International Journal of Research Studies in Medical and Health Sciences
Volume 6, Issue 7, 2021, PP 24-32
ISSN : 2456-6373
DOI: https://doi.org/10.22259/ijrsmhs.0607004

Vitamin D Deficiency during Pregnancy: The Health Consequences of Vitamin D Supplementation in Mother and Infant

Behnaz Abiri, Ph.D[1], Shirin Amini, Ph.D[2], Mohammadreza Vafa, Ph.D[3]*

[1]Obesity Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Nutrition, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran
[3]Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

***Corresponding Author:** Mohammadreza Vafa, Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran. Email: Vafa.m@iums.ac.ir*

ABSTRACT

Purpose of review: *Pregnancy describes a time of rapid change, including notable shifts in vitamin D metabolism. In this review, we summarize the benefits of vitamin D supplementation and the data surrounding vitamin D requirements during this important period. Both observational and clinical trials are reviewed in the context of vitamin D health impacts during pregnancy in association with preeclampsia, preterm birth, and later disease conditions such as asthma and multiple sclerosis.*

Recent findings: *Significant amounts of vitamin Dare needed during pregnancy to protect the mother and her fetus and impart genomic imprinting on the fetus to ensure long term health consequences.*

Summary: *With enhanced knowledge about vitamin D's role as a preprohormone, it is clear that recommendations about supplementation must mirror what is clinically relevant and evidence-based. Future research that focuses on the critical period(s) leading up to conception and during pregnancy to correct deficiency or maintain optimal vitamin D states remains to be investigated. Moreover, the effects that vitamin D has on genetic signatures that minimize the risk to the mother and her developing fetus have not been elucidated.*

Keywords: *vitamin D, pregnancy, mother, infant*

INTRODUCTION

Pregnancy describes a time of rapid bodily alteration. During these notable times of physiological changes, the roles of vitamin D in pregnant compared to lactating women are different. In the pregnant woman, the primary role of vitamin D appears to be immunomodulatory rather than a calcium regulating factor, although it also would retain that function. In addition, vitamin D deficiency/insufficiency in early life is clearly an instance of the "Barker Hypothesis" (1). This theory states that certain adult-onset diseases might have their roots in nutritional disorders sustained in the perinatal period, either in utero or in the early months of infancy or both. Clearly, some conditions related to vitamin D deficiency such as asthma, multiple sclerosis and other neurological disorders would qualify (2,3,4,5,6,7,8,9,10,11).

The aim of this paper is to present new insights into the vitamin D requirements and function during pregnancy, as supported by the evidence.

VITAMIN D AND HEALTHY PREGNANCY

Achieving optimal maternal and infant health with sufficient vitamin D state is not the only objective during pregnancy. An adequate vitamin D status is needed to ensure the health of the pregnancy. A pregnancy can expand to severe disease processes such as preeclampsia and glucose intolerance that risk the health of both the mother and the infant. Preeclampsia is a pregnancy-specific disease process that influences 3–7% of all pregnancies. Development of preeclampsia likely involves abnormal placental implantation, immune dysfunction, surplus inflammation, and defects in angiogenesis (12-15). The placenta expresses 1α-hydroxylase, the enzyme needed to convert 25(OH)D to the active metabolite $1,25(OH)_2D$ (12). This active vitamin D metabolite has been demonstrated to regulate the transcription and function of genes related to placental invasion, implantation, and angiogenesis (12,16) and is being evaluated for its role in early pregnancy loss, preterm birth, and preeclampsia (12). In a

case–control study, lower vitamin D condition both in the early pregnancy and in the newborn was related to the risk of preeclampsia during pregnancy. After adjustment for confounders, a deficiency of 20 ng/mL was reported to double the preeclampsia risk (16).

In the case of another disease process in pregnancy, glucose intolerance, a cross-sectional study reported women with gestational diabetes were more probably to indicate vitamin D deficiency (<12.5 ng/ mL) than women with normal glucose control during pregnancy (17). With the known relationships of both type I and type II diabetes with vitamin D condition, this association is not unexpected (18-21). Other maternal health markers, including maternal weight gain in pregnancy, have shown adiscrepant relationship with maternal vitamin D condition (22,23). More investigation to identify the vitamin D condition required to support the health of the pregnancy is vital.

Vitamin D and Fetal Development

The maternal vitamin D condition is vital for fetal development because the fetus receives all vitamin D support from the mother (24-26). Maternal 25(OH) Dreadily transfers the placenta and is metabolized to 1, $25(OH)_2$ D by the fetal kidneys for endocrine function and by other tissues for paracrine function(24-26). At birth the neonate's serum 25(OH) Dcondition is 50–70% of maternal serum 25(OH) D levels (24-26).

Observational studies have investigated the role of vitamin D and calcium in bone development and fetal growth. The results of these studies indicate roles for both vitamin D and calcium (27, 28), but the exact mechanism, as well as the role of parathyroid hormone (PTH) concentration, remains to be elucidated. Failure of sufficient intrauterine bone mineralization, secondary to both vitamin D and calcium deficiency, has led to the development of congenital rickets (29,30). In a study of the effects of maternal vitamin D supplementation of 1000 IU/day onneonatal bone mineralization, no significant difference was reported in infant bone mineral content, as evaluated by single photon absorptiometry (31). Conversely, a longitudinal study of 198 children indicated a positive relationship between maternal serum 25(OH)D in late pregnancy and child whole-body and lumbar-spine bone mineral content by dual-energy X-ray absorptiometry (DEXA) at 9 years old (27). Another investigation of neonatal bone mineralization by DEXA demonstrated higher whole-body bone mineral content not only related to greater gestational age and higher weight at birth and higher infant 25(OH)D levels but also related to lower maternal 25(OH)D levels(32). Moreover, another study of maternal vitamin D deficiency and infant bone indicated a relationship between maternal vitamin D deficiency with delayed development of neonatal bone formation centers at birth (33). However, low maternal vitamin D levels, often associated with low maternal calcium and increased maternal PTH, has been associated with reduced birth weight (28), neonatal length (28), and head circumference at 3 and 6 months of age (34), but these results are not constant.

Observational Studies Proposing the Effect of Vitamin Dextended Beyond Calcium Homeostasis During Pregnancy

Early observational studies revealed strong associations between maternal circulating levels of 25(OH)D and glucose tolerance (35), preeclampsia (36,37), changed placental vascular pathology (38), Cesarean section (39), adverse birth outcomes (40), infection rates (2), brain function (10,11), and respiratory function (3). Recent investigations have turned to examining maternal vitamin D deficiency as a risk factor for abnormal fetal growth patterns, adverse birth outcomes, reproductive failure (41,42,43,44) and further strengthened the role of vitamin D as a contributing agent for preeclampsia (45). Also, a meta-analysis of observational studies has established the fact that maternal vitamin D deficiency enhances the risk of preterm birth (46).

While public policy cannot be set for vitamin D supplementation practices according to observational studies, this information is necessary at pointing research in the regard that could yield public policy alterations in vitamin D consumption.

Fetal Vitamin D Exposure and Health Outcomes

In a case–control study of infants with acute lower respiratory infection, the cases and their mothers indicated significantly lower serum 25(OH) Dlevels than the healthy controls (47). The newborns with infection hada mean serum 25(OH) Dlevel of 9.1 ng/mL, while the controls exhibited a mean of 16.3 ng/mL (47). Another area of immune development associated with fetal vitamin D exposure is allergic disease. In

two birth cohorts, higher maternal vitamin D condition in pregnancy was related to reduced prevalence of wheezing at 3 and 5 years-old(48,49). Conversely, in a third birth cohort, higher maternal serum 25(OH)D levels in late pregnancy was related to elevated risk of asthma at 9 years of age (50). Epidemiological studies of other disease processes that raise the likelihood for positive relationships with maternal vitamin D in pregnancy include multiple sclerosis, schizophrenia, and osteoporosis (51-54). With long-term programming in fetal development, identifying the impact of this vitamin which is important for bone health, immune function, and cell proliferation, is crucial (55).

A double-blind randomized clinical trial was conductedinat three clinical centers in the USA, which involved giving supplemental vitamin D (400 or 4400 IU/day) to pregnant women from 16 weeks of gestation until delivery. The primary outcome measure was prevention of asthma/wheezing in the child at 1, 2 and 3 years after birth. Nearly 900 high-risk participants were recruited and completed the study (56). The results showed that vitamin D supplementation during pregnancy can decrease asthma or recurrent wheezing rates in children.

A clinical trial study conducted in Denmark was also recently published (57). The results from these clinical trials and meta-analysis studies indicate that vitamin D therapy in a pregnant woman will prevent asthma/wheeze in her child (56-58). The mechanisms by which this occurs remain unclear but it is probable that epigenetic in utero alterations triggered by the vitamin D supplementation to the pregnant women lead to functional alterations in the fetus (59-61).

In the 1960s, vitamin D was considered as the cause of supravalvular stenosis (62). The published hypothesis suggested that “toxic” amounts of vitamin D during pregnancy gave rise to a clinical status entitled “infantile hypercalcemia syndrome” (62).Now this syndrome is known as “Williams syndrome”, which is a genetic disorder characterized by multi-organ involvement such as supravalvular stenos is secondary to a deficiency in elastin formation. One in 7500–20000 people areborn with this disorder which also demonstrates a magnified response to oral vitamin D supplementation (63). Abnormal vitamin D metabolism has now been established as a symptom of Williams syndrome and not acause of supravalvular stenosis (64). Despite the unknown etiology as to whether the cardiac failure is due to hypocalcemia alone or is also related an intrinsic vitamin D impact on cardiac function, supplementation with vitamin D and calcium was shown to prevent the requirement for cardiac transplantation (65).

Clinical Trials Investigating Vitamin D Supplementation During Pregnancy

In 2001, a research group conceived a large randomized controlled trial investigating the supplementation of vitamin D in a pregnant population. In this study, the researchers were supplementing pregnant women at less than 16 weeks of gestation with up to 4000 IU/d vitamin D until delivery in a double-blinded manner. The aim of the study was to investigate how much vitamin D was needed to raise circulating maternal 25(OH) Dlevels to at least 32 ng/mL by the end of gestation. They selected the 32 ng/mL concentration of circulating 25(OH) Dwas based on suppression of secondary hyperparathyroidism (66).The results of numerous analysis (other endpoints were analyzed as post hoc analyses) have been presented and published over the last few years (56,57,59,65-70). The important finding of these studies was that a 4000 IU/d dose of vitamin D safely increased serum circulating 25(OH)D to a level that normalized vitamin D metabolism and calcium homeostasis in the pregnant women. In addition, this dose was safe with not a single unfavorable effect observed attributable to vitamin D supplementation (56,57,65,69-72).

The data from the studies, when analyzed on an intent-to-treat basis, clearly reported vitamin D supplementation reduced complications of pregnancy and Cesarean births (73,74). Moreover, data and analysis from the clinical trials by researchers have demonstrated that higher doses of vitamin D during pregnancy improve birth outcome data (65,67,74).

Other clinical trials have recently reported that vitamin D reduced complications of birth and gestational diabetes (69,70,72), aeroallergen sensitization (71), and biomarkers of regulatory immunity (75). one of these studies recruited a vitamin D deficient population of pregnant women, with circulating 25(OH)D levels of <10 ng/ mL, and supplemented the treatment group with substantial amounts of vitamin D starting at 20 weeks of gestation (69). The control arm received placebo and hence remained notably vitamin D deficient during pregnancy. Vitamin

D therapy in these women led to notable reductions in pregnancy complications.

VITAMIN D-INDUCED GENOMIC CHANGES THROUGH PREGNANCY

Vitamin D supplementation in pregnancy seems to influence genetic information of several highly functional modules associated with systemic inflammation and immune responses and implicates the emergence of a distinctive immune response in women which makes them susceptible to develop preeclampsia (60,76) and other adverse consequences of pregnancy including gestational diabetes (35,70,77) and infections (78).

A recent study by Al-Garawi et al. (61) provides direct evidence of the ability of vitamin D to induce genomic alterationsin pregnancy. This study was a randomized clinical trial of vitamin D supplementation in pregnancy aimed at decreasing pediatric asthma risk (79). The trial recruited 881 women at 10-18 weeks of gestation. Longitudinal gene expression evaluations were obtained for30pregnant women, using RNA isolated from peripheral blood samples obtained in the first and third trimesters. These data propose that maternal gene expression alterations through pregnancy occur and that these alterations are associated with vitamin D supplementation which elevates the circulating vitamin D concentrations. What remains unclear is whether these alterations in maternal vitamin D concentration affect fetal development directly or via downstream impacts, and whether or not there is adirect impact of maternal gene expression on the fetus. New evidence proposes that there are direct genomic changes induced by vitamin D treatment through pregnancy that can change birth outcomes (66,68).

The VDAART study reported that vitamin D supplementation starting at approximately 14 weeks of gestation failed in anintent to-treat manner to affect preeclampsia (69). Entering pregnancy with a serum 25(OH) Dconcentration of at least 40 ng/mL gives ideal protection against development of preeclampsia. This impact of vitamin D is predicted by experimental animal models, which collectively indicated vitamin D deficiency changed placental development and embryo implantation (80,81).

In areport by Mirzakhani et al. (82), their gene expression study indicated that a set of vitamin D-elated genes were related to preeclampsia. The study reported genomic connectivity to known vitamin D-signaling pathways demonstrating the functional cohesiveness of vitamin D to the preeclampsia disease model. Most of the genes in this replication model were related to maternal systemic alterations in immune, both innate and humoral, and inflammatory biomarkers.

Maternal vitamin D supplementation is also contributed in the epigenetic regulation, DNA methylation, in children. Pathways influenced by this metabolic process include antigen processing and presentation, inflammation, regulation of cell death, cell proliferation, transmission of nerve impulse, neurogenesis, neuron differentiation, sensory organ development (59•) and vitamin D metabolism (83).

What is clear from these recent clinical trials is that a 4000 IU/d vitamin D supplement is advantageous to both mother and child and these advantages have nothing to do with the classic role of vitamin D in calcium homeostasis. What is not clear is the dose and time of supplementation required to achieve optimum outcomes. It is believed that targetinga circulating 25(OH) Dlevel of 40 ng/mL should be achieved as early as possiblein pregnancy. Because of biochemical heterogeneity in attaining a given level of 25(OH)D, it is believed all women should consume at least 4000 IU/d vitamin D before conception (84).

It has long been reported that the development of multiple sclerosis (MS) is a result of a complex interaction between genes and environment, with an important environmental agent being vitamin D deficiency (8). It is not yet clear how and when vitamin D performs to modulate risk of MS, although there is growing evidence that this occurs via genetic changes (7). Evidence demonstrates that vitamin D supplementation in pregnancy induces transcriptome and epigenetic changes through DNA methylation ingenes that regulate inflammation, metabolic processes, antigen processing, regulation of cell death, cell proliferation, transmission of nerve impulses, neurogenesis, neuron differentiation and sensory organ development (59). Along these lines, an article by Mokry et al. on Mendelian randomization provides strong support of a causal relationship of vitamin D and lower risk of MS in humans (85).

Strong experimental evidence points to dire neurological outcomes if vitamin D is restricted throughout pregnancy (86). For further information on the biochemical basis for this, it is recommended to read a recent review by Patrick and Ames (87). This review makes an excellent case for intrauterine vitamin D deficiency as it relates to autism, attention deficit disorder, bipolar disorder, schizophrenia and impulse behavior, via control of serotonin synthesis in the neonatal brain (87). There is also a fair amount of observational data available to support these notions (9,10,11,86).

Current Recommendation for Vitamin D Supplementation through Pregnancy

Currently, based on clinical trial data and substantial observational and interventional evidence, it is suggested that all pregnant women maintain a circulating 25(OH) Dlevel of at least 40 ng/mL during the earliest stages of pregnancy (65,67). This will insure maximum protection from pregnancy complications, such as preeclampsia in the mother and asthma development in the infant. To achieve this aim, intakes of at least 4000 IU/d vitamin D will be needed because of variable individual abilities to convert vitamin D to 25(OH)D (84). This amount of supplementation lies within the safe intake level as defined by The Endocrine Society (88). Finally, it can be noted vitamin D qualifies as a substance as described by the Barker Hypothesis, as the lack of this vitamin during pregnancy leads to detrimental genetic alterations on both mother and fetus.

Conclusion

Current evidence in pregnancy refers to both short-term and long-term impacts of vitamin D deficiency in maternal and infant health consequences, which include bone development, immune function, and health of the pregnancy. During pregnancy, the vitamin D status is more important than other times through lifespan as this influences not only the mother but also her growing fetus and, later, her growing infant. While there have been notable discrepancies surrounding the daily requirement of vitamin D and what constitutes sufficiency during these critical periods, there is growing evidence of the importance of vitamin D supplementation in pregnancy to achieve a total circulating 25(OH) D level of at least 40 ng/mL, the level at which the conversion of 25(OH)D to $1,25(OH)_2D$ is optimized and related to a lower risk of co-morbidities of pregnancy and better outcomes. Past data proposing that vitamin D is a teratogenic agent appears to be unfounded at the physiological doses reviewed in this chapter. As has been demonstrated, significant amounts of vitamin Dare needed during pregnancy to protect the mother and her fetus and impart genomic imprinting on the fetus to ensure long term health consequences. With increased knowledge about the effects of vitamin D as a pre-prohormone, recommendations about supplementation must mirror what is clinically relevant and evidence-based. More research that focuses on the critical periods leading up to conception and through pregnancy to correct deficiency or hold optimal vitamin D condition is needed. Moreover, the impacts that vitamin D has on genetic signatures that minimize the risk to the mother and developing fetus have not been clarified. While there is much more research that requires to be conducted, our understanding of vitamin D requirements in pregnancy has advanced significantly during the last decades.

Author Contributions

BA, SA, and MV were involved in literature review and writing the manuscript. BA and MV read and approved the final draft of the manuscript. MV has primary responsibility for final content.

References

[1] Heaney, R.P., 2016. Is vitamin D inadequacy in early life an instance of the “Barkerhypothesis”.Nutr.Today 51 (1), 14e17.

[2] Camargo Jr., C.A., Ingham, T., Wickens, K., Thadhani, R., Silvers, K.M., Epton, M.J., et al., 2011. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma.Pediatrics 127 (1) e180ee7.

[3] Litonjua, A.A., 2009. Childhood asthma may be a consequence of vitamin D deficiency. Curr.Opin.Allergy Clin.Immunol.9 (3), 202e207.

[4] Munger, K.L., Aivo, J., Hongell, K., Soilu-Hanninen, M., Surcel, H.M., Ascherio, A., 2016. Vitamin D status during pregnancy and risk of multiple sclerosis in offspring of women in the finnish maternity cohort. JAMA Neurol. 73 (5), 515e519.

[5] Greenberg, B.M., 2016. Vitamin D during pregnancy and multiple sclerosis: an evolving association. JAMA Neurol. 73 (5), 498e499.

[6] Dobson, R., Giovannoni, G., Ramagopalan, S., 2013. The month of birth effect in multiple sclerosis: systematic review, meta-analysis and

effect of latitude. J. Neurol., Neurosurg. psychiatry 84 (4), 427e432.

[7] Berlanga-Taylor, A.J., Disanto, G., Ebers, G.C., Ramagopalan, S.V., 2011. Vitamin Dgeneinteractions in multiple sclerosis.J. Neurol. Sci. 311 (1e2), 32e36.

[8] Ebers, G., 2013. Interactions of environment and genes in multiple sclerosis.J. Neurol. Sci. 334 (1e2), 161e163.

[9] Stubbs, G., Henley, K., Green, J., 2016. Autism: will vitamin D supplementation during pregnancy and early childhood reduce the recurrence rate of autism in newborn siblings? Med. Hypotheses 88, 74e78.

[10] McGrath, J.J., Eyles, D.W., Pedersen, C.B., Anderson, C., Ko, P., Burne, T.H., et al., 2010.Neonatal vitamin D status and risk of schizophrenia: a population-based case controlstudy. Arch. Gen. Psychiatry 67 (9), 889e894.

[11] Cannell, J.J., 2008. Autism and vitamin D. Med. Hypotheses 70 (4), 750e759.

[12] Evans KN, Bulmer JN, Kilby MD et al (2004) Vitamin D and placental-decidual function. J SocGynecolInvestig 11:263–271.

[13] Cardus A, Parisi E, Gallego C et al (2006) 1,25-Dihydroxyvitamin D3 stimulates vascular smooth muscle cell proliferation through a VEGF-mediated pathway. Kidney Int 69:1377–1384.

[14] Hewison M (1992) Vitamin D and the immune system. J Endocrinol 132:173–175.

[15] Li YC, Kong J, Wei M et al (2002) 1,25-Dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 110:229–238.

[16] Bodnar LM, Catov JM, Simhan HN et al (2007) Maternal vitamin D deficiency increases the risk of preeclampsia. J ClinEndocrinolMetab 92:3517–3522.

[17] Maghbooli Z, Hossein-nezhad A, Karimi F et al (2008) Correlation between vitamin D3 deficiencyand insulin resistance in pregnancy. Diabetes Metab Res Rev 24:27–32.

[18] Borissova AM, Tankova T, Kirilov G et al (2003) The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J ClinPract 57:258–261.

[19] Boucher BJ, Mannan N, Noonan K et al (1995) Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. Diabetologia 38:1239–1245.

[20] Chiu KC, Chu A, Go VLW et al (2004) Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am J ClinNutr 79:820–825.

[21] Hypponen E, Laara E, Reunanen A et al (2001) Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 358:1500–1503.

[22] Maxwell JD, Ang L, Brooke OG et al (1981) Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. Br J ObstetGynecol 88:987–991.

[23] Marya RK, Rathee S, Dua V et al (1988) Effects of vitamin D supplementation during pregnancy on foetal growth. Indian J Med Res 88:488–492.

[24] Markestad T, Aksnes L, Ulstein M, Aarskog D (1984) 25-Hydroxyvitamin D and 1,25-dihydroxy vitamin D of D2 and D3 origin in maternal and umbilical cord serum after vitamin D2 supplementation in human pregnancy. Am J ClinNutr 40:1057–1063.

[25] Bouillon R, Van Baelen H, DeMoor D (1977) 25-Hydroxy-vitamin D and its binding protein in maternal and cord serum. J Clin EndocrinolMetab 45:679–684.

[26] Hollis BW, Pittard WB (1984) Evaluation of the total fetomaternal vitamin D relationships at term: evidence for racial differences. J ClinEndocrinolMetab 59:652–657.

[27] Javaid MK, Crozier SR, Harvey NC et al (2006) Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. Lancet 367:36–43.

[28] Sabour H, Hossein-Nezhad A, Maghbooli Z et al (2006) Relationship between pregnancy outcomes and maternal vitamin D and calcium intake: a cross-sectional study. Gynecol Endocrinol 22: 585–589.

[29] Russell JGB, Hill LF (1974) True fetal rickets. Br Radiol 47:732–734.

[30] Moncrief M, Fadahunsi TO (1974) Congenital rickets due to maternal vitamin D deficiency. Arch Dis Child 49:810–811.

[31] Congdon P, Horsman A, Kirby PA et al (1983) Mineral content of the forearms of babies born to Asian and white mothers. Br Med J (Clin Res Ed) 286:1233–1235.

[32] 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 172:757–761.

[33] Specker B, Ho M, Oestreich A et al (1992) Prospective study of vitamin D supplementation andrickets in China. J Pediatr 120:733–739.

[34] Pawley N, Bishop NJ (2004) Prenatal and infant predictors of bone health: the influence of vitamin D. Am J ClinNutr 80(suppl):1748S–1751S.

[35] Zhang, C., Qiu, C., Hu, F.B., David, R.M., van Dam, R.M., Bralley, A., et al., 2008. Maternal plasma 25-hydroxyvitamin D concentrations

and the risk for gestational diabetes mellitus. PLoS One 3 (11), e3753.

[36] Bodnar, L.M., Simhan, H.N., Catov, J.M., Roberts, J.M., Platt, R.W., Diesel, J.C., et al., 2014. Maternal vitamin D status and the risk of mild and severe preeclampsia.Epidemiology 25 (2), 207e214.

[37] Baker, A.M., Haeri, S., Camargo Jr., C.A., Espinola, J.A., Stuebe, A.M., 2010. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. J. Clin. Endocrinol.Metab.95 (11), 5105e5109.

[38] Gernand, A.D., Bodnar, L.M., Klebanoff, M.A., Parks, W.T.,Simhan, H.N., 2013. Maternal serum 25-hydroxyvitamin D and placental vascular pathology in a multicenter US cohort. Am. J. Clin. Nutr.98 (2), 383e388.

[39] Merewood, A., Mehta, S.D., Chen, T.C., Bauchner, H., Holick, M.F., 2009. Association between vitamin D deficiency and primary cesarean section. J. Clin. Endocrinol.Metab.94 (3), 940e945.

[40] Bodnar, L.M., Simhan, H.N., 2010. Vitamin D may be a link to black-white disparities in adverse birth outcomes. Obstet. Gynecol. Surv. 65 (4), 273e284.

[41] Pal L, Zhang H, Williams J, Santoro NF, Diamond MP, Schlaff WD, et al. Vitamin D status relates to reproductive outcome in women with polycystic ovary syndrome: secondary analysis of a multicenter randomized controlled trial. J. Clin. Endocrinol. Metabol..0(0):jc.2015-4352.

[42] Miliku, K., Vinkhuyzen, A., Blanken, L., McGrath, J., Eyles, D., Burne, T., et al., 2016. Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes. Am. J. Clin. Nutr.103, 1514e1522.

[43] Hou, W., Yan, X.T., Bai, C.M., Zhang, X.W., Hui, L.Y., Yu, X.W., 2016. Decreased serum vitamin D levels in early spontaneous pregnancy loss. Eur. J. Clin. Nutr.70 (9), 1004e1008.

[44] Lindqvist, P.G., Silva, A.T., Gustafsson, S.A., Gidlof, S., 2016. Maternal vitamin D deficiency and fetal distress/birth asphyxia: a population-based nested casecontrolstudy. BMJ Open 6 (9), e009733.

[45] Gernand, A.D., Simhan, H.N., Baca, K.M., Caritis, S., Bodnar, L.M., 2016 October 5. Vitamin D, pre-eclampsia, and preterm birth among pregnancies at high risk for pre-eclampsia: an analysis of data from a low-dose aspirin trial. BJOG.

[46] Qin, L.L., Lu, F.G., Yang, S.H., Xu, H.L., Luo, B.A., 2016. Does maternal vitamin D deficiency increase the risk of preterm birth: a meta-analysis of observational studies. Nutrients 8 (5).

[47] Karatekin G, Kaya A, Saliho˘glu O et al (2007) Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers.Eur J ClinNutr [Epub ahead of print].

[48] Devereux G, Litonjua AA, Turner SW et al (2007) Maternal vitamin D intake during pregnancy andearly childhood wheezing. Am J ClinNutr 85:853–859.

[49] Camargo CAJ, Rifas-Shiman SL, Litonjua AA et al (2007) Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 years of age. Am J ClinNutr 85:788–795.

[50] Gale CR, Robinson SM, Harvey NC et al (2008) Maternal vitamin D status during pregnancy and child outcomes. Eur J ClinNutr 62:68–77.

[51] Dennison EM, Arden NK, Keen RW et al (2001) Birthweight, vitamin D receptor genotype and the programming of osteoporosis. PaediatrPerinatEpidemiol 15:211–219.

[52] Willer CJ, Dyment DA, Sadovnick AD et al (2005) Timing of birth and risk of multiple sclerosis: population based study. BMJ 330:120–124.

[53] McGrath J, Selten JP, Chant D (2002) Long-term trends in sunshine duration and its association with schizophrenia birth rates and age at first registration – data from Australia and the Netherlands. Schizophrenia Res 54:199–212.

[54] Kirkpatrick B, Tek C, Allardyce J (2002) Summer birth and deficit schizophrenia in Dumfries and Galloway, Southwestern Scotland. Am J Psychiatry 150:1382–1387.

[55] Moore SE (1998) Nutrition, immunity and the fetal and infant origins of disease hypothesis in developing countries. ProcNutrSoc 57:241–247.

[56] Litonjua, A.A., Carey, V.J., Laranjo, N., Harshfield, B.J., McElrath, T.F., O'Connor, G.T., et al., 2016. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 Years: the VDAART randomized clinical trial. JAMA 315 (4), 362e370.

[57] Chawes, B.L., Bonnelykke, K., Stokholm, J., Vissing, N.H., Bjarnadottir, E., Schoos, A.M., et al., 2016. Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring: a randomized clinical trial. JAMA 315 (4), 353e361.

[58] Vahdaninia, M., Mackenzie, H., Helps, S., Dean, T., 2016 Nov 22. Prenatal intake of vitamins and allergic outcomes in the offspring:

a systematic review and metaanalysis. J. Allergy Clin. Immunol. Pract. http://dx.doi.org/10.1016/j.jaip.2016.09.024pii: S2213-2198(16)30425-1, [Epub ahead of print].

[59] Vitamin D Workshop; 2016 March 29-31. In: Zhu, H., Wagner, C., Pan, Y., Wang, X., Shary, J., Hollis, B., et al. (Eds.), 2016. Maternal Vitamin D Supplementation and Cord Blood Genome-wide DNA Methylation Analysis. Boston, MA. http://www.vitamindworkshop. org/.

[60] Schulz E, CruzeL,WeiW, Garrett-Meyer E, Shary J, Forestieri N, et al., editors. Effects of Maternal Vitamin D Supplementation on Placental Gene Expression (Platform Presentation). Pediatric Academic Societies; 2016 April 30-May 3, 2016; Baltimore, MD: Pediatric Academic Societies.

[61] Al-Garawi, A., Carey, V.J., Chhabra, D., Mirzakhani, H., Morrow, J., Lasky-Su, J., et al., 2016. The role of vitamin D in the transcriptional program of human pregnancy.PLoS One 11 (10), e0163832.

[62] Friedman WF (1967) Vitamin D as a cause of the supravalvular aortic stenosis syndrome. Am HeartJ 73:718–720.

[63] Morris CA, Mervis CB (2000) William's syndrome and related disorders. Ann Rev Genomics Hum Genet 1:461–484.

[64] Hypponen E, Laara E, Reunanen A et al (2001) Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 358:1500–1503.

[65] Carlton-Conway D, Tulloh R, Wood L et al (2004) Vitamin D deficiency and cardiac failure in infancy. J R Soc Med 97:238–239.

[66] Souberbielle, J.C., Cormier, C., Kindermans, C., Gao, P., Cantor, T., Forette, F., et al., 2001. Vitamin D status and redefining serum parathyroid hormone reference range in the elderly. J. Clin. Endocrinol.Metab.86 (7), 3086e3090.

[67] Wagner, C.L., Baggerly, C., McDonnell, S., Baggerly, K.A., French, C.B., Baggerly, L., et al., 2016. Post-hoc analysis of vitamin D status and reduced risk of preterm birth in two vitamin D pregnancy cohorts compared with South Carolina March of Dimes 2009-2011 rates. J. Steroid Biochem. Mol. Biol. 155 (Pt B), 245e251.

[68] Goldring, S.T., Griffiths, C.J., Martineau, A.R., Robinson, S., Yu, C., Poulton, S., et al., 2013. Prenatal vitamin d supplementation and child respiratory health: a randomised controlled trial. PLoS One 8 (6), e66627.

[69] Sablok, A., Batra, A., Thariani, K., Batra, A., Bharti, R., Aggarwal, A.R., et al., 2015. Supplementation of vitamin D in pregnancy and its correlation with fetomaternaloutcome. Clin. Endocrinol.(Oxf) 83 (4), 536e541.

[70] Mojibian, M., Soheilykhah, S., FallahZadeh, M.A., JannatiMoghadam, M., 2015. The effects of vitamin D supplementation on maternal and neonatal outcome: a randomized clinical trial. Iran. J. Reprod. Med. 13 (11), 687e696.

[71] Grant, C.C., Crane, J., Mitchell, E.A., Sinclair, J., Stewart, A., Milne, T., et al., 2016. Vitamin D supplementation during pregnancy and infancy reduces aeroallergen sensitization: a randomized controlled trial. Allergy 71 (9), 1325e1334.

[72] Zhang, Q., Cheng, Y., He, M., Li, T., Ma, Z., Cheng, H., 2016. Effect of various doses of vitamin D supplementation on pregnant women with gestational diabetes mellitus: a randomized controlled trial. Exp. Ther. Med. 12 (3), 1889e1895.

[73] Hollis, B.W., Johnson, D., Hulsey, T.C., Ebeling, M., Wagner, C.L., 2011. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. Journal of bone and mineral research : Off. J. Am. Soc. Bone Miner.Res. 26 (10), 2341e2357.

[74] Hollis, B.W., Wagner, C.L., 2013. Vitamin d and pregnancy: skeletal effects, nonskeletal effects, and birth outcomes. Calcif.Tissue Int. 92 (2), 128e139.

[75] Zerofsky, M., Jacoby, B., Pedersen, T., Stephensen, C.B., 2016 Nov. Daily cholecalciferolsupplementation during pregnancy alters markers of regulatory immunity, inflammation, and clinical outcomes in a randomized controlled trial. J. Nutr. 146 (11), 2388e2397 [Epub 2016 Sep 21].

[76] Kiely, M.E., Zhang, J.Y., Kinsella, M., Khashan, A.S., Kenny, L.C., 2016. Vitamin D status is associated with uteroplacental dysfunction indicated by pre-eclampsia and small-for-gestational-age birth in a large prospective pregnancy cohort in Ireland with low vitamin D status. Am. J. Clin. Nutr.104 (2), 354e361.

[77] Parlea, L., Bromberg, I.L., Feig, D.S., Vieth, R., Merman, E., Lipscombe, L.L., 2012 Jul. Association between serum 25-hydroxyvitamin D in early pregnancy and risk of gestational diabetes mellitus. Diabet.Med. a J. Br. Diabet. Assoc. 29 (7), e25ee32. http://dx.doi.org/10.1111/j.1464-5491.2011.03550.

[78] Hensel, K.J., Randis, T.M., Gelber, S.E., Ratner, A.J., 2011. Pregnancy-specific association of vitamin D deficiency and bacterial vaginosis. Am. J. Obstet. Gynecol. 204(1) (41), e1e9.

[79] Olsen, S.F., Secher, N.J., 1990. A possible preventive effect of low-dose fish oil on early delivery and pre-eclampsia: indications from a 50-year-old controlled trial. Br. J. Nutr. 64 (3), 599e609.

[80] Song, J., Li, Y., An, R., 2017 Jan. Vitamin D restores angiogenic balance and decreases tumor necrosis factor-alpha in a rat model of pre-eclampsia. J. Obstet. Gynaecol. Res. 43 (1), 42e49.http://dx.doi.org/10.1111/jog.13186 [Epub 2016 Nov 12].

[81] Faulkner, J.L., Cornelius, D.C., Amaral, L.M., Harmon, A.C., Cunningham Jr., M.W., Darby, M.M., et al., 2016 Feb 15. Vitamin D supplementation improves pathophysiology in a rat model of preeclampsia. Am. J. Physiol. Regul. Integr.Comp. Physiol. 310 (4), R346eR354.http://dx.doi.org/10.1152/ajpregu.00388.2015[Epub 2015 Dec16].

[82] Mirzakhani, H., Litonjua, A.A., McElrath, T.F., O'Connor, G., Lee-Parritz, A., Iverson, R., et al., 2016b Dec 1. Early pregnancy vitamin D status and risk of preeclampsia. J. Clin. Invest. 126 (12), 4702e4715. http://dx.doi.org/ 10. 1172/JCI89031 [Epub2016 Nov 14].

[83] Anderson, C.M., Ralph, J.L., Johnson, L., Scheett, A., Wright, M.L., Taylor, J.Y., et al., 2015. First trimester vitamin D status and placental epigenomics in preeclampsia among Northern Plainsprimiparas. Life Sci. 129, 10e15.

[84] Heaney, R., Davies, K., Chen, T., Holick, M., Barger-Lux, M., 2003. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol.Am. J. Clin. Nutr.77, 204e210.

[85] Mokry, L.E., Ross, S., Ahmad, O.S., Forgetta, V., Smith, G.D., Goltzman, D., et al., 2015. Vitamin D and risk of multiple sclerosis: amendelian randomization study. PLoS Med. 12 (8), e1001866.

[86] McGrath, J.J., Feron, F.P., Burne, T.H., Mackay-Sim, A., Eyles, D.W., 2004. Vitamin D3- implications for brain development. J. Steroid Biochem. Mol. Biol. 89e90 (1e5), 557e560.

[87] Patrick, R.P., Ames, B.N., 2014. Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. FASEB J. 28 (6), 2398e2413.

[88] Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., et al., 2011 Jul. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab.96 (7), 1911e1930. http://dx.doi.org/10.1210/jc.2011-0385 [Epub 2011 Jun 6].

Citation: *Behnaz Abiri, Ph.D et al., "Vitamin D Deficiency during Pregnancy: The Health Consequences of Vitamin D Supplementation in Mother and Infant", International Journal of Research Studies in Medical and Health Sciences. 2021; 6(7):24-32. DOI: https://doi.org/10.22259/ijrsmhs.0607004*