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Vitamin D and its impact on maternal-fetal outcomes in pregnancy: A critical review

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Abstract

The role of vitamin D beyond its classical function in calcium homeostasis has been of significant interest in recent years. There has been expanding research on the pleiotropic role of vitamin D in pregnancy and the implications of its deficiency on maternal-fetal outcomes. Several studies have associated low maternal vitamin D status to adverse outcomes in pregnancy, including preeclampsia, gestational diabetes, preterm births, low birth weight, and others. Several randomized controlled clinical trials of Vitamin D supplementation during pregnancy have also been conducted. Though some of the studies found improvement in pregnancy outcomes with vitamin D supplementation, others have not shown any association. In this article, we have critically reviewed the observational and interventional studies, published primarily within the past two years (January 2014 to February 2016) on the influence of vitamin D deficiency on pregnancy and the impact of its supplementation. The potential underlying mechanisms of vitamin D in regulating each of the outcomes have also been discussed.

Keywords

Pregnancy; Vitamin D; Maternal outcomes; Neonatal outcomes; Vitamin D supplementation

Introduction

Vitamin D is a secosteroid, which is also considered an important prohormone (Weinert et al, 2015). Since vitamin D receptors (VDRs) are present in many cells and tissues throughout the body, many studies support the role of vitamin D in several physiological functions beyond bone and muscle health (Joergensen et al, 2014). During pregnancy,

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vitamin D plays a vital role in embryogenesis, especially fetal skeletal development and calcium homeostasis (Hollis et al, 2011). Vitamin D deficiency is a growing health concern worldwide in both adults and children (Weinert et al, 2015). Indeed, the findings from several studies suggest the increasing prevalence of vitamin D deficiency in pregnancy and the associated adverse maternal and fetal outcomes, such as gestational diabetes mellitus (GDM), preeclampsia, small for gestational age (SGA), preterm births among others (Palaniswamy et al, 2016) (Figure 1).

To further investigate the role of vitamin D in pregnancy and the improvement of outcomes on its supplementation, many interventional and observational studies have been undertaken but the results have not been consistent. Heterogeneity in the findings could be attributed, but not limited, to the differences in ethnicity, geographical locations, amount of vitamin D supplementation, and duration of supplementation. The methodology of the studies is not consistent and cannot be compared since the studies were conducted at different stages of gestation. It is still not well defined as to how vitamin D supplementation modifies the risk of the outcomes and whether vitamin D contributes to the etiopathogenesis of these diseases or it is just a marker (Yin et al, 2014). Given the low cost of vitamin D supplementation, if proven effective in pregnancy, it could bring about some major improvements in public health worldwide (Christensen et al, 2012).

The impact of vitamin D deficiency during pregnancy has been discussed in a few recent reviews and metaanalyses (Perez-Lopez et al, 2015; Harvey et al, 2014; Wei et al, 2015); however, more randomized clinical trials (RCTs) and observational studies have been conducted after the publication of the last review. Hence, this review article summarizes the recent studies on the influence of vitamin D deficiency during pregnancy. The impact of vitamin D supplementation on various maternal and fetal clinical endpoints has also been reviewed with critical discussion on the clinical and translational application of these findings and identified gaps in our knowledge to conduct future prospective studies.

Methods

Literature search was performed using PubMed Database of the National Library of Medicine, with date limits from January 2014 to February 2016, as the major emphasis of our review was to critically review the recent findings on Vitamin D in pregnancy. We used the keywords: Vitamin D, pregnancy, vitamin D supplementation, hypovitaminosis D, preeclampsia, gestational diabetes, preterm birth, and other related terms. The studies of interest included original papers and review articles on the influence of vitamin D deficiency in pregnancy and the impact of vitamin D supplementation on the maternal and fetal outcomes. References in these articles were searched for any other related articles. Duplicate articles were excluded. Articles were also excluded if they were not published in English language; were unavailable in full text, or if the studies did not involve human subjects. Sixty studies fit the criteria and hence, were critically evaluated in this review.

Physiology of vitamin D and vitamin D deficiency

Vitamin D is a fat-soluble vitamin with two major physiological forms: Ergocalciferol, vitamin D2 and Cholecalciferol vitamin D3 (DeLuca, 2014). These two forms basically differ in their side chain structure. While D2 is mainly obtained from plants and vegetable sources, D3 is majorly synthesized in the skin on exposure to sunlight (UVB radiation) from 7 dehydrocholesterol (De-Regil et al, 2016). Both forms of vitamin D are also available as dietary supplements. All the forms of vitamin D are activated only on enzyme-mediated hydroxylation. The first hydroxylation reaction is mediated by 25α-hydroxylase, to produce 25 hydroxyvitamin D (25OHD) or calcidiol and takes place in the liver (Harvey et al, 2014). This is followed by the next hydroxylation step in the kidney, mediated by 1α-hydroxylase, to produce 1,25-dihydroxycholecalciferol (1,25-DHCC) or calcitriol (Wagner et al, 2012). While 25OHD is the most abundant circulating form of vitamin D, 1,25-DHCC is the most active form (Sahota, 2014). The hydroxylation reactions and the availability of active vitamin D are regulated by serum calcium and phosphorus and parathyroid hormone (PTH) (Lips P, 2006).

Apart from its critical role in the regulation of calcium and phosphorus homeostasis for skeletal development, vitamin D also mediates other functions, including anti-inflammation, regulation of innate and acquired immunity, and prevention of cardiovascular diseases (Christakos et al, 2016).

Based on the recommendations by the Institute of Medicine (IOM), the recommended daily intake of vitamin D during pregnancy and lactation is 600 IU, taking into account the fetal demands as well (Grant et al, 2014). The serum 25OHD is regarded as the best stable and circulating biomarker for vitamin D status (Brannon et al, 2014). The cut-off value for vitamin D deficiency is set at 20 ng/ml while for vitamin D insufficiency it ranges from 20–30 ng/ml (Ross CA et al IOM, 2011).

Vitamin D deficiency is a global epidemic affecting people of all age groups with the principal cause being the lack of exposure to sunlight (Holick et al, 2008). Others include darker skin (high melanin content), aging, use of sunscreen and winters, all associated with decreased dermal synthesis of vitamin D (Holick et al, 2008). Some pathological conditions associated with low vitamin D include kidney failure, intestinal malabsorption, chronic inflammation and liver failure and use of concurrent medications (Dusilova-Sulkova, 2009). As a consequence, there is decreased bone density and greater susceptibility to fractures. Children suffer from rickets, while adults develop osteopenia or osteoporosis. Additionally, vitamin D deficiency is also associated with other co-morbid conditions like type 1 diabetes mellitus, neoplasms, cardiovascular diseases and others (Dusilova-Sulkova, 2009).

Vitamin D in pregnancy

During pregnancy, mobilization of maternal calcium increases to meet the demands of adequate fetal bone mineralization (Olmos-Ortiz et al, 2015). As a consequence, a number of physiological adaptations take place, including increased maternal serum calcitriol, vitamin D binding protein (DBP), placental VDR and renal and placental CYP27B1 activity

to maintain normal serum levels of 25OHD and calcium (Olmos-Ortiz et al, 2015). Maternal 25OHD crosses the placenta and is the main form of vitamin D for the fetus (Marshall et al, 2016). Calcitriol rises during pregnancy, almost doubled by the end of third trimester and then returns to normal levels after delivery (Marshall et al, 2016). During pregnancy, even placenta and fetal kidney express 1α-hydroxylase stimulated by prolactin and placental lactogen, though the major function is still performed by the maternal renal hydroxylase(Olmos-Ortiz et al, 2015). Maternal serum calcium levels fall during pregnancy, which can be attributed to a decrease in the serum albumin, but the ionized calcium levels remain unchanged (Olausson et al, 2012). In fact, fetal serum calcium levels are higher than maternal serum calcium levels, thereby requiring specific trans-placental carriers to transfer calcium against the concentration gradient (Olmos-Ortiz et al, 2015). This is mediated by the expression of calcium binding proteins in placenta, including calbindin D-9k and D-28k (Halhali et al, 2010).

The most important contribution of vitamin D during pregnancy is to escalate calcium absorption and placental calcium transport (Olmos-Ortiz et al, 2015). Additionally, vitamin D also regulates immune system and inhibits inflammation by restraining inflammatory cytokines. including TNF-α, IFN-γ, IL-6, while promoting the release of antimicrobial peptide cathelicidin hCTD in the placenta (Olmos-Ortiz et al, 2014). Calcitriol also plays an important role in placental physiology. It stimulates endometrial decidualization, synthesis of estradiol and progesterone and regulation of the expression of human chorionic gonadotrophin (hCG) and human placental lactogen(hPL) in the placenta(Olmos-Ortiz et al, 2014).

All these effects indicate the vital importance of vitamin D during gestation and the potential role of its deficiency on adverse maternal-fetal outcomes (Figure 2). Each maternal and fetal outcome investigated in the recent papers has been discussed in detail below with a tabular representation of the recent observational studies in Table 1 and Table 2. The impact of vitamin D supplementation has also been reviewed with a depiction of the recent Randomized Controlled Trials shown in Table 3. Table 4 summarizes the level of evidence of the impact of vitamin D on various maternal-fetal outcomes based on the GRADE system.

Adverse Maternal Outcomes associated with vitamin D deficiency

Preeclampsia

Preeclampsia is defined as newly diagnosed hypertension (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg) after 20 weeks of gestation along with proteinuria (>300mg/day), and other organ dysfunction, including liver involvement, hematological disturbance, neurological or renal complications (Roberts et al, 2016). Pathogenesis is related to the release of angiogenic factors into maternal circulation, which causes inadequate remodeling and trophoblastic invasion of spiral arteries, and consequently shallow implantation and hypoxia, and even release of inflammatory mediators (Sircar et al, 2015; Singla et al, 2015). The protective role of vitamin D in preeclampsia can be explained by multiple mechanisms. One of them is the immunomodulatory role of calcitriol in regulating immune response. Defective control of effector T cells by regulatory T cells can

lead to poor placental invasion, thereby leading to the release of placenta-derived vasoconstrictive factors, and consequently maternal hypertension and proteinuria (Hyppönen et al, 2013). Vitamin D helps in maintaining the immune homeostasis and thus prevents placental vasoconstriction and ultimately, preeclampsia (Hyppönen et al, 2013). Also, vitamin D regulates the endothelial and vascular smooth muscle cell proliferation and therefore, plays a role in regulating blood pressure through RAAS (Renin-Angiotensin-Aldosterone system) (Hyppönen et al, 2013). Vitamin D has also been found to regulate angiogenesis via its receptor elements in VEGF promoter and stimulating the expression of VEGF in vascular smooth muscle cells. Calcitriol also helps to prevent cholesterol uptake by the macrophages and vascular smooth muscle cells of the arterial walls, which is the observed pathology in utero placental vessels of patients with preeclampsia (Hyppönen et al, 2013). Despite these findings, in other studies no causal relationship was found between vitamin D supplementation and improvement/prevention of preeclampsia. These studies are discussed below.

Several observational studies were recently performed to investigate an association between vitamin D deficiency and preeclampsia but the findings have been inconsistent. Eleven observational studies have examined the association between preeclampsia and vitamin D; Achkar et al (2015) carried out a nested case control study in Canada and concluded that vitamin D deficiency (<30 ng/ml) was associated with increased risk of preeclampsia (adjusted Odd's Ratio (OR), 2.23; 95% Confidence Interval (CI) 1.29–3.83). Similar results were also reported by other recent studies (Singla et al, 2015; Mohaghegh et al, 2015; Abedi et al, 2014; Sadin et al, 2015). On the contrary, Bomba-Opon et al (2014) measured the 25OHD levels in 280 pregnant women in Poland and found no association between vitamin D levels and markers of preeclampsia, including Pregnancy-associated plasma protein A (PAPP-A), Placenta Growth Factor (PlGF), uterine artery pulsatility index and mean arterial pressure. Similarly, Schneuer et al(2014) reported no increased risk of preeclampsia in vitamin D deficient pregnant women in a nested case control study conducted in 5109 pregnant women. Some other studies also described comparable outcomes (Gidlof et al, 2015; van Weert et al, 2016; Wetta et al, 2014; Burris et al, 2014).

Many randomized controlled trials (RCT) have been undertaken to determine the impact of vitamin D supplementation in preeclampsia patients. In the past two years, three of the investigations took place in Iran (Mojibian et al, 2015; Samimi et al, 2015; Asemi et al, 2015)and one each in India (Sablok et al, 2015) and Pakistan (Hossain et al, 2014). Positive impact was found in some (Samimi et al, 2015; Asemi et al. 2015; Sablok et al, 2015)while no significant impact was reported in others (Hossain et al, 2014). Similarly, Karamali et al (2015) conducted a double blind placebo-controlled RCT in pregnant women at risk of preeclampsia determined by abnormal uterine artery waveform, and reported no significant change in blood pressure with vitamin D supplementation. When combined supplementation of vitamin D and calcium was given in an interventional study to at-risk preeclampsia patients, significant improvement in the outcomes with reduced systolic and diastolic blood pressure was observed in the vitamin D and calcium supplemented group compared to the placebo group (Samimi et al, 2015). Similarly, Asemi et al (2015) also reported positive outcomes on supplementation with vitamin D (400 IU) and multi-minerals (800 mg calcium, 200 mg magnesium, 8 mg zinc) over 9 weeks compared to placebo in at-risk preeclampsia

patients. Recently, the published Cochrane review on vitamin D supplementation studies reported that women who receive vitamin D supplementation had lower risk of preeclampsia but with only borderline significance (RR 0.52, CI 0.25–1.05), whereas combined vitamin D and calcium supplementation significantly reduces the risk of preeclampsia (Risk Ratio (RR): 0.51, CI 0.32–0.80) (De-Regil et al, 2016). Our analysis also supports the conclusion of Cochrane review that vitamin D supplementation reduces the risk of preeclampsia.

Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus is defined as hyperglycemia from glucose intolerance that develops or is first diagnosed during pregnancy (Baz et al, 2016). Vitamin D plays a role in glucose homeostasis by multiple mechanisms (Lithy et al, 2014). Firstly, it regulates the calcium levels, which in turn regulates insulin production and secretion by the endocrine pancreas (Al-Shoumer et al, 2015). It also improves the sensitivity of the target cells like adipose tissue, liver and skeletal muscles to insulin (Lithy et al, 2014). Through its role in regulation of immune cells, it protects β cells from detrimental immune attacks and even enhances their function (Al-Shoumer et al, 2015). Vitamin D deficiency or the dysfunction of vitamin D receptors relates to the pathogenesis of type 1 and type 2 diabetes, but its role in GDM remains inconclusive.

Eight observational studies have been recently conducted to study the association of vitamin D with GDM. Arnold et al(2015) conducted a nested case control study in the United States among pregnant women and reported an inverse relationship between vitamin D status in early pregnancy and risk of gestational diabetes. A 5 ng/ml increase in vitamin D3 levels was associated with reduction in GDM risk by 14%. Similar effects were reported by Lacroix and colleagues (2014) in a prospective observational study in Canada and Lithy et al(2014) in a cross sectional observational study in Arab women. On the contrary, multiple studies failed to establish a role of vitamin D in the prevention of GDM (Schneuer et al, 2014; Sunmin et al, 2014; Whitelaw et al, 2014; Loy et al, 2015; Flood-nichols et al, 2015). The lack of consistent findings calls for large-scale prospective studies to evaluate the role of vitamin D in GDM.

To test the effectiveness of vitamin D supplementation in the prevention or reduction of risk of GDM, many randomized controlled clinical trials have been conducted. Six RCTs have been conducted in this regard from January 2014 onwards (Mojibian et al, 2015; Sablok et al, 2015; Hossain et al, 2014; Asemi et al, 2014; Asemi et al, 2013; Yap et al, 2014). Asemi et al(2014) performed a randomized placebo controlled trial in Iranian pregnant women and found positive impact of vitamin D and calcium supplementation on the metabolic profiles of GDM patient with decrease in free plasma glucose, serum insulin, HOMA–IR, LDL cholesterol and total cholesterol. Few other studies, on the contrary, reported no beneficial effects of vitamin D supplementation on GDM outcome (Sablok et al, 2015; Hossain et al, 2014). To compare and contrast the efficacy of different dosing patterns of vitamin D on GDM, recently two clinical trials were undertaken; Yap et al (2014) conducted the study in women with 25OHD levels less than 32 ng/ml before 20 weeks and randomized them to receive oral vitamin D3 at 5,000 IU daily or 400 IU daily from 14 weeks until delivery, and found no difference in the outcomes. Mojibain et al (2015) randomized pregnant women

with 25OHD less than 30 ng/ml to receive 400 IU daily or 50,000 IU every 2 weeks until delivery, and found improved outcomes with high dose vitamin D supplementation. The difference in the outcomes could be attributed to different dosages of vitamin D used for intervention, as well as the varying dosing schedules in the two studies. Two recently published meta-analyses of RCTs (De-Regil et al, 2016; Pérez-López et al, 2015), however, showed same incidence of GDM with and without vitamin D supplementation. While studies have shown varying results, the overall level of evidence is high for vitamin D supplementation playing no role in the prevention of GDM.

Cesarean section (C-section)

Vitamin D receptors are present on smooth muscle cells, including uterine muscles, and skeletal muscle cells. Vitamin D regulates the contractile proteins of uterine myometrial cells (Loy et al, 2015). Vitamin D deficiency, therefore, may decrease the strength of the contractile muscles, causing prolonged labor or obstructed labor, indicating the need for C-section (Sebastian et al, 2015). Vitamin D deficiency has also been postulated to cause malformation of pelvis, which is yet another indication for C-section (Gernand et al, 2015).

Few studies have analyzed the association between vitamin D levels and cesarean sections. Recently, five observational studies were conducted with mixed outcomes (Loy et al, 2015; Sebastian et al, 2015; Gernand et al, 2015; Rodriguez et al, 2015). In a prospective cohort study conducted in Spain in 2,382 mother child pairs, Rodriguez et al (2015) reported that adequate vitamin D (25 OHD ≥ 30ng/ml) decreased the risk of C-section by obstructed labor (RR=0.60, 95% CI 0.37, 0.97). In a multiethnic Asian cohort study conducted by GUSTO study group (Loy et al, 2015), it was found that low vitamin D levels were associated with increased risk of emergency C-sections in Chinese and Indian women, and not in Malay women and overall there was no significant association. No association between vitamin D deficiency and risk of C-section was reported in other recent studies (Sebastian et al, 2015; Gernand et al, 2015). The inconsistency in the findings might be due to the difference in defining C-section in terms of indication, primary or secondary, emergency or elective (Gernand et al, 2015).

There have not been any interventional studies undertaken to determine the association between the two. Although analysis of the recent observational studies suggests that vitamin D deficiency can increase the risk of C section, there is a need for investigators to conduct RCTs to study the impact of vitamin D supplementation on C-section rates.

Preterm Delivery

One of the most common causes for preterm delivery is infection (Sangkomkamhang et al, 2015). Vitamin D, through its role in anti-inflammatory pathways via nuclear factor-kB inhibition, could play a role in decreasing the incidence of infections thereby, preterm births (Thota et al, 2014). But the exact role of vitamin D in the pathogenesis of preterm birth has not yet been clearly defined. Five observational and four interventional studies have investigated their association with lack of consistency in the results. Bodnar et al (2015) conducted a case control study with 1,126 cases and 2,327 controls in Pittsburgh, PA, USA. Serum 25OHD was measured using liquid chromatography- tandem mass spectroscopy and

a protective association of vitamin D sufficiency and preterm birth was found after adjusting confounding factors. Thota et al (2014) reported similar results. However, other studies did not support the above findings (Schneuer et al, 2014; Wetta et al, 2014; Rodriguez et al, 2015).

Few recent interventional studies on vitamin D supplementation examined its role in the prevention of preterm births. Hossain et al(2014) carried out a RCT of routine care (200 mg ferrous sulfate and 600 mg calcium) vs vitamin D3 supplementation (4,000 IU daily) from 20 weeks of gestation till delivery in 207 pregnant women and reported comparable outcomes in both the groups ($p > 0.05$). Mojibian et al(2015) also reported similar findings. On the contrary, Sablok et al (2015) found decreased incidence of preterm delivery in the group with vitamin D supplementation (8.3%) compared to no intervention (21.1%) though it was not statistically significant. Wagner et al(2015) carried out a post hoc analysis to measure the strength of association between serum 25OHD levels at 3 times, one in each trimester and preterm birth. They found that maternal vitamin D status closest to the delivery was most significantly associated with preterm birth, thereby proposing that later intervention could be used as a rescue treatment to decrease the risk of preterm deliveries (Wagner et al, 2015). Meta-analysis carried out by Pérez López et al (2015) showed no significant impact of vitamin D supplementation on the prevention of preterm deliveries. Though the level of evidence is moderate, our analysis shows no significant association between vitamin D and preterm deliveries.

Recurrent pregnancy loss

One of the non-classical functions of vitamin D is the regulation of immune system. To maintain maternal fetal interaction for a successful pregnancy, a dominant Th2 cell response is required (Garrido-gimenez et al, 2015). Therefore, dysregulated immune function and autoimmunity could alter the immune response leading to pregnancy loss. Vitamin D reportedly inhibits Th1 cells-mediated immune response and also the production of their cytokines, including IFN-γ, IL-2 and TNF-α, while promoting the proliferation of Th2 cells and their cytokines, including IL-4, IL-5, IL-6, IL-9, IL-13 (Wei et al, 2015). Such an effect of vitamin D supports its role in the immunoregulation during implantation. This hypothesis was examined by Ota et al, (2014) who conducted a retrospective study of 133 pregnant women with a history of three or more pregnancy loss before 20 weeks of gestation. Serum vitamin D levels and the markers of immunity were measured. The 47.4% of these women had low vitamin D levels (<30 ng/ml). The levels of autoantibodies were significantly higher in vitamin D-deficient group. These include anti-phospholipid antibody (APA) ($p<0.005$, adjusted OR 2.22, CI 1.0–4.7), antinuclear antigen antibody, anti-ssDNA and thyroperoxidase antibody. This was also followed by *in vitro* experiments and significantly decreased ratio of TNF-α/IL-10 expressing CD3+/CD4+ cells with 100 nM of vitamin D3 (31.3 ± 9.4 ng/ml, $p<0.05$) was found in cases compared to controls (40.4± 11.3 ng/ml). Although no conclusion can be drawn based on the findings of a single study, but this calls for more observational and interventional studies to establish the association between the two.

Postpartum depression

Postpartum depression is the most common psychiatric condition occurring in the postpartum period (Cherry et al, 2014). Vitamin D is believed to be a neurosteroid and has been linked to the occurrence of depression (Anglin et al, 2013). There are various plausible mechanisms relating postpartum depression with vitamin D deficiency. Firstly, VDRs are located throughout the body including brain, so, in case of vitamin D-deficiency, the VDRs in the brain may affect the hormones that are involved in the occurrence of mood disorders (Fu et al, 2015). Vitamin D also plays a role in brain processes like neurotransmission, neuro-immunomodulation and neuroprotection (Christesen et al, 2012). Thirdly, vitamin D is involved in the synthesis of norepinephrine and dopamine, which gets imbalanced in mood disorders (Eyles et al, 2013). Additionally, vitamin D maintains the antioxidant glutathione in brain, thereby protecting brain from oxidative damage. Lastly, VDRs are present in the areas of brain involved in planning, processing and formation of new memories (Eyles et al, 2013).

Many studies have been designed to investigate an association between postpartum depression and vitamin D. Recently, four observational studies were performed in this regard. Fu et al(2015) conducted a prospective cohort study in 248 pregnant women in China to examine an association between serum vitamin D levels 24 hours after delivery and postpartum depression. The investigators reported that serum 25OHD levels were significantly higher in women with no postpartum depression ($p<0.001$). After adjusting for confounders and using multivariate analysis, they found increased risk of postpartum depression with 25OHD levels ≤ 10.2 ng/ml (OR 7.17, CI 3.81–12.94, $p< 0.001$). Gur et al(2015) reported a significant association between mid-pregnancy vitamin D levels and postpartum depression. They conducted this study in 678 Turkish pregnant women, measured serum 25OHD level between 24–28 weeks of gestation and then assessed these women for postpartum depression using Edinburgh Postnatal Depression Scale (EPDS) at 1 week, 6 weeks and 6 months postpartum. The investigators also found significant negative correlation between vitamin D levels and EDPS at all the three follow-up periods ($r= -0.2$, -0.2, -0.3, respectively). Robinson et al (2014) also demonstrated a positive association between vitamin D deficiency and postpartum depression. On the contrary, Gould et al(2015) performed a similar study on a large cohort of 1,040 women in Australia. They measured cord blood 25OHD and then evaluated these women for postpartum depression symptoms using EPDS at six weeks and six months postpartum. They reported no association between cord blood vitamin D levels and postpartum depression. Although the results from various studies are conflicting, postpartum depression might be associated with vitamin D deficiency but the studies have been inconsistent in their results and warrant more extensive studies in this regard.

Adverse fetal outcomes associated with vitamin D deficiency

Low birth weight (LBW) and Small for Gestational Age (SGA)

Vitamin D plays a role in fetal growth by regulating calcium homeostasis and parathyroid hormone levels (Hollis et al, 2011). Maternal vitamin D adequacy improves the fetal outcomes in the form of birth weight sufficiency that has been proven by many but not all

studies. Most of them are observational studies. In our search, we found 9 studies that reported this correlation; 3 were cross sectional studies, 3 were case control studies and 3 were prospective cohorts. Chen et al(2015) performed a population-based cohort, recruiting 3,658 mother-fetus pairs. Maternal serum 25OHD level was measured at anytime during pregnancy. A positive correlation was found between maternal 25OHD levels and neonatal birth weight ($r = 0.477$, $p < 0.001$). Similar results were reported by other investigators (Khalessi et al, 2015; Morgan C et al, 2016; Gernand et al, 2014; Mirzaei et al, 2015; Aydogmus et al, 2016). Another study undertaken in China by Zhu et al(2015) measured the cord blood 25OHD levels and its association with low birth weight and SGA in 1,491 neonates. They reported that per 10 nmol/L increase in the cord blood 25OHD level, birth weight increased by 61.0 gm at concentration less than 40 nmol/L of 25OHD, and then decreased by 68.5 gm at concentrations from 40–70 nmol/L. This is the first study to report inverted U-shaped relationship between neonatal vitamin D status and fetal growth. However, other studies failed to establish any association between vitamin D levels and fetal birth weight (Schneuer et al, 2014; Rodriguez et al, 2015). Conflicting results were found in the interventional studies for vitamin D supplementation and its impact on offspring birth weight. One of these studies conducted by Mojibian et al (2015) in Iranian pregnant women found no difference on vitamin D supplementation on the fetal outcomes. Another RCT carried out by Hossain et al(2014) found improved outcomes with vitamin D supplementation, but the results did not reach statistical significance. Thus, most of the findings suggest that vitamin D deficiency increases the risk of low birth weight infants. However, large scale well-designed interventional studies are required to further establish the role of vitamin D supplementation to improve fetal outcomes.

Respiratory infections

Vitamin D receptors (VDRs) are present on almost every immune cells, and activation of VDRs play a critical role in adaptive and innate immunity, along with the regulation of inflammatory response (Esposito et al, 2015). There are multiple mechanisms by which vitamin D could regulate inflammatory response: (i) vitamin D controls the activity of macrophages and dendritic cells and various events in response to the activation of Toll-like receptors in neutrophils (Greiller et al, 2015), (ii)vitamin D inhibits the function of dendritic cells by restricting their maturation, antigen presentation and the production of cytokines, like IL-12 and IL-23 (Esposito et al, 2015), (iii) vitamin D induces the expression of two antimicrobial peptides, cathelicidin and β-defensin, which are critical in innate immunity through chemotactic action and neutralization of toxins (Sá et al, 2015), and (iv) vitamin D shifts the cytokine expression from type 1 to type 2 cells response, thus contributing to the maintenance of self-tolerance (Wei et al, 2015). Thus, based on the potent immunomodulatory effect of vitamin D, several studies have linked vitamin D deficiency to the increased risk of respiratory tract infections in children. It has been hypothesized that maternal vitamin D deficiency increases the risk of respiratory tract infections in their offspring. Few investigators recently studied this association. Five observational studies have been conducted. Onwuneme et al(2015) performed a study in 94 preterm infants and found that low serum 25OHD levels (<30 nmol/L) in pre-terms were associated with increased oxygen requirements ($p=0.008$), increased duration of intermittent positive pressure ventilation ($p=0.032$), and more requirement of assisted ventilation ($p=0.013$). Luczynska et

al (2014) performed a prospective cohort study on 777 mother-child pairs in Germany and found a statistically significant association between 25OHD levels in cord blood and susceptibility to lower respiratory tract infection (LRTI). The adjusted risk-ratio for vitamin D deficient infants (<25 nmol/L) was 1.32 in comparison to the reference group (>50 nmol/L). In Turkey, Dinlen et al(2016) reported the same conclusions. They performed a study in 60 infants, 30 with acute LRTI term infants and 30 controls matched for gestational age, weight and gender and reported lower serum 25OHD levels in mothers of the study group (p=0.0001). However, Jongh et al(2014) reported no association between the two based on a cohort study performed on 2,025 mother child pairs in Southampton, UK with mother's serum 25OHD measured at 34 weeks' gestation and infants followed up at 6,12 and 24 months for respiratory symptoms. In summary, maternal vitamin D deficiency can increase the risk of respiratory infections in infants. This conclusion is yet to be confirmed by interventional studies.

Immunity and Allergies

As mentioned earlier, Vitamin D plays an important role in the immunomodulation through its effect on the function of T and B lymphocytes. While in T cells, it promotes Th2 cell-mediated anti-inflammatory response, in B cells vitamin D promotes the production of immunoglobulins and inhibition of memory B cells and generation of plasma cells (Szymczak et al, 2016).

To validate the association between maternal vitamin D status and development of allergies, including eczema and asthma in their offspring, recently four observational studies and two interventional studies have been carried out. In Taiwan, a study was conducted in 164 mother-child pairs cohort to study this association (Chiu et al, 2015) and reported protective effect of vitamin D in protecting children from allergies, eczema and asthma after following up children for up to 4 years of age. Maslova et al(2014) conducted a prospective cohort study in Denmark in 965 pregnant women and their offspring were followed until adulthood for airway allergic diseases and lung function. In this study, higher levels of maternal vitamin D ≥ 125 nmol/L was found to be associated with higher incidence of allergies in children (Hazard Ratio, HR=1.81, 95% CI = 0.78–4.16). In UK, Miller et al(2015) studied the association between maternal vitamin D and neonatal inflammatory and allergic response by studying the response of neonatal nasal airway epithelial cells (AECs). They reported that increased maternal vitamin D was associated with increased release of IL-10 by AECs after stimulation with TNF-α/IL-1β (p=0.024) or house dust mite (p=0.049). It was concluded that there exists an association between maternal micronutrient intake and the function of neonatal airway cells and hence may impact the development of asthma or allergies later in life. Jones et al (2015) selected a cohort of mothers with history of atopy and investigated the association of vitamin D in them to the immune response in their children and found that improving serum 25OHD level during pregnancy or early infancy can lower the risk of allergies by inhibiting the inflammatory cytokines associated with allergies.

This association has been of interest for carrying out interventional studies as well. Vitamin D Antenatal Asthma Reduction Trial (VDAART) (Litonjua et al, 2016) was a randomized,

double blind, placebo controlled trial conducted across three centers in the United States. A total of 881 pregnant women at 10–18 weeks' gestation at high risk of having children with asthma were included in the study. They reported that the risk of asthma and wheeze-related disorders were lower in vitamin D supplemented women by 6.1% compared to the placebo group, although it did not reach statistical significance. Another interventional study took place in Japan (Norizoe et al, 2014) which studied the impact of maternal vitamin D supplementation during lactation to improve the outcomes in infantile allergic disorders like eczema. They concluded that although vitamin D supplementation did not decrease the incidence of eczema, but it enhanced the risk of food allergies up to 2 years of age (RR 3.42, 95% CI: 1.02–11.77; p=0.030). In conclusion, there is still no definite evidence of whether vitamin D supplementation increases or decreases the risk of allergies and therefore, requires further exploration.

Anthropometry

Vitamin D plays a primary role in bone remodeling, calcium homeostasis and muscle functioning. Its deficiency in pregnancy is associated with impaired bone development, fetal growth and other unfavorable effects on musculoskeletal system of the offspring (Kovacs et al, 2014).

Some studies have shown adverse effects of maternal vitamin D deficiency on the anthropometric measures of the offspring. This includes one cohort study (Morales et al, 2015) and four RCTs (Hashemipour et al, 2013; Hossain et al, 2014; Nandal et al 2015; Roth et al, 2015). Morales and colleagues(2015) conducted a study in a cohort of 2,358 pregnant women in Spain and measured serum 25OHD levels at any time during gestation. Child's femur length, bi-parietal diameter and abdominal circumference were noted through ultrasound findings at 12, 20 and34 weeks of gestation. They found no association of maternal serum 25OHD level with femur length and a weak inverse association with bi-parietal diameter at 34 weeks.

A single center randomized clinical trial in Pakistan reported no favorable outcomes on fetal growth by vitamin D supplementation (Hossain et al, 2014). Nandal et al(2015) conducted a case control study of 120 pregnant women in India and found that the women's offspring supplemented with vitamin D had higher birth weight and crown heel length compared to the non-supplemented group (3.1 ± 0.485 kg vs 2.8 ± 0.705 kg and 49.35 ± 1.36 cm vs 48.67 ± 2.12 cm, respectively). Similarly, Hashemipour et al (2013) conducted a randomized controlled trial in 130 Iranian pregnant women and reported that mean length (p=0.01), head circumference (p=0.001) and weight (p=0.01) were higher in the intervention group compared to the control group. There is an ongoing trial in Dhaka, Bangladesh to estimate the effects of prenatal and postnatal supplementation of different doses of vitamin D vs placebo on infant length at 1 year of age (Roth et al, 2015). In this study, healthy pregnant women in second trimester have been randomized to receive either vitamin D 4,200 IU/wk, 16,800 IU/wk or 28,000 IU/wk and placebo in the postpartum period or 28,000 IU/wk in the prenatal and postpartum period, and the infants will be followed up at regular intervals for growth monitoring upto 1 year of age. A recently published meta-analysis of RCTs by Pérez-López et al (2015) also concludes positive outcomes of vitamin D supplementation in

pregnancy on offspring birth weight and length. Thus, our analysis of the published findings also supports that vitamin D supplementation in pregnancy has a positive impact on fetal growth.

Vitamin D and autism

A recent meta-analysis by Wang et al (2015) investigated the possible mechanisms by which vitamin D could potentially influence the occurrence of autism spectrum disorders in children. Firstly, it influences the early brain development in children. It plays a role in neuronal differentiation, neurotransmission and synaptic functions (Wang et al, 2015). Secondly, as vitamin D is involved in the immune system homeostasis and autism is considered an autoimmune disorder, so it is considered that vitamin D deficiency may alter T cell activation profile and affect the adaptive immunity and cause preponderance to autism (Currenti, 2010). Also, oxidative stress may increase the susceptibility to autism by their lethal interaction with genetically susceptible genes. Glutathione is an antioxidant that protects the brain from the oxidative stress and vitamin D increases the level of glutathione in the brain, thereby protecting it from preventable conditions like autism (Cannell, 2008). Serotonin plays an essential role in controlling emotions. Vitamin D activates the serotonin-synthesizing gene in the brain and inversely affects the serotonin production in peripheral tissues (Patrick et al, 2014). It is seen that autistic individuals have lower concentration of serotonin in brain and higher in their blood, indicating that vitamin D could be potentially involved in the underlying pathogenesis. Lastly, vitamin D deficiency could increase the risk of genetic mutations by inhibiting DNA repair of early mutations, and thus could contribute to the appearance of autism (Wang et al, 2015).

An interventional study recently reviewed the benefits of vitamin D supplementation in pregnant women to decrease the incidence of autism in the offspring. This was conducted by Stubbs et al(2016) whereby the investigators supplemented pregnant women with previous autistic child, with 5,000 IU/day of vitamin D followed by supplementation of newborn with 1,000 IU/day vitamin D for first three years of life. These children were followed up at 18 and 36 months of age. The results were promising, with only 1 out of 19 children developing autism (5%), compared to the general recurrence risk of 20%. This single recent study suggests that vitamin D supplementation in pregnancy could reduce the risk of autism in children, but more studies are warranted to confirm the conclusion.

CONCLUSION

Vitamin D deficiency is increasing worldwide, both in general population and in pregnant women. In pregnancy, it has been found to be associated with increased incidence of adverse maternal and fetal outcomes, primarily preeclampsia, GDM, low birth weight and preterm births. Other outcomes are still under study and no definite conclusions have been drawn yet. The critical evaluation of the published findings on the maternal and fetal outcomes in a large number of observational studies and critical trials in a large cohort provide high level of evidence for an association between vitamin D and preeclampsia, GDM in maternal outcomes and, small for gestational age and anthropometry in fetal outcomes (Table 4). Other maternal-fetal outcomes have moderate level of evidence of association with vitamin

D, as reported in other reports and meta analyses. In our review of the findings, we also found association between vitamin D and recurrent pregnancy loss and association between vitamin D and autism, although the level of evidence remains low, thereby requiring additional studies to confirm the association. However, the question still remains whether there is any causal relationship between vitamin D deficiency and the maternal and fetal outcomes or it is just one of the manifestations of these conditions. The etiology of the various maternal and fetal outcomes is complex and multifactorial with many confounding factors. To determine the benefits of vitamin D supplementation in pregnancy would require further evaluation through large, multicenter double-blind randomized controlled clinical trials, with a focus on specific adverse pregnancy outcomes. Additionally, dose-response randomized trials would be helpful in identifying the optimal dosage for supplementation and potential long-term side effects of vitamin D therapy.

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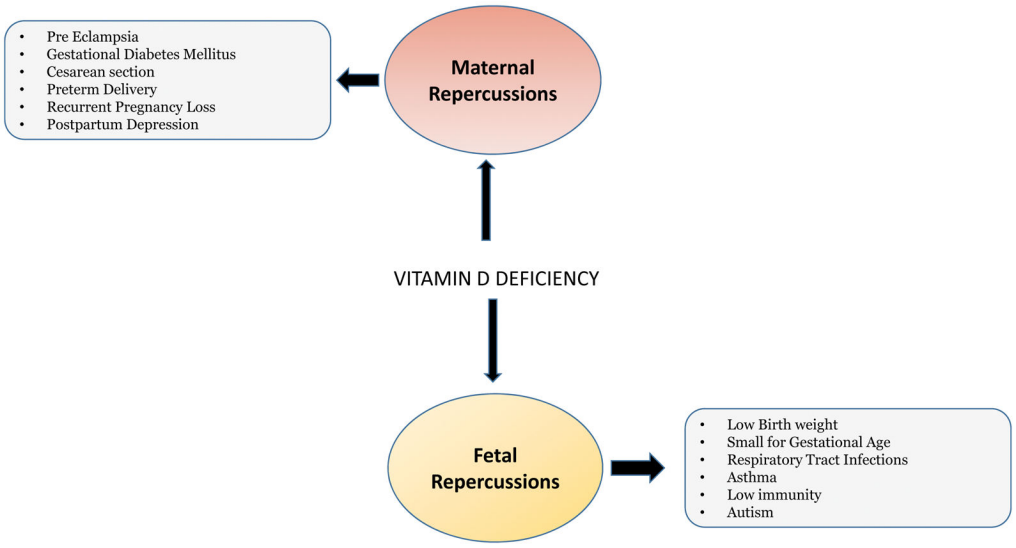

Figure 1.

The schematic diagram depicts the adverse maternal and fetal outcomes associated with vitamin D deficiency.

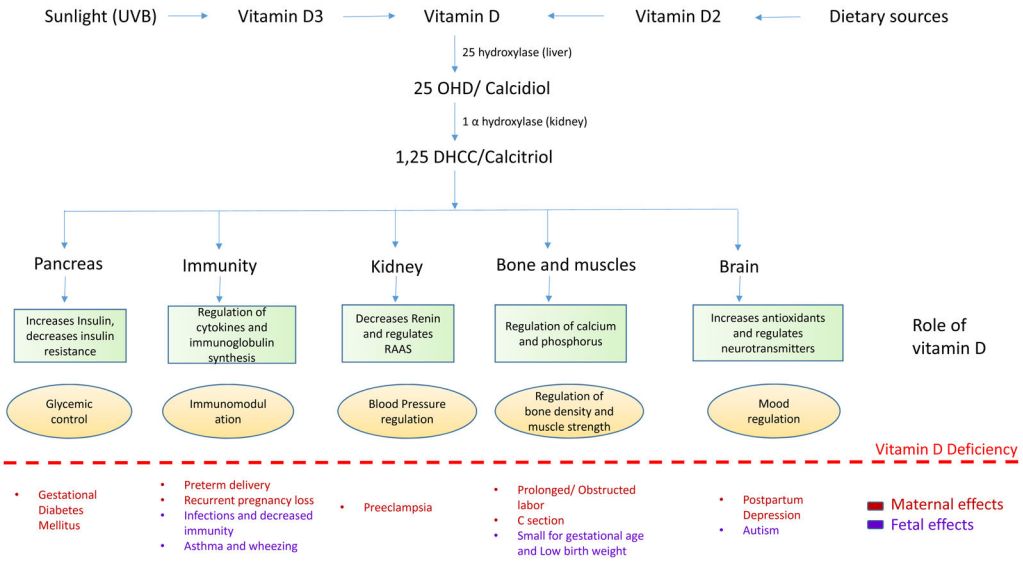

Figure 2.

The sxhematic diagram depicts the activation of vitamin D by two hyroxylation steps, one each in liver and kidney, followed by the normal physiological role of vitamin D in each organ. The specific maternal and fetal repercussion of vitamin D deficiency are mentioned below the dotted line.

Table 1

Observational studies of vitamin D status in pregnancy and maternal outcomes

Study design	Place of study	Sample size	Gestational age at Vit D assay	Vit D Assay method	Outcome analyzed	Statistics (95% CI)	Study authors	Quality of evidence (GRADE system)
Case control	India	74 cases and 100 controls	On enrollment	ELISA	Preeclampsia	p= 0.0001	Singla et al, 2015	Moderate
Case control	Iran	59 cases and 59 controls	Before the onset of labor	ELISA, HPLC	Preeclampsia	OR 24.04 (2.10–274.8)	Abedi et al, 2014	Low
Case control	Iran	41 cases and 50 controls	Onset of labor	ELISA	Preeclampsia	P=0.0001	Mohagegh et al, 2015	Moderate
Case control	USA	717 cases and 2986 controls	<26 weeks	LC-MS	Preeclampsia	Adjusted RR 0.65 (0.43–0.98)	Bodnar et al, 2014	Moderate
Case control	Iran	40 cases and 40 controls	Anytime	CLIA	Preeclampsia	P=0.002	Sadin et al, 2015	Moderate
Case control	USA	1126 cases and 2327 controls	<20 weeks	LC-MS	PTL	P<0.01	Bodnar et al, 2015	Moderate
Case control	USA	79 cases and 113 controls	At delivery	CLIA, RIA	PTL (Caucasian) (African American)	 P<0.01 P<0.04	Thota et al, 2014	Moderate
Case control	USA	839 cases and 2629 controls	<26 weeks	LC-MS	PTL	-	Bodnar et al, 2015	Moderate
Case control	China	821	On admission	ELISA	PTL	P<0.001	Zhu et al, 2015	High
Case control	India	46 cases and 46 controls	At delivery	ECLIA	C-section	OR 2.31 (0.77–6.92)	Sebastian et al, 2015	Moderate
Nested case control	Sweden	39 cases and 120 controls	12 weeks	ELISA	Preeclampsia	p=0.3	Gidlof et al, 2015	High
Nested case control	Canada	169 cases and 1975 controls	<20 weeks	ELISA	Preeclampsia	OR 2.23 (1.29–3.83)	Achkar et al, 2015	Moderate

Study design	Place of study	Sample size	Gestational age at Vit D assay	Vit D Assay method	Outcome analyzed	Statistics (95% CI)	Study authors	Quality of evidence (GRADE system)
Nested case control	USA	400	15–21 weeks	LC-MS	Preeclampsia	OR 1.4 (0.7–3.0)	Wetta et al, 2014	Moderate
					Spontaneous preterm birth	OR 1.3 (0.6–3.0)		
Nested case control	Australia	5109	10–14 weeks	CLIA	Adverse pregnancy outcomes (SGA, preterm births, preeclampsia, GDM, miscarriage and stillbirth)	OR 1.20 (0.69–2.07)	Schnueur et al, 2014	High
Nested case control	USA	135 cases and 517 controls	On enrollment (Avg 16 weeks)	LC-MS/MS	GDM	P<0.05	Arnold et al, 2015	Low
Cross sectional study	Poland	280	11–13 weeks	ECLIA	Preeclampsia	Not significant	Bomba Opon et al, 2014	Low
Cross sectional study	USA	1591	16.4–36.9 weeks (mean 27.9 weeks)	CLIA/RIA	Preeclampsia	Adjusted OR 1.14 (0.77–1.67)	Burris et al, 2014	Moderate
					Gestational hypertension	Adjusted OR 1.32 (1.01–1.72)		
Cross sectional study	Egypt	160	On enrollment	RIA	Glycemic control in GDM	P<0.05	Lithy et al, 2014	Low
Cross sectional study	UK	1467	26 weeks	LC-MS	GDM	NS	Whitelaw et al, 2014	Moderate
Cross sectional study	Turkey	687	24–28 weeks	ELISA	Postpartum depression at		Gur et al, 2015	Moderate
					1 week	P=0.003		
					6 weeks	P=0.004		
					6 months	P<0.001		
Retrospective cross sectional study	US	133	-	LC-MS/MS	Recurrent pregnancy loss	-	Ota et al, 2014	Low
Prospective study	Canada	655	6–13 weeks	LC-MS/MS	GDM	OR 1.48, p=0.04	Lacroix et al, 2014	Moderate
Prospective study	Korea	523	12–14, 20–22, 32–34 weeks	ECLIA	GDM and pregnancy outcomes (Apgar, miscarriage, birth weight)	Adjusted OR 0.647.	Park et al, 2014	Moderate
Prospective cohort study	Netherlands	2074	12 weeks	ELISA	Pregnancy related hypertensive disorders	OR 1.88 (0.79–4.48)	Weert et al, 2016	Low

Study design	Place of study	Sample size	Gestational age at Vit D assay	Vit D Assay method	Outcome analyzed	Statistics (95% CI)	Study authors	Quality of evidence (GRADE system)
Prospective cohort study	Spain	2382	Avg 13.5 weeks	HPLC	GDM	RR=0.92 (0.55,1.55)	Rodriguez et al, 2015	High
					PTL	p>0.4		
					C-section	RR=0.60 (0.37,0.97)		
					FGR, SGA, HC, B wt, length	p>0.4		
Prospective cohort study	Australia	796	18 weeks	ELISA, LC-MS	Postpartum depression	OR 2.19 (1.26–3.78)	Robinson et al, 2014	Moderate
Cohort study	Australia	1040	At delivery	LC-MS/MS	Postpartum depression at		Gould et al, 2015	Moderate
					6 weeks	Adjusted RR 0.92, p=0.11 (0.84–1.02)		
					6 months	Adjusted RR=0.96, p=0.41 (0.88–1.05)		
Cohort study	Singapore	940	26–28 weeks	ID-LC-MS	GDM	(0.01–0.14)	Loy et al, 2015	Moderate
					C-section	OR 1.39 (0.95–2.05)		
Cohort study	China	213	24–48 hrs after delivery	LC-MS/MS	Postpartum depression	P<0.0001, OR 7.17 (3.81–12.94)	Fu et al, 2015	Moderate
Retrospective cohort study	USA	235	5–12 weeks	ELISA	Pre- eclampsia, PTL, GDM, spontaneous abortion	Adjusted OR 1.01 (0.961–1.057)	Flood-Nichols et al, 2015	Low
Cohort study	US	2798	<26 weeks	LC-MS/MS	C-section, prolonged labor and instrumental delivery		Gernand et al, 2015	Moderate
Retrospective cohort study	UK	995	11–13 weeks	LC-MS/MS	Mode of delivery	P=0.53	Savvidou et al, 2012	Moderate

Abbreviations used: Vit D (vitamin D), ELISA (Enzyme Linked Immune sorbent Assay), CLIA (Chemiluminescent Immunoassay), LC-MS/MS (Liquid Chromatography tandem Mass Spectrometry), HPLC (High performance liquid chromatography), RIA (Radio Immune sorbent Assay), GDM (gestational diabetes mellitus), PTL (Preterm labor), SGA (small for gestational age), B Wt (birth weight), HC (head circumference), C-section (Cesarean section), FGR (Fetal growth rate)

Table 2

Observational studies of vitamin D status in pregnancy and fetal outcomes

Study design	Place of study	Sample size	GA at vit D assay	Vit D assay method	Fetal Outcome	Statistics (CI)	Study authors	Quality of evidence (GRADE system)
Case control	Iran	40 cases	At delivery	ELISA	SGA	P=0.003	Mirzaei et al, 2015	Moderate
Case control	Turkey	30 cases and 30 controls	On admission	LC-MS/MS	LRTI in infants	P=0.001	Dinlen et al, 2016	Moderate
Case control	India	60 cases and 60 controls	At delivery	ELISA	Birth weight	P=0.004	Nandal et al, 2015	Moderate
Nested case control	Canada	607 cases and 1027 controls	At delivery	CLIA	Neonatal outcomes (LBW, SGA, preterm births)	OR 0.47 (0.23–0.97)	Morgan et al, 2016	Moderate
Cohort study	China	1491	At delivery	RIA	Birth weight and risk of SGA	P<0.001	Zhu et al, 2015	Moderate
Cohort study	China	3658	Anytime during pregnancy	RIA	Birth weight	r=0.477, p<0.001	Chen et al, 2015	Moderate
Cohort study	Spain	2358	13–15 weeks	HPLC	Fetal growth and risk of overweight.		Morales et al, 2015	High
					AC >= 90th percentile	OR 1.50, P=0.041 (1.01–2.21)		
					EFW >= 90th percentile	OR 1.47, P=0.046 (1.00–2.16)		
Cohort study	Taiwan	164	Before delivery	LC-MS/MS	Allergic disorders		Chiu et al, 2015	Moderate
					Eczema (at age 4)	OR 0.12, p=0.012 (0.02–0.63)		
					Asthma (at age 4)	OR 0.22, p=0.038 (0.06–0.92)		
Cohort study	Denmark	32456	Mid pregnancy	-	Allergic diseases and asthma	P=0.21	Maslova et al, 2014	Low
Prospective cohort	Germany	777	At delivery	EIA	Risk of LRTIs	Adjusted RR 1.32 (1.00, 1.73)	Luczynska et al, 2014	Moderate
Cross sectional	Turkey	152	Anytime during pregnancy	ELISA	Perinatal outcomes		Aydogmus et al, 2015	Low

Study design	Place of study	Sample size	GA at vit D assay	Vit D assay method	Fetal Outcome	Statistics (CI)	Study authors	Quality of evidence (GRADE system)
					C-section	p=0.176		
					Perinatal complications	OR 4.30 (1.85–9.99)		
					SGA	OR 4.7 (1.41–15.78)		
Cross sectional	Ireland	94	At delivery	Vit D total automated competitive binding protein assay	Respiratory outcomes in preterm infants		Onwuneme et al, 2015	Low
					Oxygen requirement	P=0.008		
					Need for assisted ventilation	P=0.13		
					Duration of IPPV	P=0.32		
Cross sectional	Iran	102	At delivery	EIA	LBW	P=0.001	Khalessi et al, 2015	Moderate
Cross sectional	Australia	225	At delivery	LC-MS/MS	Immunity and Allergies		Jones et al, 2015	Moderate
					Response to HDM by			
					IL-13	P=0.002		
					IL-5	P=0.001		
					IL-5 response to OVA	P=0.009		
Cohort study	US	792	12–26 weeks	LC-MS/MS	SGA	P=0.028	Gernand et al, 2014	Moderate

Abbreviations used: GA (Gestational age), Vit D (vitamin D), ELISA (Enzyme Linked Immune sorbent Assay), CLIA (Chemiluminescent Immunoassay), LC-MS/MS (Liquid Chromatography tandem Mass Spectrometry), HPLC (High performance liquid chromatography), RIA (Radio Immune sorbent assay), EIA (Enzyme Immune assay), GDM (gestational diabetes mellitus), GHTN (Gestational Hypertension), SGA (small for gestational age), LBW (low birth weight), HC (head circumference), CI (Confidence Interval), OR (Odd's Ratio), RR (Risk Ratio), IPPV (Intermittent positive pressure ventilation), AC (Abdominal circumference), ADHD (attention deficit hyperactivity disorder), EFW (estimated fetal weight), LRTI (Lower respiratory tract infections), C-section (Cesarean section), HDM (House dust mites), OVA (ovalbumin).

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Table 3

Randomized Controlled Trials of vitamin D supplementation in pregnancy

Place of study	No. of participants	Intervention	Vit D assay method	Duration of intervention	Outcomes	Study authors	Quality of evidence (GRADE system)
Iran	50	Placebo Calcium 1000 mg/day + Vit D3 50,000 U on day 1 and 21	ELISA	6 weeks	Metabolic profile of women with GDM	Asemi et al, 2013	High
Australia	209	LD vit D3 400 U/day HD vit D3 5,000 U/day	CLIA	till delivery	Primary: GDM Secondary: maternal and neonatal outcomes	Yap et al, 2014	High
Iran	500	LD vit D 400 U/day HD vit D 50,000 U/day	-	till delivery	GDM, GHTN, pre-eclampsia, preterm, LBW.	Mojibian et al, 2015	High
Pakistan	193	FeS04 200mg + Calcium 600mg/day + Vit D3 4,000 U/day	CLIA	20 weeks to delivery	Pregnancy outcomes (GDM, GHTN, preterm labor, SGA, B wt, length, HC, Apgar at 1 and 5 min)	Hossain et al, 2014	High
India	180	No intervention Vit D3 120,000 IU at 20, 24, 28 and 32 weeks	ELISA		Preterm, pre- eclampsia, GDM, LBW and Apgar scores at 1 and 5 minutes	Sablok et al, 2015	High
Iran	60	Placebo Calcium 1000mg/day + vit D3 50,000 IU every 2 weeks	ELISA	12 weeks	Metabolic profiles in women at risk of pre-eclampsia	Samimi et al, 2015	High
Iran	46	Placebo MM 800mg Ca+ 200mg Mg+ 8mg Zn + Vit D3 400 IU	ELISA	9 weeks	Outcomes in Pre-eclampsia patients	Asemi et al, 2015	High
Iran	60	Placebo Vit D3 50,000 IU every 2 wks	ELISA	12 weeks	Metabolic profile and outcomes in pre-eclampsia patients	Karamali et al, 2015	High
US	440	Placebo+ MV with Vit D 400 IU/day Vit D +MV with Vit D 4400 IU/day	CLIA, LC-MS	till delivery	Asthma and recurrent wheezing in offspring	Litonjua et al, 2016	High
Japan	164	Placebo Vit D3 800 IU/day		6 weeks	Allergies like infantile eczema, atopic dermatitis, food allergy and wheeze	Norizoe et al, 2014	High
Iran	130	MVI + Ca 400 IU/day MVI+ Ca 400 IU/day + Vit D3 50,000 IU/ week	ELISA	8 weeks	Fetal growth (length, HC, weight)	Hashemipour et al, 2013	Moderate

Abbreviations used: Vit D (vitamin D), MVI (Multivitamin Injection), ELISA (Enzyme Linked Immune sorbent Assay), CLIA (Chemiluminescent Immunoassay), LC-MS/MS (Liquid Chromatography tandem Mass Spectrometry), GDM (gestational diabetes mellitus), GHTN (Gestational Hypertension), SGA (small for gestational age), LBW (low birth weight), HC (Head circumference),

Table 4

Summary of the various maternal-fetal outcomes studies with the level of evidence of association with vitamin D.

Outcomes	Total no. of studies (observational)	Total no. of studies (interventional)	Quality of evidence (GRADE system)
Preeclampsia	11	3	High
Gestational Diabetes Mellitus	8	6	High
Cesarean section	5	0	Moderate
Preterm Delivery	5	4	Moderate
Recurrent pregnancy loss	1	0	Low
Postpartum Depression	4	0	Moderate
Low Birth weight and Small for gestational age	9	2	High
Respiratory infections	5	0	Moderate
Immunity and allergies	4	2	Moderate
Anthropometry	1	4	High
Autism	0	1	Moderate