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Review Article

IMPACT OF VITAMIN D DEFICIENCY DURING PREGNANCY ON THEIR OFFSPRING HEALTH

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ABSTRACT

Vitamin D deficiency is acommon health problem in pregnant women throughout world. It adversely influences their neonatal and early childhood health & growth.Vitamin D has a classical function of calcium homeostasis but its role beyond the classical function has been of growing interest in recent years. There have been multiple researches on pleiotropic role of vitamin D in pregnancy and the implications of its deficiency on maternal-fetal outcomes. Several studies have been carried out to establish the adverse effect of vitamin D deficiency during pregnancy on their offspring, including preterm birth, low birth weight, respiratory infections, eczema, allergies, autism, etc. Some randomized controlled trials have also been conducted to see the effect of vitamin D supplementation during pregnancy and their outcomes. Though some studies reported improvement in outcomes with supplementation, others have not shown any association. In this article, we have reviewed the observational and interventional studies which have been published primarily after 2014 onwards to see the outcomes of offspring given birth by vitamin deficient mother. The potential underlying mechanisms of vitamin D in regulating each of the outcomes have also been discussed.

Keywords: Vitamin D, Pregnancy, Offspring, Calcium, Deficiency, Outcome.

INTRODUCTION

Vitamin D deficiency is a global problem affecting people of all age groups, races and gender. More than billion people are suffering from its deficiency. Its deficiency is highly prevalent among pregnant women.[1] Pregnancy is a special condition during which the body experience physiological alterations, including changes in Vitamin D metabolism.[1, 2] The percentage of vitamin D deficiency in pregnant women is higher than the general population and its prevalence is reported to be 85% in review articles.[3-5]

Vitamin D is an essential micronutrient acts as a prohormone and plays an important role in calcium homeostasis and bone health in addition to its neuromuscular functions. During pregnancy, vitamin D plays a vital role in embryogenesis, especially fetal skeletal development and calcium homeostasis.[6] Vitamin D deficiency is a growing health concern worldwide in both adults and children.[7]The developing fetuses are entirely dependent on their mother for their vitamin D supply as a source via transplacental route in the form of 25-OHD of vitamin. On that account, pregnant women need to be vitamin replete at the time of giving birth to sufficient level in their baby to last 3 months of life.[11, 12] The dependence of newborns on maternal reserves of vitamin D is reflected in the high level of correlation between maternal and cord blood level of 25-OHD. These observations were consistent with previous reports. Hypovitaminosis D during pregnancy and its turn neonatal period and infancy is of special concern.[13, 14]

Vitamin D status during pregnancy has important implications for the general health of developing fetus and newborn child. Its deficiency or insufficiency has been associated with allergies, impaired immune functions, low birth weight, impaired bone development, diabetes mellitus, and heart failure.[17, 18]

Likewise, mother also unfavorably affected by deficiency of the same vitamin in the form of gestational diabetes, preeclampsia, decreased weight gain, infection and many others. All these mentioned maternal complications may have negative impact on health of their offspring. Factors attributed to maternal vitamin D deficiency are numerous though exposure to sunlight, seasonal variation, younger age, later gestational age, higher pre pregnancy BMI, low ambient UVB level, co-morbidities and vitamin D Supplementation are major contributing ones.[1, 8]

The serum 25-OH D is regarded as the main circulating vitamin D metabolite and its serum level serves as the best stable biomarker of the vitamin status. Deficiency is defined as a serum 25-OH D concentration less than 20 ng/ml while vitamin D insufficiency is defined as concentrations less than 30ng/ml.[9, 10]

Indeed, the findings from several studies suggest the increasing prevalence of vitamin D deficiency in pregnancy and the associated adverse fetal outcome.[15] The impact of vitamin D deficiency has been discussed in a few recent reviews and meta-analysis.[56, 16, 25] This review article sums up conclusions drawn from the recent studies on the Effect of vitamin D deficiency during pregnancy on their offspring. 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.

Vitamin D in pregnancy:

During pregnancy, there are number of physiological adaptations take place including mobilization of maternal calcium increases to meet the demands of adequate fetal bone mineralization , an 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.[26] Maternal 25OHD crosses the placenta and is the major form of vitamin D for the fetus.[27] Calcitriol increases during pregnancy, almost twice by the end of last trimester and then returns to normal after delivery.[27] Fetal serum calcium levels use to be higher than maternal serum calcium; thereby specific transplacental carriers are required to transfer calcium against the concentration gradient.[26] This is mediated by the expression of calcium binding proteins in placenta, including calbindin D-9k and D-28k.[28]

The major function of vitamin D in pregnancy is to increase calcium absorption and placental calcium transport.[26] Furthermore, it 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 cathelicidinh(CTD) in the placenta.[26] Calcitriol also plays an important role in placental physiology.

All these effects shown there is vital importance of vitamin D during gestation and the potential role of its deficiency on adverse fetal outcomes. Each fetal outcomes investigated in the recent papers has been discussed in detail below.

Adverse fetal outcomes associated with vitamin D deficiency.

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

Vitamin D takes part an important role in fetal growth by maintaining calcium homeostasis and parathyroid hormone levels.[29] There are several studies which showed adequate maternal vitamin D improves the fetal outcomes in the form of birth weight sufficiency. Most of them are observational studies. Chen et al performed a population-based cohort in which Maternal serum 25OHD level was measured at anytime during pregnancy and found a positive correlation between maternal 25OHD levels and neonatal birth weight ($r = 0.477$, $p < 0.001$).[30] Similar results were reported by other investigators.[31-35] Another study carried out in China by Zhu et al (2015) measured the cord blood 25OHD levels and its relation with LBW and SGA in 1,491 neonates. They reported that every 10 nmol/L rise in the cord blood 25OHD level, birth weight increased by 61.0 gm at concentration < 40 nmol/L of 25OHD, and then decreased by 68.5 gm at concentrations ranging from 40 to 70 nmol/L. This is the first study to report inverted U-shaped relationship between neonatal vitamin D status and fetal growth.[36] However, other studies are inconclusive to establish any relation between vitamin D levels and fetal birth weight.[37, 38] Conflicting results were found in the interventional studies for vitamin D supplementation and its impact on offspring birth weight. Another RCT carried out by Hossain found improved outcomes with vitamin D supplementation.[39] 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 most of immune cells, and its activation plays a vital role in adaptive and innate immunity, along with the regulation of inflammatory response.[40]There are various mechanisms by which vitamin D regulate inflammatory response: (i) vitamin D controls the activity of macrophages &dendritic cells and various events in response to the activation of Toll-like receptors in neutrophils,[41] (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,[40] (iii) vitamin D induces the expression of two antimicrobial peptides, cathelicidin and β-defensin, which are essential in innate immunity via chemotactic action and neutralization of toxins,[42] and (iv) vitamin D shifts the cytokine expression from type 1 to type 2 cells response, hence taking part into the maintenance of self-tolerance.[43] Thus, based on the potent immunomodulatory effect of vitamin D, several studies have demonstrated relation of vitamin D deficiency to the increased incidence of respiratory tract infections in children. There has been hypothesized that vitamin D deficiency during pregnancy increases the risk of pulmonary infections in their offspring. Recently, few studies have shown their association. Onwuneme conducted a study in 94 preterm infants which revealed that low serum Vitamin D (<30 nmol/L) in preterms were associated with increased requirements of oxygen (p=0.008), prolonged span of intermittent positive pressure ventilation (p=0.032), and more need of assisted ventilation (p=0.013)[44]. Similarly a prospective cohort study on 777 mother child pairs in Germany conducted by Luczynska and found a association statistically significant between 25OHD levels in cord blood and vulnerability to lower respiratory tract infection. The adjusted risk-ratio for 25OHD deficient infants (<25 nmol/L) was 1.32 as compared to the reference group (>50 nmol/L).[45] The study conducted by Dinlen in Turkey draw the same conclusions, in 60 infants, 30 with acute lower respiratory tract infections term infants and 30 controls matched for gestational age, gender and weight and reported lower serum vitamin D levels in mothers of the study group (p=0.0001).[46] In summary, vitamin D deficiency during pregnancy increases the susceptibility of respiratory infections in infants. This conclusion is further required to be confirmed by interventional studies.

Immunity and Allergies:

As described above, Vitamin D plays a vital role in the immunomodulation via its effect on the function of T and B lymphocytes. Vitamin D promotes Th2 cell mediated anti-inflammatory response while in B cells it promotes the immunoglobulins production, memory B cells inhibition and plasma cells generation.[47]

To endorse the association between vitamin D status in pregnancy and development of allergies, including asthma and eczema in their offspring, lately four observational studies and two interventional studies have been conducted. In Taiwan, a study was performed in 164 mother child pair's cohort to see the association[48] and found protective effect of vitamin D in protecting children from allergies, asthma, and eczema after following up children for 4 years of age. Jones selected a cohort of mothers with history of atopy and explore the association of 25OHD in them to the immune response in their children and found that improving 25OHD level during pregnancy or early infancy can reduces the risk of allergies by inhibiting the

inflammatory cytokines related with allergies. This relation has been exceedingly encouraging for carrying out interventional studies as well.[49]

A large trial "Vitamin D Antenatal Asthma Reduction Trial (VDAART)" (Litonjua) was conducted in the United States enrolling 881 pregnant women of 10–18 weeks' gestation at high risk of having children with asthma. It reported that the incidence of asthma and wheeze associated disorders were lower in vitamin D supplemented group by 6.1% as compared to the placebo group, although it did not achieve statistical significance.[49] Another interventional study performed in Japan by Norizoe reported similar impact of vitamin D supplementation during lactation period to improve the outcomes in infantile allergic conditions like eczema. They found that vitamin D supplementation did not decrease the risk of eczema rather it escalated the chance of food allergies up to 2 years age (RR 3.42, 95% CI: 1.02–11.77; p=0.030).[50] In conclusion, there are mixed results coming out of studies whether vitamin D supplementation increases or decreases the risk of allergies and therefore, requires further exploration.

Anthropometry:

Vitamin D takes part a principal role in calcium homeostasis, bone remodeling and muscle functioning. Its insufficiency or deficiency during pregnancy is correlated with impaired bone development, fetal growth and other adverse effects on musculo-skeletal system of the offspring.[51]Multiple studies have shown negative effect of maternal deficiency of vitamin D on the anthropometric measurements of the offspring. These studies include 1 cohort study[52] and 4 randomized controlled trials.[39, 53-55]

Morales and colleagues (2015) carried out a cohort study in 2,358 pregnant women at Spain and measured serum vitamin D levels at any time during gestation. Child's femur length, biparietal diameter and abdominal circumference were noted through ultrasound findings at 12, 20 and34 weeks of gestation.[52]

A single center randomized clinical trial in Pakistan reported no favorable outcomes on fetal growth by vitamin D supplementation.[39] Nandal 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).[54] Similarly, Hashemipour 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.[53] 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.[55] 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 also concludes positive outcomes of vitamin D supplementation in pregnancy on offspring birth weight and length.[56] 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:

Autism is a group of dysfunctions in social interactions and behavior. Numerous studies have demonstrated that vitamin D deficiency during pregnancy significantly increases the possiblity of autism. Wang in his meta-analysis explored the potential mechanism by which this vitamin could possibly influence the appearance of autism spectrum disorder in children. He explained firstly, it has a role in neuronal differentiation, synaptic functions and neurotransmissions thus it is vital to early brain development in children.[57] Secondly, Vit D contributes to immune system homeostasis. Its deficiency alters the T cell activation profile and has an effect on the adaptive immunity and cause preponderance to autism.[58] In addition, vitamin D increases the level of antioxidant, a glutathione, in the brain and protects the brain from oxidative stress and consequently prevents from autism. Vitamin D deficiency makes the gene more susceptible to lethal interaction with oxidative stress and makes more prone to developing Autism.[59]Serotonin, as one of the major function, plays an important role in controlling the emotions and Vitamin D activates the genes involved in its synthesis in the brain. It has been found that serotonin levels are lower in the brain of autistic children so gives the firm thought of vitamin D linked to underlying pathogenesis of Autism. Lastly, vitamin D deficiency could hamper the DNA repair and increase the risk of genetic mutations and thus contribute to the emergence of autism.[57, 60]

There are studies which conclude the benefits of vitamin D supplementation in pregnant women to decrease the incidence of autism in their offspring. Study recently conducted by Stubbs et all whereby pregnant women with previous autistic child were supplemented Vit D at dose of 5000 IU/ day followed by dose of 1000 IU/day to the newborn for first three consecutive years of life. These children were followed up at 18 and 36 months of age and found to have 5% children were only developed autism as compared to general recurrence risk of 20%.[61] As yet further to firm the conclusion more studies are required.

CONCLUSION

Vitamin D deficiency or insufficiency is a significant prevalent in pregnant ladies. There is increasing evidence showing that vitamin D status during pregnancy is integral to maternal health, fetal development and optimal neonatal outcomes as well as future health of the offspring. Its deficiency in pregnancy has several adverse impacts on their child health as evidenced in various studies. Adverse outcomes are mainly preterm birth, low birth weight, respiratory infections, eczema, allergies, autism, etc. Vitamin D supplementation during pregnancy could help avoid these above mentionedconsequences. It is a fearsome public health concern and its consequences are preventable by formulating and implementing the plan to avoid vitamin D deficiency.

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