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Maternal–Fetal Impact of Vitamin D Deficiency: A Critical Review

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Abstract Research into the extra-skeletal functions of vitamin D has been expanding in recent years. During pregnancy, maternal vitamin D status may be of concern because of the key role of this vitamin in fetal skeletal development and due to the association between hypovitaminosis D and adverse maternal–fetal outcomes. Therefore, the objective of this manuscript was to review the maternal–fetal impact of gestational vitamin D deficiency and the benefits of vitamin D supplementation during pregnancy. A literature search was performed in PubMed and Embase employing the following keywords: vitamin D deficiency, pregnancy, 25-hydroxyvitamin D, and hypovitaminosis D. All relevant articles in English language published since 1980 were analysed by the two authors. Neonatal complications derived from vitamin D deficiency include low birth weight, growth restriction, and respiratory tract infection. In the mother, vitamin D deficiency has been associated with altered glucose homeostasis and increased incidence of gestational diabetes mellitus, preeclampsia, and bacterial vaginosis. However, the current state of the evidence is controversial for some other endpoints and the actual benefit of vitamin D supplementation in pregnancy remains unclear. Additional longitudinal studies may clarify the actual impact of vitamin D deficiency during pregnancy, and randomised trials are required to define the benefits of vitamin D supplementation in reducing the incidence of adverse outcomes in the mother and infant.

Keywords Vitamin D deficiency · Hypovitaminosis D · Pregnancy

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Introduction

Several functions of vitamin D have been studied in the last years [1], and vitamin D deficiency has been associated with co-morbidities beyond bone health [1, 2]. During pregnancy, vitamin D actions are still under evaluation, but it is considered essential for fetal skeletal development. Furthermore, vitamin D deficiency in the pregnant women has been associated with adverse outcomes to the mother, such as gestational diabetes mellitus (GDM) and preeclampsia, and to the offspring, such as small for gestational age (SGA) newborns [3–5].

Many studies have been published in recent years on this subject of vitamin D deficiency and pregnancy and, therefore, the objective of this manuscript was to critically review the available literature about the maternal–fetal impact of vitamin D deficiency.

Methods

Literature search was performed in PubMed and Embase, employing the following keywords: vitamin D deficiency, pregnancy, 25-hydroxyvitamin D, and hypovitaminosis D. The studies of interest were original papers and critical reviews on the subject of vitamin D and pregnancy. All relevant articles in English language published since 1980 were analysed by the two authors. Only human research

was considered. Additional studies were considered when a relevant data was cited by any reviewed paper. Data were organized as maternal or fetal repercussions of vitamin D deficiency or as vitamin D supplementation during pregnancy. Limitations of the studies were discussed in the text.

Therefore, this manuscript is an updated non-systematic review of the literature about vitamin D and pregnancy, with emphasis on the maternal–fetal impact of vitamin D deficiency.

Physiology and Biological Role of Vitamin D

Vitamin D, or calciferol, is currently considered an essential pro-hormone. The term vitamin D actually comprises a series of fat-soluble secosteroids, of which vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are the main representatives. Vitamin D2 is added to foods and differs from vitamin D3 in their side chain structure. Vitamin D3 is synthesized in the skin from 7-dehydrocholesterol after exposure to ultraviolet B (UVB) radiation, and is under the influence of several factors, including the seasons of the year, skin colour, latitude, altitude, sunscreen use, age, and exposed skin area [2]. Therefore, exposure to sunlight is the main source of vitamin D, although some foods provide a direct supply of vitamin D_3 [6]. Both ergocalciferol and cholecalciferol are manufactured commercially and available as dietary supplements. They are pro-hormones and exhibit identical responses in the body [7, 8], although there is not an agreement in literature regarding the potency of these two forms of vitamin D and evidence in humans is lacking [8, 9]. All forms of vitamin D are considered biologically inactive until they undergo enzyme-mediated hydroxylation reactions. The first such reaction takes place in the liver, mediated by 25α-hydroxylase, and produces 25-hydroxyvitamin D, the most abundant circulating form of vitamin D; the second reaction takes place in the kidney, mediated by 1α-hydroxylase, and produces 1,25-dihydroxyvitamin D, a biologically active hormone. Renal 1,25-dihydroxyvitamin D synthesis is regulated positively by parathyroid hormone (PTH) and negatively by fibroblast growth factor-23. Serum calcium and phosphorus levels also influence these reactions [2].

The classic effect of vitamin D is regulation of calcium and phosphorus homeostasis and maintenance of bone health. However, most tissues in the body express receptors for the active form of vitamin D and many of these contain the enzyme required for conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D for local use [1]. Hence, several extra-skeletal roles have been ascribed to vitamin D, such as regulation of the innate and adaptive immune system, reduction of proliferation of cancer cells, regulation of cardiovascular function and blood pressure and of hormone secretion, including stimulation of insulin secretion [1].

In view of the importance of vitamin D, the Institute of Medicine (IOM) recently published [8] new recommended daily intakes for calcium and vitamin D based on the current evidence of bone health, chronic disease, and health outcome indicators for the United States population. During pregnancy and lactation, the recommended daily intake is 600 IU, taking into account the needs of the fetus and maternal milk output.

Vitamin D Deficiency

The IOM recommends [8] that the diagnosis of vitamin D deficiency should be performed by 25-hydroxyvitamin D measurement, since it is the best biomarker of deficiency and reflects both endogenous vitamin D synthesis and vitamin D supplementation. The cut-off value for diagnosis of vitamin D deficiency should be set at 20 ng/mL (50 nmol/L) [8] (To convert from ng/mL to nmol/L, multiply by 2.5; vitamin D levels will be expressed as ng/mL throughout this article). Cut-off values for vitamin D insufficiency in the current literature, including the latest Endocrine Society recommendations, range from 20 to 30 ng/mL [2, 6], although the IOM stresses that higher cut-offs may artificially inflate the prevalence of hypovitaminosis D.

There is no evidence to suggest any benefit of population-wide screening for vitamin D deficiency, with current recommendations suggesting measurement of 25-hydroxyvitamin D status in at-risk individuals [6]. Therefore, screening is indicated in patients with rickets, osteomalacia, osteopenia or osteoporosis, chronic kidney disease, liver failure, malabsorption, obesity, and patients on anti-epileptics, anti-retroviral drugs, and glucocorticoids, as well as in pregnant and nursing women [6].

Vitamin D deficiency has been increasingly recognized as a worldwide epidemic, affecting children, adults and the elderly alike [2]. The leading cause of vitamin D deficiency is lack of sun exposure. Sunscreen use, ageing, darker skin pigmentation, and winter (especially above the 33rd parallel north and below the 33rd parallel south) are associated with reduced vitamin D synthesis [2, 3]. Intestinal malabsorption, increased vitamin D catabolism (i.e., due to anti-epileptic or anti-retroviral therapy), kidney failure, nephrotic syndrome, and liver failure are also associated with vitamin D deficiency [2]. Obesity, in turn, is associated with hypovitaminosis D due to deposition of vitamin D (whether of dietary origin or endogenous) in adipose tissue, thus reducing its bioavailability [10].

The consequences of hypovitaminosis D have been the object of extensive study. They include reduced intestinal

Table 1 Prevalence of vitamin D deficiency among different populations of pregnant women

Study	Prevalence (%)	Location, latitude	Cut off level (ng/mL)	Vitamin D supplementation[a]
Grant et al. [76]	57.7	Auckland, New Zaeland, 36°	<20	5 %
Weinert et al. [77][b]	53.3	Porto Alegre, Brazil, 30°	<20	0
McAree et al. [17]	36	London, England, 51°N	<10	NA
Gernard et al. [18]	34.8	12 U.S. Medical Centers, variable latitude	<15	NA
Aly et al. [78]	14.2	Khafji Joint Operation Hospital, Arabia Saudita, 28°	<12	0
Song et al. [79]	96.8	Beijing, China, 39°	<20	46.4 %
Toher et al. [80]	60.7	Dublin, Ireland, 53°	<12	10 %
Parildar et al. [81][c]	35.8	Istanbul, Turkey, 41°	<20	0
Bartoszewicz et al. [82]	31.3	Warsaw, Poland, 52°	<20	72.7 %
Vandevijvere et al. [83]	44.6	Belgium, variable latitude	<20	62 %
Collins-Fulea et al. 2012 [84]	71.7	Michigan, U.S.A., 42°	<20	NA[d]
Haggarty et al. [85]	21.5	North Scotland, 57°	<10	21 %
Gale et al. [27]	21.2	Southampton, England, 50°	<11	6.5
Bodnar et al. [86]	29.2	Pittsburgh, U.S.A., 40°	<15	90 %
Lee et al. [87]	50	Boston, U.S.A., 42°	<12	70 %
Waiters et al. [19]	6	Inuvik, Canada, 68°	<12	71.9 %

NA not available

[a] Vitamin D supplementation at the moment of serum 25-hydroxyvitamin D measurement

[b] Women with gestational diabetes

[c] Control group (non-diabetic pregnant women)

[d] All women with vitamin D insufficiency received supplementation, but the data about how many women were taking supplements at the time of vitamin D measurement is not available

absorption of calcium and phosphorus and increased PTH levels [11], leading to bone density loss. In adults, this condition may result in osteomalacia, osteopenia, osteoporosis and increased risk of fractures; in children, it may lead to rickets [2]. Studies have shown that, in addition to bone damage, vitamin D deficiency is associated with other co-morbidities [1, 2], such as neoplasms [12], autoimmune diseases (including type 1 diabetes mellitus), infections, insulin resistance and type 2 diabetes mellitus (DM) [13], cardiovascular and all-cause mortality [14].

Vitamin D and Pregnancy

Significance and Prevalence of Vitamin D Deficiency

During pregnancy, mobilization of maternal calcium stores is required for fetal skeletal development. This leads to a variety of physiological adaptations, such as increased maternal bone mobilization and increased absorption of calcium in the bowel, which are at least partly mediated by 1,25-dihydroxyvitamin D. Total 1,25-dihydroxyvitamin D status increases in the first trimester, whereas free 1,25-dihydroxyvitamin D levels increase in the third trimester, both returning to normal during the puerperal period and lactation [15, 16]. Renal synthesis, stimulated by prolactin and placental lactogen, appears to play the most important role, although the placenta, decidua, and fetal kidneys also express 1α-hydroxylase [16]. It bears stressing that vitamin D circulates almost entirely in a form bound to serum protein, and that, in pregnancy, vitamin D-binding protein levels are increased. Nevertheless, free 1,25-dihydroxyvitamin D levels are elevated in pregnancy [15]. Hence, maintenance of optimal mineral metabolism during pregnancy without compromising maternal or fetal bone mass may be challenging in women with vitamin D deficiency.

Prevalence of hypovitaminosis D in pregnancy is considered high in different populations (Table 1), although it may vary according the latitude, ethnicity, supplementation of vitamin D, body mass index, season and the cut-off used to define deficiency of vitamin D among studies [17, 18].

Fetal Repercussions

As noted above, the fetus depends on maternal 25-hydroxyvitamin D and calcium stores; therefore, the high rate of vitamin D deficiency in pregnancy has repercussions in the offspring of affected women [3, 4]. Plasma levels of vitamin D in the neonate correspond to approximately 60–70 % of maternal levels [19], although some studies have reported even lower values [20]. In a Canadian study, the prevalence of vitamin D deficiency (defined as cord blood levels of vitamin D < 11 ng/mL) among neonates born to mothers who were on vitamin D replacement during pregnancy was 46 %, with variations attributed to season and skin colour [21].

In observational studies, the incidence of SGA birth was related to vitamin D status in many studies [5, 18, 22–25]. In a prospective cohort study, vitamin D levels below 10 ng/mL in the second trimester were associated with a threefold risk of SGA, although there was no significant, continuous association between vitamin D and birth weight [22]. In another multi-ethnic cohort study of over 3,000 pregnancies, vitamin D deficiency at 13 weeks gestational age was associated with low birth weight and increased risk of SGA [23]. In a U.S. study of over 2,000 births, 25-hydroxyvitamin D levels >15 ng/mL before 26 weeks gestational age was associated with higher birth weight and larger head circumference and halved the risk of SGA birth [18]. Conversely, other observational studies have failed to demonstrate an association between vitamin D deficiency and birth weight or length [26, 27]. Nevertheless, a meta-analysis of observational studies, published in 2013, reinforced the association between vitamin D deficiency and risk of SGA birth [5]. Therefore, the increased risk of SGA newborns in pregnancies with vitamin D deficiency is one of the most studied endpoints until this moment and this association is demonstrated in many observational studies and meta-analysis.

An established association exists between low birth weight and increased risk of cardiovascular disease and type 2 DM in adulthood [28, 29]. However, despite the likely association between hypovitaminosis D during pregnancy and SGA newborns, their long-term consequences have yet to be fully elucidated. In the longest UK cohort studied thus far on the topic, only 30 % of the children of mothers assessed for hypovitaminosis D in late pregnancy returned for follow-up at age 9 years [27]. The cardiovascular parameters assessed in these children were not associated with maternal vitamin D status during pregnancy [27].

Longitudinal growth and bone mineralization in childhood may also be affected by gestational vitamin D deficiency [4, 26, 30, 31]. During the fetal period, vitamin D appears to be associated with femoral growth [4, 30]; at birth, infants born to women with lower vitamin D status have been found to have decreased long-bone length [26]. However, it is not a universal finding and some studies disagree with this results [27, 31]. Bone mass was reported to be lower in the offspring of women with lower vitamin D status [32], but a recent prospective and well-designed study did not find any association [33]. Therefore, the real influence of maternal vitamin D upon offspring bone health is still under study.

Although a Japanese study reported lower levels of vitamin D in women with preterm labour [34], other longitudinal studies have not corroborated this association [35]. Likewise, gestational age at birth was similar between vitamin D-deficient and non-deficient groups in some cohorts [36]. Other investigators have reported lower gestational age at delivery among vitamin D-deficient women [23, 26], although the difference in gestational age was as small as 0.2 weeks in one study [23] and lost statistical significance after adjustment in the other [26]. The association between vitamin D deficiency and prematurity is still controversial.

The role of maternal vitamin D in childhood respiratory illnesses has also been studied. The risk of lower respiratory tract infection by the respiratory syncytial virus [37] and of any history of respiratory tract infection [38] were associated with lower cord blood vitamin D levels in neonates. The risk of recurrent wheezing also appears to be lower in children whose mothers had higher vitamin D intake during pregnancy [39] and when cord blood vitamin D levels are higher [38]. However, the association with asthma remains uncertain [27, 38]. Therefore, neonatal respiratory infections appear to be associated with maternal hypovitaminosis D, but more corroborative studies should be performed.

The risk of other atopic manifestations, such as eczema [27] and food allergies [40], may be positively associated with maternal vitamin D status. On the other hand, in a study of 231 infants assessed during the first year of life, the risk of eczema was higher among those with a cord blood vitamin D level below 20 ng/mL [41]. Therefore, the relationship between vitamin D and immune response remains contradictory and under-explored.

The evidence for an association between vitamin D deficiency and risk of type 1 DM in children is also controversial. A recent nested case–control study found a twofold risk of type 1 DM development in the offspring of women with gestational vitamin D levels at the lowest quartile [42]. Conversely, a Finnish study found no differences in vitamin D levels between women whose children developed type 1 DM and those who did not [43].

In a Spanish cohort, maternal vitamin D status correlated positively with child mental and psychomotor development scores at age ~14 months [44]. A systematic

review reported an association between birth month and risk of developing multiple sclerosis, particularly in areas with poor sunlight exposure, which may suggest an influence of vitamin D during pregnancy [45]. Maternal milk intake and vitamin D status may also be associated with reduced risk of multiple sclerosis in the offspring [46]. However, a case–control study found no such association [47]. Further research is required to ascertain whether a relationship exists between maternal vitamin D status during pregnancy and psychomotor development and neurological disease in children.

Maternal Repercussions

One of the maternal complications most closely associated with vitamin D deficiency during pregnancy is pre-eclampsia. Many observational studies have reported an increased risk of pre-eclampsia among women with low vitamin D status [48–51]. However, other studies have failed to confirm this association [35, 52–54], particularly in high-risk subgroups [52, 54]. A meta-analysis of observational studies published in 2013 suggested a relationship between hypovitaminosis D and the incidence of pre-eclampsia, but the association was non-significant in the studies that adjusted for confounders [5]. Therefore, the association between hypovitaminosis D and pre-eclampsia seems probable, but it should be confirmed by additional well-designed prospective studies, especially in women of high-risk.

The role of vitamin D in type 2 DM and GDM development has also been studied, and vitamin D deficiency appears to be associated with altered glucose homeostasis during pregnancy [5, 55]. Hypovitaminosis D in early pregnancy or in the second trimester is associated with increased incidence of GDM, an association that appears to be independent of maternal age, race, and body weight [36, 56]. In a cohort of pregnant women whose vitamin D levels were measured before gestational age 16 weeks, increased vitamin D status were associated with a reduction in risk of maternal hyperglycaemia at gestational age 24 and 28 weeks, although only in smokers [57]. Therefore, vitamin D may be a potentially modifiable risk factor for GDM.

Vitamin D deficiency has also been consistently associated with increased incidence of bacterial vaginosis during pregnancy [58], and this association was recently supported by a systematic review [5]. Bacterial vaginosis incidence is relevant since it has been associated with adverse obstetrical outcomes such as premature rupture of membranes, preterm birth, early labor, postpartum endometritis [59] and preclinical pregnancy loss [60]. It may also has gynaecological consequences to women's health, such as endometritis, increased risk of acquiring sexually transmitted disease [59], including HIV [61], cervical intraepithelial neoplasia [62] and tubal infertility [60].

Increased rates of caesarean section among women with hypovitaminosis D have been reported by some authors [63, 64], but other studies suggest this outcome is independent of maternal vitamin D status [35]. This association must be clarified since caesarean delivery may bring short and long term complications to women, such as rehospitalization, postpartum infections [65], deep vein thrombosis [66], and abnormal placentation in future pregnancies [67].

In the Amsterdam cohort, maternal vitamin D deficiency in early pregnancy was associated with increased levels of depression symptoms as detected on a questionnaire administered at 16 weeks gestational age [68]. However, a causal relationship cannot be established, as vitamin D measurements were obtained at a time very close to questionnaire administration [68]. In a sample of African-American women, serum vitamin D status in early pregnancy were inversely correlated with scores on a depression scale [69]. Therefore, initial data suggests a possible association of depression and hypovitaminosis D, but further studies are necessary.

Vitamin D Supplementation During Pregnancy

Clinical trials of vitamin D replacement during pregnancy have been heterogeneous, and their findings on the reduction of adverse maternal–fetal outcomes remain controversial. In 1980, supplementation with ergocalciferol at a dose of 1,000 IU daily in Asian women during the third trimester of pregnancy led to a non-significant reduction in the rate of SGA birth, from 29 to 15 %, and neonates in the control group had larger fontanelles, suggesting impaired ossification [20]. There were no between-group differences in gestational age at birth [20]. In a clinical trial led by Hollis et al. [70], 350 women were randomly allocated to receive 400, 2,000 or 4,000 IU/day of vitamin D and followed until delivery. The highest dose (4,000 IU/day) was the most effective in inducing sufficient maternal levels of vitamin D. However, supplementation was not associated with any difference in gestational age at birth, birth weight, or need for neonatal intensive care unit admission [70]. A 2012 Cochrane Collaboration analysis reported a lower incidence of birth weight <2,500 g when vitamin D supplementation was provided during pregnancy, although the difference was only borderline significant (relative risk 0.48; 95 % CI 0.23–1.01), and there were no reductions in rates of pre-eclampsia, nephritic syndrome, stillbirth, or neonatal mortality [71]. Other clinical trials have since been published in 2013. In one such trial, vitamin D supplementation at doses of 2,000 or 4,000 IU/day versus 400 IU/day was not associated with differences in fetal anthropometric parameters or gestational age at birth, although the main objective of the study was to assess

serum 25(OH)D levels in maternal and cord blood [72]. Wagner et al. [73] randomized 257 pregnant women to receive 2,000 or 4,000 IU/day of vitamin D and found a positive association between vitamin D dose and neonatal weight percentile, as well as a negative association between end 25(OH)D levels and premature labour and infection. It bears stressing that, in all of the aforementioned studies, higher doses were considered safe during pregnancy and more effective at inducing adequate 25(OH)D status [70, 72, 73]. Therefore, the authors consider traditional recommendations for vitamin D supplementation during pregnancy to be insufficient [73]. Two other studies assessed vitamin D doses of 35,000 U/week [74] and 50,000 U/week [75], which increased maternal and neonatal/cord blood vitamin D status without any adverse effects. Therefore, additional studies are still required to define optimal dosages for vitamin D supplementation during pregnancy and, particularly, their actual benefits in reducing the incidence of adverse outcomes in the mother and infant.

Conclusion

Vitamin D deficiency is highly prevalent worldwide, both in the general population and among pregnant women. The long-term consequences of hypovitaminosis D have yet to be fully elucidated. Specifically in pregnancy, studies have found it to be associated with increased incidence of adverse maternal and fetal outcomes. The better studied endpoints until this moment are the increased incidence of SGA newborns, gestational diabetes, pre-eclampsia and bacterial vaginosis; and other consequences of hypovitamosis D are still under study. However, at this time, many studies have methodological flaws and definitive conclusions cannot be drawn. It is also important to highlight that available observational data do not confirm causality.

Most international experts and organizations agree on the need to screen for vitamin D deficiency during pregnancy and provide supplementation when indicated, although there is no consensus as to the optimal dosage of supplementation and no agreement on the actual benefit it provides in terms of maternal and fetal endpoints. Further research is required to clarify the association between vitamin D deficiency and adverse maternal and fetal outcomes, particularly among high-risk populations (such as women with diabetes and hypertension), and to define optimal strategies for vitamin D supplementation in pregnancy.

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Conflict of interest None.

References

1. Wolden-Kirk, H., Gysemans, C., Verstuyf, A., et al. (2012). Extraskeletal effects of vitamin D. *Endocrinology and Metabolism Clinics of North America, 41*(3), 571–594.
2. Holick, M. F. (2007). Vitamin D deficiency. *The New England Journal of Medicine, 357*(3), 266–281.
3. Principi, N., Bianchini, S., Baggi, E., et al. (2013). Implications of maternal vitamin D deficiency for the fetus, the neonate and the young infant. *European Journal of Nutrition, 52*(3), 859–867.
4. Walsh, J. M., Kilbane, M., McGowan, C. A., et al. (2013). Pregnancy in dark winters: Implications for fetal bone growth? *Fertility and Sterility, 99*(1), 206–211.
5. Aghajafari, F., Nagulesapillai, T., Ronksley, P. E., et al. (2013). Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: Systematic review and meta-analysis of observational studies. *BMJ: British Medical Journal, 346*, f1169.
6. Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., et al. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism, 96*(7), 1911–1930.
7. Jones, G., Strugnell, S. A., & DeLuca, H. F. (1998). Current understanding of the molecular actions of vitamin D. *Physiological Reviews, 78*(4), 1193–1231.
8. Institute of Medicine. (2011). Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press. Acesso em janeiro 2013. http://books.nap.edu/openbook.php?record_id=13050.
9. Holick, M. F., Biancuzzo, R. M., Chen, T. C., et al. (2008). Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *The Journal of Clinical Endocrinology and Metabolism, 93*(3), 677–681. doi:10.1210/jc.2007-2308.
10. Wortsman, J., Matsuoka, L. Y., Chen, T. C., et al. (2000). Decreased bioavailability of vitamin D in obesity. *The American Journal of Clinical Nutrition, 72*(3), 690–693.
11. Premaor, M. O., Paludo, P., Manica, D., et al. (2008). Hypovitaminosis D and secondary hyperparathyroidism in resident physicians of a general hospital in southern Brazil. *Journal of Endocrinological Investigation, 31*(11), 991–995.
12. Holick, M. F., & Vitamin, D. (2013). Sunlight and cancer connection. *Anti-Cancer Agents in Medicinal Chemistry, 13*(1), 70–82.
13. Afzal, S., Bojesen, S. E., & Nordestgaard, B. G. (2013). Low 25-hydroxyvitamin D and risk of type 2 diabetes: A prospective cohort study and meta-analysis. *Clinical Chemistry, 59*(2), 381–391.
14. Dobnig, H., Pilz, S., Scharnagl, H., et al. (2008). Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Archives of Internal Medicine, 168*(12), 1340–1349.
15. Bikle, D. D., Gee, E., Halloran, B., et al. (1984). Free 1,25-dihydroxyvitamin D levels in serum from normal subjects, pregnant subjects, and subjects with liver disease. *The Journal of Clinical Investigation, 74*(6), 1966–1971.
16. Kovacs, C. S. (2005). Calcium and bone metabolism during pregnancy and lactation. *Journal of Mammary Gland Biology and Neoplasia, 10*(2), 105–118.
17. McAree, T., Jacobs, B., Manickavasagar, T., et al. (2013). Vitamin D deficiency in pregnancy—Still a public health issue. *Maternal and Child Nutrition, 9*(1), 23–30.
18. Gernand, A. D., Simhan, H. N., Klebanoff, M. A., et al. (2013). Maternal serum 25-hydroxyvitamin D and measures of newborn and placental weight in a U.S. multicenter cohort study. *The Journal of Clinical Endocrinology and Metabolism, 98*(1), 398–404.

19. Waiters, B., Godel, J. C., & Basu, T. K. (1998). Perinatal vitamin D and calcium status of northern Canadian mothers and their newborn infants. *Journal of the American College of Nutrition, 18*(2), 122–126.
20. Brooke, O. G., Brown, I. R., Bone, C. D., et al. (1980). Vitamin D supplements in pregnant Asian women: Effects on calcium status and fetal growth. *The British Medical Journal, 280*(6216), 751–754.
21. Basile, L. A., Taylor, S. N., Wagner, C. L., et al. (2007). Neonatal vitamin D status at birth at latitude 32 degrees 72': Evidence of deficiency. *Journal of Perinatology: Official Journal of the California Perinatal Association, 27*(9), 568–571.
22. Burris, H. H., Rifas-Shiman, S. L., Camargo, C. A, Jr, et al. (2012). Plasma 25-hydroxyvitamin D during pregnancy and small-for-gestational age in black and white infants. *Annals of Epidemiology, 22*(8), 581–586.
23. Leffelaar, E. R., Vrijkotte, T. G., & van Eijsden, M. (2010). Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: Results of the multi-ethnic Amsterdam Born Children and their Development cohort. *The British Journal of Nutrition, 104*(1), 108–117.
24. Bodnar, L. M., Catov, J. M., Zmuda, J. M., et al. (2010). Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. *The Journal of Nutrition, 140*(5), 999–1006.
25. Robinson, C. J., Wagner, C. L., Hollis, B. W., et al. (2011). Maternal vitamin D and fetal growth in early-onset severe pre-eclampsia. *American Journal of Obstetrics and Gynecology, 204*(6), 556 e1–556 e4.
26. Morley, R., Carlin, J. B., Pasco, J. A., et al. (2006). Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. *The Journal of Clinical Endocrinology and Metabolism, 91*(3), 906–912.
27. Gale, C. R., Robinson, S. M., Harvey, N. C., et al. (2008). Maternal vitamin D status during pregnancy and child outcomes. *European Journal of Clinical Nutrition, 62*(1), 68–77.
28. Barker, D. J. (2004). The developmental origins of adult disease. *Journal of the American College of Nutrition, 23*(6 Suppl), 588S–595S.
29. Kaijser, M., Bonamy, A. K., Akre, O., et al. (2008). Perinatal risk factors for ischemic heart disease: Disentangling the roles of birth weight and preterm birth. *Circulation, 117*(3), 405–410. doi:10.1161/CIRCULATIONAHA.107.710715.
30. Ioannou, C., Javaid, M. K., Mahon, P., et al. (2012). The effect of maternal vitamin D concentration on fetal bone. *The Journal of Clinical Endocrinology and Metabolism, 97*(11), E2070–E2077.
31. Weiler, H., Fitzpatrick-Wong, S., Veitch, R., et al. (2005). Vitamin D deficiency and whole-body and femur bone mass relative to weight in healthy newborns. *CMAJ: Canadian Medical Association Journal = journal de l'Association medicale canadienne, 172*(6), 757–761.
32. Javaid, M. K., Crozier, S. R., Harvey, N. C., et al. (2006). Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: A longitudinal study. *Lancet, 367*(9504), 36–43.
33. Lawlor, D. A., Wills, A. K., Fraser, A., et al. (2013). Association of maternal vitamin D status during pregnancy with bone-mineral content in offspring: A prospective cohort study. *Lancet, 381*(9884), 2176–2183. doi:10.1016/S0140-6736(12)62203-X.
34. Shibata, M., Suzuki, A., Sekiya, T., et al. (2011). High prevalence of hypovitaminosis D in pregnant Japanese women with threatened premature delivery. *Journal of Bone and Mineral Metabolism, 29*(5), 615–620.
35. Fernandez-Alonso, A. M., Dionis-Sanchez, E. C., Chedraui, P., et al. (2012). First-trimester maternal serum 25-hydroxyvitamin D(3) status and pregnancy outcome. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics, 116*(1), 6–9.
36. Burris, H. H., Rifas-Shiman, S. L., Kleinman, K., et al. (2012). Vitamin D deficiency in pregnancy and gestational diabetes mellitus. *American Journal of Obstetrics and Gynecology, 207*(3), 182 e1–182 e8.
37. Belderbos, M. E., Houben, M. L., Wilbrink, B., et al. (2011). Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. *Pediatrics, 127*(6), e1513–e1520.
38. Camargo, C. A, Jr, Ingham, T., Wickens, K., et al. (2011). Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics, 127*(1), e180–e187.
39. Camargo, C. A, Jr, Rifas-Shiman, S. L., Litonjua, A. A., et al. (2007). Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *The American Journal of Clinical Nutrition, 85*(3), 788–795.
40. Weisse, K., Winkler, S., Hirche, F., et al. (2013). Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. *Allergy, 68*(2), 220–228.
41. Jones, A. P., Palmer, D., Zhang, G., et al. (2012). Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. *Pediatrics, 130*(5), e1128–e1135.
42. Sorensen, I. M., Joner, G., Jenum, P. A., et al. (2012). Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. *Diabetes, 61*(1), 175–178.
43. Miettinen, M. E., Reinert, L., Kinnunen, L., et al. (2012). Serum 25-hydroxyvitamin D level during early pregnancy and type 1 diabetes risk in the offspring. *Diabetologia, 55*(5), 1291–1294.
44. Morales, E., Guxens, M., Llop, S., et al. (2012). Circulating 25-hydroxyvitamin D3 in pregnancy and infant neuropsychological development. *Pediatrics, 130*(4), e913–e920.
45. Torkildsen, O., Grytten, N., Aarseth, J., et al. (2012). Month of birth as a risk factor for multiple sclerosis: An update. *Acta Neurologica Scandinavica. Supplementum, 195*, 58–62.
46. Mirzaei, F., Michels, K. B., Munger, K., et al. (2011). Gestational vitamin D and the risk of multiple sclerosis in offspring. *Annals of Neurology, 70*(1), 30–40.
47. Salzer, J., Hallmans, G., Nystrom, M., et al. (2012). Vitamin D as a protective factor in multiple sclerosis. *Neurology, 79*(21), 2140–2145.
48. Baker, A. M., Haeri, S., Camargo, C. A, Jr, et al. (2010). A nested case–control study of midgestation vitamin D deficiency and risk of severe preeclampsia. *The Journal of Clinical Endocrinology and Metabolism, 95*(11), 5105–5109.
49. Bodnar, L. M., Catov, J. M., Simhan, H. N., et al. (2007). Maternal vitamin D deficiency increases the risk of preeclampsia. *The Journal of Clinical Endocrinology and Metabolism, 92*(9), 3517–3522.
50. Robinson, C. J., Alanis, M. C., Wagner, C. L., et al. (2010). Plasma 25-hydroxyvitamin D levels in early-onset severe pre-eclampsia. *American Journal of Obstetrics and Gynecology, 203*(4), 366 e1–366 e6.
51. Wei, S. Q., Audibert, F., Hidiroglou, N., et al. (2012). Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia. *BJOG: An International Journal of Obstetrics and Gynaecology, 119*(7), 832–839.
52. Azar, M., Basu, A., Jenkins, A. J., et al. (2011). Serum carotenoids and fat-soluble vitamins in women with type 1 diabetes and preeclampsia: A longitudinal study. *Diabetes Care, 34*(6), 1258–1264.
53. Powe, C. E., Seely, E. W., Rana, S., et al. (2010). First trimester vitamin D, vitamin D binding protein, and subsequent pre-eclampsia. *Hypertension, 56*(4), 758–763.
54. Shand, A. W., Nassar, N., Von Dadelszen, P., et al. (2010). Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for pre-eclampsia. *BJOG: An International Journal of Obstetrics and Gynaecology, 117*(13), 1593–1598.

55. Senti, J., Thiele, D. K., & Anderson, C. M. (2012). Maternal vitamin D status as a critical determinant in gestational diabetes. *Journal of Obstetric, Gynecologic, and Neonatal Nursing: JOGNN/NAACOG, 41*(3), 328–338.
56. Parlea, L., Bromberg, I. L., Feig, D. S., et al. (2012). Association between serum 25-hydroxyvitamin D in early pregnancy and risk of gestational diabetes mellitus. *Diabetic Medicine: A Journal of the British Diabetic Association, 29*(7), e25–e32.
57. Tomedi, L. E., Simhan, H. N., & Bodnar, L. M. (2013). Early-pregnancy maternal vitamin D status and maternal hyperglycaemia. *Diabetic Medicine*: *A Journal of the British Diabetic Association, 30*(9), 1033–1039. doi:10.1111/dme.12229.
58. Hensel, K. J., Randis, T. M., Gelber, S. E., et al. (2011). Pregnancy-specific association of vitamin D deficiency and bacterial vaginosis. *American Journal of Obstetrics and Gynecology, 204*(1), 41 e1–41 e9.
59. Martin, D. H. (2012). The microbiota of the vagina and its influence on women's health and disease. *The American Journal of the Medical Sciences, 343*(1), 2–9. doi:10.1097/MAJ.0b013e31823ea228.
60. van Oostrum, N., De Sutter, P., Meys, J., et al. (2013). Risks associated with bacterial vaginosis in infertility patients: A systematic review and meta-analysis. *Human Reproduction, 28*(7), 1809–1815. doi:10.1093/humrep/det096.
61. Mirmonsef, P., Krass, L., Landay, A., et al. (2012). The role of bacterial vaginosis and trichomonas in HIV transmission across the female genital tract. *Current HIV Research, 10*(3), 202–210.
62. Gillet, E., Meys, J. F., Verstraelen, H., et al. (2012). Association between bacterial vaginosis and cervical intraepithelial neoplasia: Systematic review and meta-analysis. *PLoS One, 7*(10), e45201. doi:10.1371/journal.pone.0045201.
63. Merewood, A., Mehta, S. D., Chen, T. C., et al. (2009). Association between vitamin D deficiency and primary cesarean section. *The Journal of Clinical Endocrinology and Metabolism, 94*(3), 940–945.
64. Scholl, T. O., Chen, X., & Stein, P. (2012). Maternal vitamin D status and delivery by cesarean. *Nutrients, 4*(4), 319–330.
65. Declercq, E., Barger, M., Cabral, H. J., et al. (2007). Maternal outcomes associated with planned primary cesarean births compared with planned vaginal births. *Obstetrics and Gynecology, 109*(3), 669–677. doi:10.1097/01.AOG.0000255668.20639.40.
66. Simpson, E. L., Lawrenson, R. A., Nightingale, A. L., et al. (2001). Venous thromboembolism in pregnancy and the puerperium: Incidence and additional risk factors from a London perinatal database. *BJOG: An International Journal of Obstetrics and Gynaecology, 108*(1), 56–60.
67. Marshall, N. E., Fu, R., & Guise, J. M. (2011). Impact of multiple cesarean deliveries on maternal morbidity: A systematic review. *American Journal of Obstetrics and Gynecology, 205*(3), 262 e1–262 e8. doi:10.1016/j.ajog.2011.06.035.
68. Brandenbarg, J., Vrijkotte, T. G., Goedhart, G., et al. (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*(7), 751–757.
69. Cassidy-Bushrow, A. E., Peters, R. M., Johnson, D. A., et al. (2012). Vitamin D nutritional status and antenatal depressive symptoms in African American women. *Journal of Women's Health, 21*(11), 1189–1195.
70. Hollis, B. W., Johnson, D., Hulsey, T. C., et al. (2011). Vitamin D supplementation during pregnancy: Double-blind, randomized clinical trial of safety and effectiveness. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 26*(10), 2341–2357.
71. De-Regil, L. M., Palacios, C., Ansary, A., et al. (2012). Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews, 2*, CD008873.
72. Dawodu, A., Saadi, H. F., Bekdache, G., et al. (2013). Randomized controlled trial (RCT) of vitamin D supplementation in pregnancy in a population with endemic vitamin D deficiency. *The Journal of Clinical Endocrinology and Metabolism, 98*(6), 2337–2346.
73. Wagner, C. L., McNeil, R., Hamilton, S. A., et al. (2013). A randomized trial of vitamin D supplementation in 2 community health center networks in South Carolina. *American Journal of Obstetrics and Gynecology, 208*(2), 137 e1–137 e13.
74. Roth, D. E., Al Mahmud, A., Raqib, R., et al. (2013). Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: The AViDD trial. *Nutrition Journal, 12*(1), 47.
75. Hashemipour, S., Lalooha, F., Zahir Mirdamadi, S., et al. (2013). Effect of vitamin D administration in vitamin D-deficient pregnant women on maternal and neonatal serum calcium and vitamin D concentrations: A randomised clinical trial. *The British Journal of Nutrition, 110*(9), 1611–1616. doi:10.1017/S0007114513001244.
76. Grant, C. C., Stewart, A. W., Scragg, R., et al. (2014). Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. *Pediatrics, 133*(1), e143–e153. doi:10.1542/peds.2013-2602.
77. Weinert, L. S., Reichelt, A. J., Schmitt, L. R., et al. (2014) Serum vitamin D insufficiency is related to blood pressure levels in diabetic pregnancy. *American Journal of Hypertension*. doi:10.1093/ajh/hpu043.
78. Aly, Y. F., El Koumi, M. A., & Abd El Rahman, R. N. (2013). Impact of maternal vitamin D status during pregnancy on the prevalence of neonatal vitamin D deficiency. *Pediatric Reports, 5*(1), 6. doi:10.4081/pr.2013.e6.
79. Song, S. J., Zhou, L., Si, S., et al. (2013). The high prevalence of vitamin D deficiency and its related maternal factors in pregnant women in Beijing. *PLoS One, 8*(12), e85081. doi:10.1371/journal.pone.0085081.
80. Toher, C., Lindsay, K., McKenna, M., et al. (2013). Relationship between vitamin D knowledge and 25-hydroxyvitamin D levels amongst pregnant women. *Journal of Human Nutrition and Dietetics: The Official Journal of the British Dietetic Association,*. doi:10.1111/jhn.12150.
81. Parildar, H., Dogruk Unal, A., Aksan Desteli, G., et al. (2013). Frequency of vitamin D deficiency in pregnant diabetics at Baskent University Hospital, Istanbul. *Pakistan Journal of Medical Sciences, 29*(1), 15–20. doi:10.12669/pjms.291.2896.
82. Bartoszewicz, Z., Kondracka, A., Krasnodebska-Kiljanska, M., et al. (2013). Vitamin D insufficiency in healthy pregnant women living in Warsaw. *Ginekologia Polska, 84*(5), 363–367.
83. Vandevijvere, S., Amsalkhir, S., Van Oyen, H., et al. (2012). High prevalence of vitamin D deficiency in pregnant women: A national cross-sectional survey. *PLoS One, 7*(8), e43868. doi:10.1371/journal.pone.0043868.
84. Collins-Fulea, C., Klima, K., & Wegienka, G. R. (2012). Prevalence of low vitamin D levels in an urban midwestern obstetric practice. *Journal of Midwifery and Women's Health, 57*(5), 439–444. doi:10.1111/j.1542-2011.2012.00167.x.
85. Haggarty, P., Campbell, D. M., Knox, S., et al. (2013). Vitamin D in pregnancy at high latitude in Scotland. *The British Journal of Nutrition, 109*(5), 898–905. doi:10.1017/S0007114512002255.
86. Bodnar, L. M., Simhan, H. N., Powers, R. W., et al. (2007). High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. *The Journal of Nutrition, 137*(2), 447–452.
87. Lee, J. M., Smith, J. R., Philipp, B. L., et al. (2007). Vitamin D deficiency in a healthy group of mothers and newborn infants. *Clinical Pediatrics, 46*(1), 42–44. doi:10.1177/0009922806289311.