fetus (Al-Shaikh et al., 2016; Asemi et al., 2013; Bener et al., 2013; De-Regil et al., 2016; Hobel, 2015; Kalra et al., 2012; McDonnell et al., 2017; Morales et al., 2012; Perez-Lopez et al., 2015; Roth et al., 2017; Vaziri et al., 2016). A recent randomized, double-blind, placebo-controlled clinical trial of vitamin D supplementation in 48 pregnant women resulted in significant decreases in serum hs-CRP, fasting plasma glucose, systolic blood pressure, and diastolic blood pressure compared with placebo (Asemi et al., 2013). However, depressive symptoms were not measured. Depression as an outcome was also not included in Roth et al. (2017) recent systematic review and meta-analysis of 43 randomized controlled trials including 8406 participants. They showed that prenatal vitamin D supplementation was associated with increased maternal and cord serum 25-hydroxyvitamin D concentrations, increased mean birth weight, reduced the risk of small for gestational age, reduced the risk of wheeze in offspring, and increased infant length at one year of age. However, there was insufficient evidence of benefits of prenatal vitamin D supplementation for maternal health conditions related to pregnancy, and no effect on preterm birth. Few of the trials reviewed were designed to test the effect of vitamin D on clinical or functional outcomes, and most trials were small and at overall high or uncertain risk of bias (Roth et al., 2017). One of the largest (N = 1024), most diverse and most recent trials of vitamin D supplementation, not included in Roth's meta analysis, found that pregnant women with 25(OH)D $\geq$ 40 ng/ml had a 62% lower risk of PTB compared to those $<$ 20 ng/ml ($p < 0.0001$). After adjusting for socioeconomic variables, this lower risk persisted (OR = 0.41, $p = 0.002$). The authors found a considerably lower PTB rate (60%) for those who reached $\geq$ 40 ng/ml versus those who did not (78%), particularly among non-white women (McDonnell et al., 2017). This indicates that improving the vitamin D status of non-white women, who are known to have particularly low vitamin D concentrations, could decrease racial disparities in PTB rates and perhaps decrease rates of postpartum depression as well.

Randomized controlled trials of prenatal vitamin D supplementation to reduce PPD are merited, and to our knowledge only one such trial has been conducted. Vaziri et al. (2016) showed that consuming 2000 IU vitamin D3 daily during late pregnancy was effective in decreasing perinatal depression. The authors do not report on adverse perinatal outcomes in their study, but suggest future clinical trials in pregnant mothers who are at risk for PPD (Vaziri et al., 2016). Future evaluation of psychotherapeutic and complementary interventions designed to influence the physiological response to depression and anxiety, such as progressive muscle relaxation, yoga, biofeedback and mindfulness-based stress reduction, may provide additional insight into how inflammation and vitamin D deficiency may be influenced by depression or anxiety. The ability to minimize inflammatory responses to stress influences the burden that stressors place on an individual. If yoga, for example, dampens stress-related changes (Kiecolt-Glaser et al., 2010), then regular practice could have substantial future cardiovascular health benefits as well (Catov et al., 2007; Rich-Edwards et al., 2014). This could be especially beneficial for depressed or anxious pregnant women who might not be interested in anti-depressants or other medications during their reproductive years (Accortt & Wong, 2017).

Conclusion

The present findings provide additional evidence that low prenatal and delivery 25(OH)D predict adverse perinatal outcomes ($p < 0.05$). Women with both prenatal vitamin D deficiency and elevated prenatal depressive symptoms (EPDS $\geq$ 10) were more likely to have an adverse outcome. Specifically 60% with both risk factors had an adverse perinatal outcome versus 17% with only one or

neither risk factor ($p = 0.045$), worthy of investigation with larger samples. These results may elucidate psychological moderators linking vitamin D status to adverse perinatal outcomes.

Acknowledgements AL designed and conducted the parent (DAVID) study. EEA developed the research questions for secondary analyses and wrote the first draft of this manuscript. JM analyzed the data. AL, CH and JM assisted in writing. All authors contributed to the present study design, interpretation of data, and approved the final manuscript. The authors have no financial gain related to the outcome of this research, and there are no potential conflicts of interest. We thank the participants in this study for contributing to this research and increasing our knowledge about the experiences of pregnant women. We acknowledge the support of the research team members, Susan Jackman, MS, RN and Morgan McKay, MSW at Cedars-Sinai Medical Center.

Funding The parent (DAVID) study was partially supported by funding by a CTSA award No. UL1TR000445 from the National Center for Advancing Translational Sciences to AL and the Miriam Jacobs Chair in Maternal–Fetal Medicine (CJH).

Compliance with ethical standards

Conflict of interest The authors Eynav Elgavish Accortt, Amy Lamb, James Mirocha, and Calvin J. Hobel declare that they have no conflict of interest.

Human and animal rights and Informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients for being included in the study.

References

Accortt, E. E., Cheadle, A. C., & Dunkel, Schetter C. (2015). Prenatal depression and adverse birth outcomes: An updated systematic review. *Maternal and Child Health Journal, 19,* 1306–1337.

Accortt, E. E., Mirocha, J., Dunkel Schetter, C., & Hobel, C. J. (2017). Adverse perinatal outcomes and postpartum multisystemic dysregulation: Adding vitamin D deficiency to the Allostatic Load Index. *Maternal and Child Health Journal, 21,* 398–406.

Accortt, E. E., Schetter, C. D., Peters, R. M., & Cassidy-Bushrow, A. E. (2016). Lower prenatal vitamin D status and postpartum depressive symptomatology in African American women: Preliminary evidence for moderation by inflammatory cytokines. *Archives of Women's Mental Health, 19,* 373–383.

Accortt, E. E., & Wong, M. S. (2017). It is time for routine screening for perinatal mood and anxiety disorders in obstetrics and gynecology settings. *Obstetrical & Gynecological Survey, 72,* 553–568.

Aghajafari, F., Nagulesapillai, T., Ronksley, P. E., Tough, S. C., O'Beirne, M., & Rabi, D. M. (2013). Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. *BMJ, 346,* f1169.

Akincigil, A., Munch, S., & Niemczyk, K. (2010). Predictors of maternal depression in the first year postpartum: Marital status and mediating role of relationship quality. *Social Work in Health Care, 49,* 227–244.

Al-Shaikh, G. K., Ibrahim, G. H., Fayed, A. A., & Al-Mandeel, H. (2016). Impact of vitamin D deficiency on maternal and birth outcomes in the Saudi population: A cross-sectional study. *BMC Pregnancy Childbirth, 16,* 119. https://doi.org/10.1186/s12884-016-0901-4

Amegah, A. K., Klevor, M. K., & Wagner, C. L. (2017). Maternal vitamin D insufficiency and risk of adverse pregnancy and birth outcomes: A systematic review and meta-analysis of longitudinal studies. *PLoS ONE, 12,* e0173605.

Ananth, C. V., Balasubramanian, B., Demissie, K., & Kinzler, W. L. (2004). Small-for-gestational-age births in the United States: An age-period-cohort analysis. *Epidemiology, 15,* 28–35.

Andersson, L., Sundstrom-Poromaa, I., Bixo, M., Wulff, M., Bondestam, K., & Astrom, M. (2003). Point prevalence of psychiatric disorders during the second trimester of pregnancy: A population-based study. *American Journal of Obstetrics and Gynecology, 189,* 148–154.

Anglin, R. E., Samaan, Z., Walter, S. D., & McDonald, S. D. (2013). Vitamin D deficiency and depression in adults: Systematic review and meta-analysis. *British Journal of Psychiatry, 202,* 100–107.

Arora, C., & Hobel, C. (2010). Vitamin D—A novel role in pregnancy. *Biopolymers and Cell, 26,* 97–107.

Aseltine, R. H., Jr., Yan, J., Fleischman, S., Katz, M., & DeFrancesco, M. (2015). Racial and ethnic disparities in hospital readmissions after delivery. *Obstetrics and Gynecology, 126,* 1040–1047.

Asemi, Z., Samimi, M., Tabassi, Z., Shakeri, H., & Esmaillzadeh, A. (2013). Vitamin D supplementation affects serum high-sensitivity C-reactive protein, insulin resistance, and biomarkers of oxidative stress in pregnant women. *Journal of Nutrition, 143,* 1432–1438.

Attanasio, L., & Kozhimannil, K. B. (2017). Health care engagement and follow-up after perceived discrimination in maternity care. *Medical Care, 55,* 830–833.

Behrman, R. E., & Butler, A. S. (Eds.). (2007). *Preterm Birth: Causes, consequences, and prevention*. Washington (DC): National Academies Press (US) National Academy of Sciences.

Bener, A., Al-Hamaq, A. O., & Saleh, N. M. (2013). Association between vitamin D insufficiency and adverse pregnancy outcome: Global comparisons. *International Journal of Womens Health, 5,* 523–531. https://doi.org/10.2147/IJWH.S51403

Bennett, H. A., Einarson, A., Taddio, A., Koren, G., & Einarson, T. R. (2004). Prevalence of depression during pregnancy: Systematic review. *Obstetrics and Gynecology, 103,* 698–709.

Bodnar, L. M., Platt, R. W., & Simhan, H. N. (2015). Early-pregnancy vitamin D deficiency and risk of preterm birth subtypes. *Obstetrics and Gynecology, 125,* 439–447.

Bodnar, L. M., & Simhan, H. N. (2010). Vitamin D may be a link to black-white disparities in adverse birth outcomes. *Obstetrical & Gynecological Survey, 65,* 273–284. https://doi.org/10.1097/OGX.0b013e3181dbc55b

Bouillon, R. (2001). Vitamin D: From photosynthesis, metabolism, and action to clinical applications. In L. J. DeGroot & J. L. Jameson (Eds.), *Endocrinology* (pp. 1009–1028). Philadelphia: W.B. Saunders.

Brandenbarg, J., Vrijkotte, T. G., Goedhart, G., & van Eijsden, M. (2012). Maternal early-pregnancy vitamin D status is associated with maternal depressive symptoms in the Amsterdam Born Children and Their Development cohort. *Psychosomatic Medicine, 74,* 751–757. https://doi.org/10.1097/PSY.0b013e3182639fdb

Burt, V. K., & Stein, K. (2002). Epidemiology of depression throughout the female life cycle. *Journal of Clinical Psychiatry, 63,* 9–15.

Cassidy-Bushrow, A. E., Peters, R. M., Johnson, D. A., Li, J., & Rao, D. S. (2012). Vitamin D nutritional status and antenatal depressive symptoms in African American women. *Journal of Womens Health (Larchmt), 21,* 1189–1195.

Catov, J. M., Flint, M., Lee, M., Roberts, J. M., & Abatemarco, D. J. (2015). The relationship between race, inflammation and psychosocial factors among pregnant women. *Maternal and Child Health Journal, 19,* 401–409.

Catov, J. M., Newman, A. B., Roberts, J. M., et al. (2007). Preterm delivery and later maternal cardiovascular disease risk. *Epidemiology, 18,* 733–739. https://doi.org/10.1097/EDE.0b013e3181567f96

Chirumbolo, S., Bjorklund, G., Sboarina, A., & Vella, A. (2017). The role of vitamin D in the immune system as a pro-survival molecule. *Clinical Therapeutics, 39,* 894–916.

Christian, L. M., Glaser, R., Porter, K., & Iams, J. D. (2013). Stress-induced inflammatory responses in women: Effects of race and pregnancy. *Psychosomatic Medicine, 75,* 658–669. https://doi.org/10.1097/PSY.0b013e31829bbc89

Chung, J. H., Melsop, K. A., Gilbert, W. M., Caughey, A. B., Walker, C. K., & Main, E. K. (2012). Increasing pre-pregnancy body mass index is predictive of a progressive escalation in adverse pregnancy outcomes. *The Journal of Maternal-Fetal & Neonatal Medicine, 25,* 1635–1639.

Cox, J. L., Holden, J. M., & Sagovsky, R. (1987). Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry, 150,* 782–786. https://doi.org/10.1192/bjp.150.6.782

Creanga, A. A., Berg, C. J., Ko, J. Y., et al. (2014). Maternal mortality and morbidity in the United States: Where are we now? *Journal of Womens Health (Larchmt), 23,* 3–9.

Creanga, A. A., Berg, C. J., Syverson, C., Seed, K., Bruce, C., & Callaghan, W. M. (2012). Race, ethnicity and nativity differentials in pregnancy-related mortality in the United States: 1993–2006. *Obstetrics and Gynecology, 120,* 261–268.

Culhane, J. F., & Goldenberg, R. L. (2011). Racial disparities in preterm birth. *Seminars in Perinatology, 35,* 234–239.

Dashe, J. S., McIntire, D. D., Lucas, M. J., & Leveno, K. J. (2000). Effects of symmetric and asymmetric fetal growth on pregnancy outcomes. *Obstetrics and Gynecology, 96,* 321–327.

Davalos, D. B., Yadon, C. A., & Tregellas, H. C. (2012). Untreated prenatal maternal depression and the potential risks to offspring: A review. *Archives of Women's Mental Health, 15,* 1–14.

de Bocanegra, H. T., Braughton, M., Bradsberry, M., Howell, M., Logan, J., & Schwarz, E. B. (2017). Racial and ethnic disparities in postpartum care and contraception in California's Medicaid program. *American Journal of Obstetrics and Gynecology, 47,* e1.

De-Regil, L. M., Palacios, C., Lombardo, L. K., & Pena-Rosas, J. P. (2016). Vitamin D supplementation for women during pregnancy. *Cochrane Database System Review, 1,* CD008873. https://doi.org/10.1002/14651858.cd008873.pub3

Deverts, D. J., Cohen, S., DiLillo, V. G., et al. (2010). Depressive symptoms, race, and circulating C-reactive protein: The Coronary Artery Risk Development in Young Adults (CARDIA) study. *Psychosomatic Medicine, 72,* 734–741. https://doi.org/10.1097/PSY.0b013e3181ec4b98

Ding, X. X., Wu, Y. L., Xu, S. J., et al. (2014). Maternal anxiety during pregnancy and adverse birth outcomes: A systematic review and meta-analysis of prospective cohort studies. *Journal of Affective Disorders, 159,* 103–110.

Fu, C. W., Liu, J. T., Tu, W. J., Yang, J. Q., & Cao, Y. (2015). Association between serum 25-hydroxyvitamin D levels measured 24 h after delivery and postpartum depression. *BJOG, 122,* 1688–1694.

Gaillard, R., Durmus, B., Hofman, A., MacKenbach, J. P., Steegers, E., & Jaddoe, V. (2013). Risk factors and outcomes of maternal obesity and excessive weight gain during pregnancy. *Obesity, 21,* 1046–1055.

Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Epidemiology and causes of preterm birth. *Lancet, 371,* 75–84.

Grote, N. K., Bridge, J. A., Gavin, A. R., Melville, J. L., Iyengar, S., & Katon, W. J. (2010). A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Archives of General Psychiatry, 67,* 1012–1024.

Gur, E. B., Gokduman, A., Turan, G. A., et al. (2014). Mid-pregnancy vitamin D levels and postpartum depression. *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 179,* 110–116.

Harris, B., Huckle, P., Thomas, R., Johns, S., & Fung, H. (1989). The use of rating scales to identify post-natal depression. *British Journal of Psychiatry, 154,* 813–817.

Hobel, C. J. (2015). Vitamin D supplementation should be routine in pregnancy: FOR: Recent research supports routine vitamin D supplementation in pregnancy. *BJOG: An International Journal of Obstetrics & Gynaecology., 122,* 1021.

Holick, M. F. (2007). Vitamin D deficiency. *New England Journal of Medicine, 357,* 266–281.

Hollis, B. W., & Wagner, C. L. (2011). Vitamin D requirements and supplementation during pregnancy. *Current Opinion in Endocrinology, Diabetes, and Obesity, 18,* 371–375. https://doi.org/10.1002/jbmr.463

Howell, E. A., Mora, P., & Leventhal, H. (2006). Correlates of early postpartum depressive symptoms. *Maternal and Child Health Journal, 10,* 149–157. https://doi.org/10.1007/s10995-005-0048-9

Huang, J. Y., Arnold, D., Qiu, C. F., Miller, R. S., Williams, M. A., & Enquobahrie, D. A. (2014). Association of serum vitamin D with symptoms of depression and anxiety in early pregnancy. *Journal of Womens Health (Larchmt), 23,* 588–595.

Kalra, P., Das, V., Agarwal, A., et al. (2012). Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. *British Journal of Nutrition, 108,* 1052–1058. https://doi.org/10.1017/S0007114511006246

Kane, H. S., Dunkel Schetter, C., Glynn, L. M., Hobel, C. J., & Sandman, C. A. (2014). Pregnancy anxiety and prenatal cortisol trajectories. *Biological Psychology, 100,* 13–19.

Kiecolt-Glaser, J. K., Christian, L., Preston, H., et al. (2010). Stress, inflammation, and yoga practice. *Psychosomatic Medicine, 72,* 113–121.

Lamb, A., Hobel, C., Pepkowitz, S., et al. (2015). Vitamin D deficiency and depressive symptoms in the perinatal period: a prospective study. *American Journal of Obstetrics and Gynecology, 212,* 371. **Manuscript submitted to Archives of Women's Health in December, 2017**.

Lee, A. M., Lam, S. K., Sze Mun Lau, S. M., Chong, C. S., Chui, H. W., & Fong, D. Y. (2007). Prevalence, course, and risk factors for antenatal anxiety and depression. *Obstetrics and Gynecology, 110,* 1102–1112.

Mancuso, R. A., Schetter, C. D., Rini, C. M., Roesch, S. C., & Hobel, C. J. (2004). Maternal prenatal anxiety and corticotropin-releasing hormone associated with timing of delivery. *Psychosomatic Medicine, 66,* 762–769.

Marshall, N. E., & Spong, C. Y. (2012). Obesity, pregnancy complications, and birth outcomes. *Seminars in Reproductive Medicine, 30,* 465–471.

Martin, J. A., Hamilton, B. E., Osterman, M. J., Driscoll, A. K., & Mathews, T. J. (2017). Births: Final data for 2015. *National Vital Statistics Reports*, *66*, 2.

Matthey, S., Henshaw, C., Elliott, S., & Barnett, B. (2006). Variability in use of cut-off scores and formats on the Edinburgh Postnatal Depression Scale: Implications for clinical and research practice. *Archives of Women's Mental Health, 9,* 309–315.

McCullough, M. L. (2007). Vitamin D deficiency in pregnancy: Bringing the issues to light. *Journal of Nutrition, 137,* 305–306.

McDonald, S. W., Lyon, A. W., Benzies, K. M., et al. (2013). The All Our Babies pregnancy cohort: Design, methods, and participant characteristics. *BMC Pregnancy Childbirth, 13,* S2.

McDonnell, S. L., Baggerly, K. A., Baggerly, C. A., Aliano, J. L., French, C. B., Baggerly, L. L., et al. (2017). Maternal 25 (OH) D concentrations $\geq$ 40 ng/ml associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. *PLoS ONE, 12,* e0180483.

Minissian, M. B, Kilpatrick, S., Eastwood, J. A., Robbins, W. A., Accortt, E. E., Wei, J., et al. (2018). Association of spontaneous preterm delivery and future maternal cardiovascular disease. *Circulation*, *137*(8), 865–871.

Misra, V. K., Hobel, C. J., & Sing, C. F. (2009). Placental blood flow and the risk of preterm delivery. *Placenta, 30,* 619–624.

Morales, E., Guxens, M., Llop, S., et al. (2012). Circulating 25-hydroxyvitamin D3 in pregnancy and infant neuropsychological development. *Pediatrics, 130,* e913–e920. https://doi.org/10.1542/peds.2011-3289

Murphy, P. K., Mueller, M., Hulsey, T. C., Ebeling, M. D., & Wagner, C. L. (2010). An exploratory study of postpartum depression and vitamin D. *The Journal of the American Psychiatric Nurses Association, 16,* 170–177.

Murray, L., & Carothers, A. D. (1990). The validation of the Edinburgh Post-natal Depression Scale on a community sample. *British Journal of Psychiatry, 157,* 288–290.

Nassar, N., Halligan, G. H., Roberts, C. L., Morris, J. M., & Ashton, A. W. (2011). Systematic review of first-trimester vitamin D normative levels and outcomes of pregnancy. *American Journal of Obstetrics and Gynecology, 205,* e201–e207.

Nielsen, N. O., Strom, M., Boyd, H. A., et al. (2013). Vitamin D status during pregnancy and the risk of subsequent postpartum depression: A case–control study. *PLoS ONE, 8,* e80686.

Norman, J. E., & Reynolds, R. (2011). The consequences of obesity and excess weight gain in pregnancy. *Proceedings of the Nutrition Society, 70,* 450–456.

Oken, E., Kleinman, K. P., Rich-Edwards, J., & Gillman, M. W. (2003). A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatrics, 3,* 6.

Orr, S. T., Blazer, D. G., & James, S. A. (2006). Racial disparities in elevated prenatal depressive symptoms among black and white women in eastern North Carolina. *Annals of Epidemiology, 16,* 463–468. https://doi.org/10.1016/j.annepidem.2005.08.004

Perez-Lopez, F. R., Pasupuleti, V., Mezones-Holguin, E., et al. (2015). Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: A systematic review and meta-analysis of randomized led trials. *Fertility and Sterility, 103,* 1278–1288.

Redman, C. W., & Sargent, I. L. (2005). Latest advances in understanding preeclampsia. *Science, 308,* 1592–1594.

Rich-Edwards, J. W., Fraser, A., Lawlor, D. A., & Catov, J. M. (2014). Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? *Epidemiologic Reviews, 36,* 57–70. https://doi.org/10.1016/j.fertnstert.2015.02.019

Robinson, M., Whitehouse, A. J., Newnham, J. P., et al. (2014). Low maternal serum vitamin D during pregnancy and the risk for postpartum depression symptoms. *Archives of Women's Mental Health, 17,* 213–219. https://doi.org/10.1007/s00737-014-0422-y

Ross, A. C., Manson, J. E., Abrams, S. A., et al. (2011). The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *Journal of Clinical Endocrinology and Metabolism, 96,* 53–58. https://doi.org/10.1210/jc.2010-2704

Roth, D. E., Leung, M., Mesfin, E., Qamar, H., Watterworth, J., & Papp, E. (2017). Vitamin D supplementation during pregnancy: State of the evidence from a systematic review of randomised trials. *BMJ, 29,* j5237.

Segre, L. S., O'Hara, M. W., & Losch, M. E. (2006). Race/ethnicity and perinatal depressed mood. *Journal of Reproductive and Infant Psychology, 24,* 99–106. https://doi.org/10.1080/02646830600643908

Steegers, E. A., von Dadelszen, P., Duvekot, J. J., & Pijnenborg, R. (2010). Pre-eclampsia. *Lancet, 376,* 631–644.

Szegda, K., Markenson, G., Bertone-Johnson, E. R., & Chasan-Taber, L. (2014). Depression during pregnancy: A risk factor for adverse neonatal outcomes? A critical review of the literature. *The Journal of Maternal-Fetal & Neonatal Medicine., 27,* 960–967.

Tamura, R. K., Sabbagha, R. E., Depp, R., Vaisrub, N., Dooley, S. L., & Socol, M. L. (1984). Diminished growth in fetuses born preterm after spontaneous labor or rupture of membranes. *American Journal of Obstetrics and Gynecology, 148,* 1105–1110.

Theodoratou, E., Tzoulaki, I., Zgaga, L., & Ioannidis, J. P. (2014). Vitamin D and multiple health outcomes: Umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ, 348,* g2035.

Tucker, M. J., Berg, C. J., Callaghan, W. M., & Hsia, J. (2007). The black–white disparity in pregnancy-related mortality from 5 conditions: differences in prevalence and case-fatality rates. *American Journal of Public Health, 97,* 247–251.

Vaziri, F., Nasiri, S., Tavana, Z., Dabbaghmanesh, M. H., Sharif, F., & Jafari, P. (2016). A randomized controlled trial of vitamin D supplementation on perinatal depression: In Iranian pregnant mothers. *BMC Pregnancy Childbirth, 16,* 239.

Wadhwa, P. D., Sandman, C. A., Porto, M., Dunkel-Schetter, C., & Garite, T. J. (1993). The association between prenatal stress and infant birth weight and gestational age at birth: A prospective investigation. *American Journal of Obstetrics and Gynecology, 169,* 858–865.

Wei, S. Q., Qi, H. P., Luo, Z. C., & Fraser, W. D. (2013). Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. *The Journal of Maternal-Fetal & Neonatal Medicine, 26,* 889–899.

Williams, D. (2003). Pregnancy: A stress test for life. *Current Opinion in Obstetrics and Gynecology, 15,* 465–471.

Williams, J. A., Romero, V. C., Clinton, C. M., et al. (2016). Vitamin D levels and perinatal depressive symptoms in women at risk: A secondary analysis of the mothers, omega-3, and mental health study. *BMC Pregnancy Childbirth, 16,* 203.

Yim, I. S., Tanner Stapleton, L. R., Guardino, C. M., Hahn Holbrook, J., & Dunkel Schetter, C. (2015). Biological and psychosocial predictors of postpartum depression: Systematic review and call for integration. *Annual Review of Clinical Psychology, 11,* 99–137.

Zuckerman, B., Amaro, H., Bauchner, H., & Cabral, H. (1989). Depressive symptoms during pregnancy: Relationship to poor health behaviors. *American Journal of Obstetrics and Gynecology, 160,* 1107–1111.