Review Article

HYPOVITAMINOSIS D IN PREGNANCY: IMPLICATION FOR THE RISK OF DEVELOPMENT OF PREGNANCY COMPLICATIONS

Abstract

Vitamin D, a prohormone known traditionally to be involved in the metabolism of the bone and teeth has over recent years been the focus of many scientific researches. This is because inadequate and deficient vitamin D status is emerging as a very common condition worldwide, and several studies ranging from animal models to clinical trials have highlighted a strong association with acute and chronic diseases. Also, a large amount of observational data have reported pathophysiological associations of vitamin D with energy homeostasis, regulation of gene expression and control of the immune and endocrine systems. Pregnancy complications like pre-eclampsia, gestational diabetes, preterm birth, and infant-related outcomes which often results in maternal and fetal mortality, and also chronic metabolic disorders are all linked to Vitamin D. Recent works have proven that Vitamin D might be a promising theurapeutic and preventive tool in the management of these complications. Therefore, this review discusses the specific mechanisms in which Vitamin D deficiency or insufficiency can contribute to the development of pregnancy complications. However, more genetic studies are needed to assess the influence of vitamin D deficiency on pregnancy.

Keywords: Pregnancy, Vitamin D, Preeclampsia, Gestational Diabetes, Preterm Birth

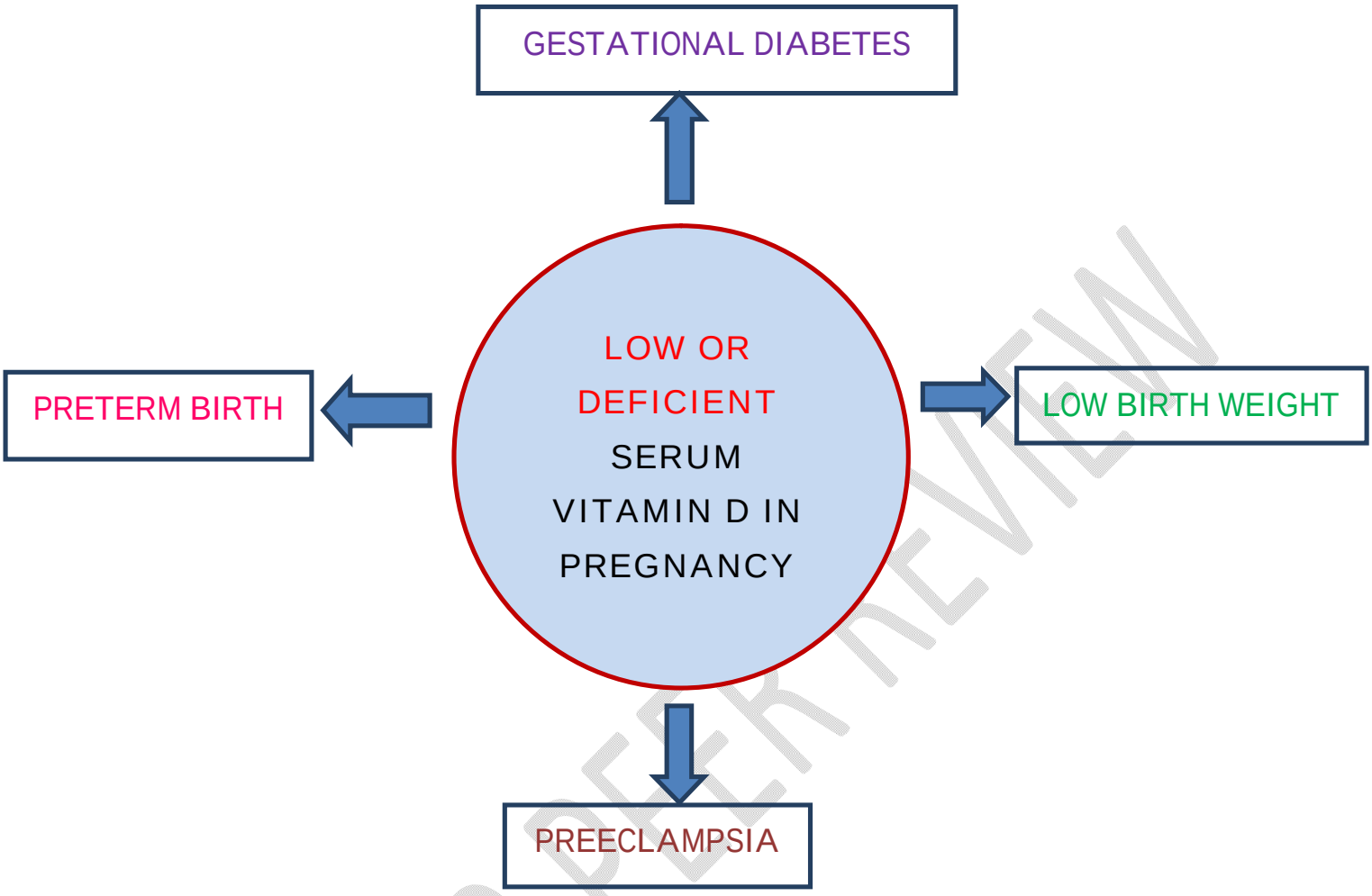

Fig 1: Graphical Abstract

1. Introduction

Vitamin D, a lipid-soluble vitamin and prohormone, is traditionally known to play important roles in bone metabolism through regulation of calcium and phosphate homeostasis [1]. However, recent researches have shown that the roles of this vitamin are numerous and cannot be

overemphasized. Calciferol, another name for vitamin D, is a class of fat-soluble seco-sterols. Vitamins D2 and D3 are the two most common types. While humans make vitamin D3 [cholecalciferol] in their skin from 7-dehydrocholesterol and also consume it through animal products, vitamin D2 [ergocalciferol] is mostly derived from plants, such as mushrooms [2]. The amount of UVB light that reaches the dermis and the availability of 7-dehydrocholesterol both influence the skin's synthesis of vitamin D3 [3]. The time of year, skin color, latitude, use of sunscreen, type of clothes, and amount of exposed skin are all factors that affect the level of synthesis. Age also plays a role; as people age, their ability to produce vitamin D decreases, partially as a result of falling levels of 7-dehydrocholesterol and changes to their skin [4].

Sources of vitamin D include both food and dietary supplements. Vitamin D occurs naturally in oily fish such as salmon, mackerel and herring, cod liver oil, and egg yolk. The vitamin D in fish is D_3, whereas that used for fortification is often D_2 [ergocalciferol] [5]. It differs from D_3 in having a double bond between C22 and C23 and a methyl group at C24 in the side chain. D_2 can be considered the first vitamin D analog] [6]. Due to its side chain's peculiarities from D3, this compound has a lesser affinity for DBP and is eliminated from circulation more quickly. In the skin, cholesterol is transformed to 7-dehydrocholesterol, which is then converted to vitamin D3 in the presence of UV-B light [spectrum 280–320 UVB]. DBP and vitamin D synthesized together deliver vitamin D to the liver. Chylomicrons carry dietary vitamin D2 and D3 to the liver, where it is processed in chylomicron remains. Once in the liver, vitamin D is hydroxylated at C-25 by one or more cytochrome P450 vitamin D 25 hydroxylases [including CYP2R1, CYP2D11 and CYP2D25], resulting in the formation of 25-hydroxyvitamin D_3 [$25(OH)D_3$][7] .The active form of vitamin D is formed with the addition of another hydroxyl group by the enzyme 1alpha-hydroxylase [1alpha-OHase] in the kidney, forming 1,25 hydroxy vitamin D [1,25(OH)2D] [8].

Vitamin D status is most commonly assessed through measurement of serum 25-hydroxyvitamin D [25(OH) D or calcidiol] levels, which reflect the vitamin D produced cutaneously and that obtained from foods or supplements. The 25(OH)D circulates bound to the vitamin-D-binding protein, and has a 2-week half-life, it is also an indicator of the endogenous vitamin D status. An adequate 25-OH-D level has been determined to be ≥32 ng/ml, vitamin D insufficiency and deficiency are diagnosed at levels of <32 ng/ml and, <20 ng/ml 25-OH-D, respectively [9]. Previous studies have shown that vitamin D receptors [VDR] occurs nearly in all tissue and there are more recent discoveries of numerous VDR binding sites throughout the genome controlling hundreds of genes, thereby impacting on multiple biologic processes [10].

Globally, 54% of pregnant women are estimated to have a plasma/serum total 25-hydroxyvitamin [25(OH)D] concentration <50 nmol/L and 18% <25 nmol/L indicating a high prevalence of vitamin D insufficiency and deficiency [11]and several studies from basic science to clinical applications have highlighted a strong association with chronic diseases, and pregnancy complications. Vitamin D has been reported to aid in gene regulation and expression in early placental development during pregnancy, fetomaternal immune tolerance, and placental antimicrobial and anti-inflammatory responses [12]. Gestational hypertension, pre-eclampsia [PE], and eclampsia, are among the major complications that account for approximately 14% of maternal mortality in pregnancy [13]. Recent researches suggests that there might be associations between vitamin D deficiency and preterm birth, fetal intrauterine growth restriction, decreased birth weight, and hypertensive disease in pregnancy[14,15] .

This review aim to discuss the recent justifications that establishes the role of Vitamin D in the pathogenesis of various pregnancy complications.

2. Vitamin D and Gestational Diabetes

Normal pregnancy is characterized by a significant reduction in maternal insulin sensitivity in the second and third trimesters. However, GDM might develop as a result of maladaptation of β cells to increased insulin demands or reduced reserve of β cells [16]. Decreased maternal insulin sensitivity, or increased insulin resistance, is the underlying pathophysiology of gestational diabetes, which starts very early in pregnancy and progresses to the third trimester. GDM complicates approximately 7–14% of pregnancies in the United States[17]. GDM subjects the mother and their infants to adverse health consequences which include: gestational hypertension, pre-eclampsia, increased rate of caesarean section, fetal macrosomia, sudden intra uterine death, birth trauma and increased perinatal mortality [18]. Infact, research have shown that women with GDM are more likely to undergo cesarean section and develop type 2 diabetes mellitus later in life [19]. Associated risk factors including advanced maternal age, obesity, family history of diabetes and ethnicity. In recent years, vitamin D deficiency has been increasingly recognized as one potential contributor to the development of GDM [20]. Several observational studies have found an association between low 25(OH)D level and increased risk of GDM. In a matched, case-control study of 54 Iranian women with GDM and 11 normoglycemic controls, Soheilykhah et al. found that maternal 25(OH)D concentrations at 24–28 weeks of gestation were significantly lower in women with GDM [21]. They noted that 83% of GDM women had 25(OH)D levels <50 nmol/L [a cutoff often used to define vitamin D deficiency in Iran] vs. 71% of controls. Clifton-Bligh and colleague studied 264 women in Australia and found that among the 32% with GDM, 25(OH)D levels were significantly lower compared to normoglycemic women [22]. A study conducted in Nigeria by Sonuga and Sonuga 2020, also found a significant lower concentration in serum vitamin D levels at second and third trimester in the GDM group when compared to the controls [14]. This was also similar to the work of Maghbooli et al. 2008 .[23] Also, Wang et al.2001 indicated a significant

difference in serum 25(OH)D concentrations between GDM and pregnant women with normal glucose tolerance even after controlling for age and pre-pregnancy BMI, and reported a 96.25% prevalence of vitamin D insufficiency and 52.75% deficiency in the GDM group [13]. There seems to be a link between vitamin D status and pathogenesis of GDM; this connection can be attributed to the role of vitamin D in glucose metabolism, inflammation, and modulation of gene expression for insulin secretion. Vitamin D is important in the regulation of gene expression by binding to the vitamin D receptor; this action can also mediate regulation of glucose metabolism by influencing insulin sensitivity, insulin secretion and insulin resistance [24]. Secondly, Vitamin D is important in glucose metabolism via the expression of 1α-hydroxylase enzymes in pancreatic β cells in the presence of a vitamin D response element in the human insulin gene promoter [25]. The effect of vitamin D on the regulation of pancreatic β-cell function and insulin secretion could be through intracellular changes in calcium flux through the cell membrane combined with its role in the synthesis and regulation of calbindin, a vitamin D-dependent calcium-binding protein in pancreatic β cells. The decrease in calcium flux across the cell membranes might result in decreased responsiveness of tissues to insulin mediated intracellular signaling [Fig. 2] [26].It seems that vitamin D increases in calcium content of the cells, in turn leading to increased transport of glucose into the muscle [27]. Furthermore, Vitamin D could also enhance insulin sensitivity by stimulating insulin receptor gene expression, thereby enhancing insulin-mediated glucose transport and activating peroxisome proliferator-activated receptors [nuclear PPAR][Fig.2] [28].

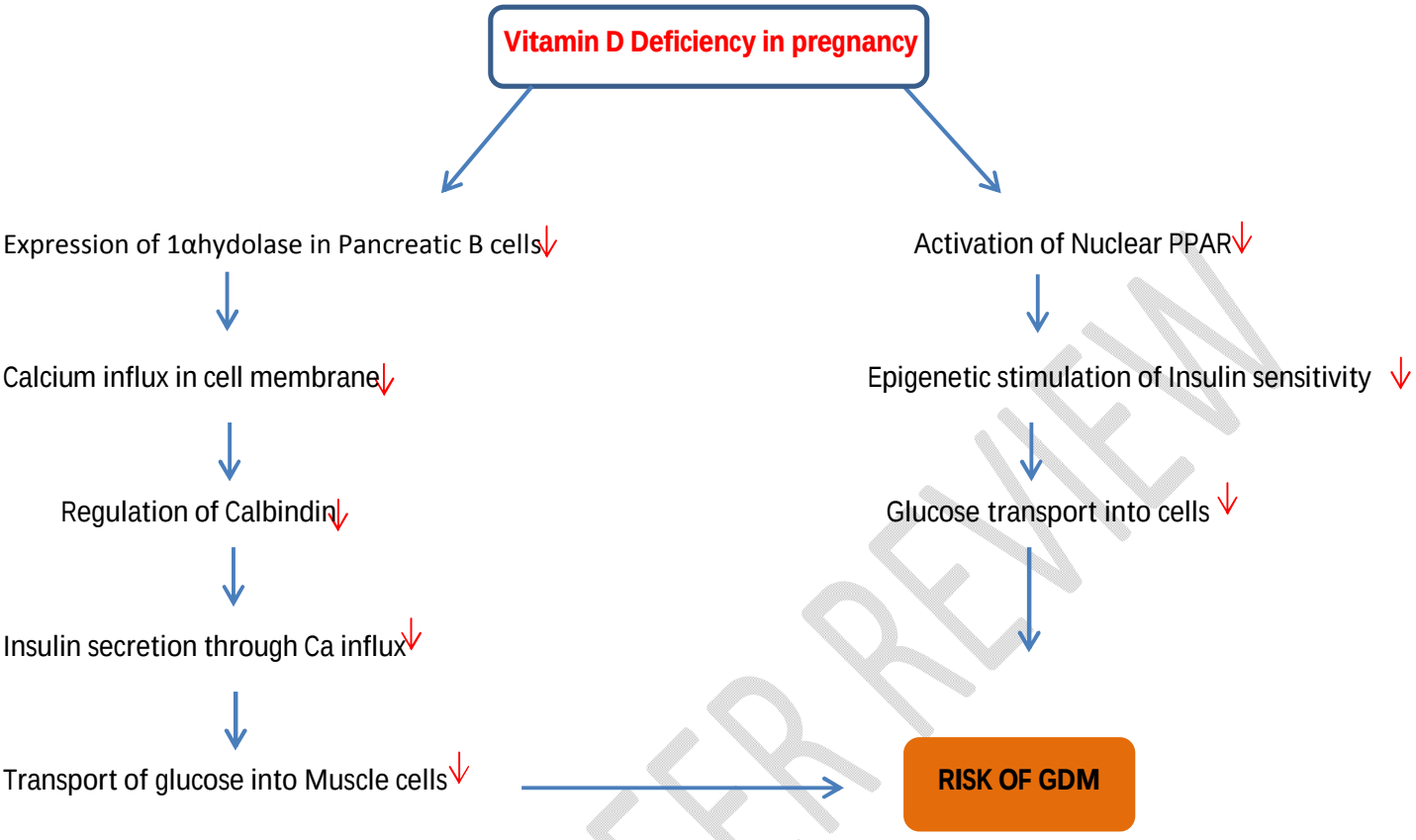

Fig. 2: Role of Vitamin D deficiency in the development of GDM

3. Vitamin D and Preeclampsia

Pre-eclampsia is defined as gestational hypertension of at least 140/90 mmHg on two separate occasions ≥4 hours apart accompanied by significant proteinuria of at least 300 mg in a 24-

hour collection of urine, or a urine dipstick result of 1+ or greater, arising de novo after the 20th week of gestation in a previously normotensive woman and resolving completely by the 6th postpartum week [29]. If left untreated; pre-eclampsia progresses to eclampsia, which refers to the development of grand mal seizures in a woman with pre-eclampsia, in the absence of other neurologic conditions that could account for the seizure [29]. It is a major cause of maternal, perinatal morbidity and mortality and complicates 2% to 8% of pregnancies [30][Report of the National High Blood Pressure Education,2000]. Pre-eclampsia has been linked to alterations in the interaction between the maternal immune response and the placenta, placental injury, endothelial cell injury, altered vascular reactivity, oxidative stress, imbalance among vasoactive substances, decreased intravascular volume, disseminated intravascular coagulation, and increased production of lipid peroxides [31].

There is compelling evidence that an improperly implanted placenta is a primary factor contributing to a woman's susceptibility to pre-eclampsia [32]. Poor uterine and placental perfusion caused by this improperly placed placenta leads to hypoxia, increased oxidative stress, and the release of anti-angiogenic proteins and inflammatory mediators into the mother's blood [32]. A major consequence of all these is generalized endothelial dysfunction. According to research demonstrating a lack of developed immunological tolerance in pregnancy, the aberrant implantation is assumed to result from the mother's immune system's reaction to the placenta. Endothelial dysfunction results in hypertension and many of the other symptoms and complications associated with pre-eclampsia [33]. Abnormal remodeling of spiral arteries entails a disorder of placental function, which is the source of many factors entering the maternal circulation responsible for increased inflammatory response, oxidative stress, apoptosis, and generalized endothelial dysfunction, which is an essential pathophysiological change in PE, explaining the development of

clinical symptoms[34]. A previous study compared the levels of Vitamin D in one hundred and twenty[120] pre-eclamptic women and normotensive pregnant women in South West Nigeria, and the results of the study confirmed that there is vitamin D insufficiency in the pre-eclamptic women in second and third trimester, while the levels of vitamin D in normotensive pregnant women was sufficient in all trimesters. However, after vitamin D supplementation in the preeclamptic women, the levels of vitamin, and antioxidant status increased significantly in the pre-eclamptic group [35]. Authors speculate that these conditions may result from the lack of action of vitamin D in immunosuppression, oxidative stress or placental development among deficient patients [36]. Another population-based investigation in Norway among 23,423 nulliparous women found that vitamin D intake of 15-20 µg/day, relative to <5 µg/day, was associated with a 27% reduction in the risk for pre-eclampsia [37]. These investigations suggest an association between vitamin D deficiency and the development of pre-eclampsia.

Vitamin D supplementation in pregnancy improves maternal vitamin D status and may positively affect the availability of vitamin D to the fetus and the neonate. The fetus is dependent on the mother for acquiring vitamin D, and 25(OH) D readily crosses the human placenta [37]. In an uncontrolled trial, supplementation with a multivitamin/mineral supplement and halibut liver oil [containing 900 IU vitamin D] provided at 20 wk gestation reduced the odds of pre-eclampsia by 32% [95% CI, 11–47%] [38].

In a cohort study, investigators found that regular supplementation with vitamin D in the first year of life halved the risk of pre-eclampsia in the female offspring's first pregnancy [39]. Additionally, vitamin D supplementation may affect pregnancy outcomes by regulating insulin-like

growth factor I and its receptor, regulating the gene expression of normal implantation and angiogenesis, and increasing insulin sensitivity[40].

The low levels of vitamin D metabolism in pre-eclampsia may be due to reduced placental 1α-hydroxylase activity [41], resulting in lower circulating calcitriol concentrations in pre-eclamptics compared to normotensives. In pre-eclampsia, the metabolism of vitamin D in placental tissue is altered, and these differences may play a role in the abnormal trophoblastic invasion found in these pregnancies [42].

Thus,1,25-dihydroxyvitamin D has a direct influence on implantation, placental invasion and angiogenesis[43]. It increases the activity of T-regulatory cells, which are essential for promoting immunological tolerance to facilitate placental implantation [44]. It also participate in modulation of embryo implantation, fetomaternal immune tolerance, and placental antimicrobial and anti-inflammatory responses [45]. According to a study, autophagy seems to be a general basis for the multiple health-promoting effects of vitamin D [46]. Autophagy is induced by several forms of cell stress including hypoxia, infection, and starvation [46]. Thus, maternal vitamin D deficiency may trigger pre-eclampsia through affecting V-ATPase activity, which seems to represent a general and basic pathogenesis of pre-eclampsia. Low vitamin D levels impair the normal Th1 to Th2 cytokine balance, with higher Th1 cytokine expression adversely affecting the immunological tolerance of embryo implantation [47] .

In pre-eclampsia, the metabolism of vitamin D in placental tissue is altered, and these differences may play a role in the abnormal trophoblastic invasion found in these pregnancies [37]. Vitamin D has been implicated in providing critical signals in gene regulation and expression in early placental development among placental trophoblast models [48]. Vitamin D receptor

[VDR],when it binds to 1,25(OH)2D_3, can generate a wide array of favorable nonclassic biological activities which are linked to its regulation of cell proliferation, cell differentiation, and immune responses [7] . When there is vitamin D deficiency, there is concern that the lack of these signals may play a critical role in stage I of placental development that leads to the ultimate recognition of stage II and a diagnosis of pre-eclampsia [41]. Finally, renal vascular endothelial growth factor [VEGF] appears to be linked to proteinuria. By altering the transcription of the VEGF gene, 1,25-dihydroxyvitamin D3 may control the angiogenesis process [45].

4. Vitamin D and Preterm Birth

Preterm labour is defined by the world health organization as the onset of labour prior to the completion of 37 weeks of gestation, in a pregnancy beyond 20 weeks of gestation. Preterm labor is a regular uterine contractions occurring at least once every 10 minutes and resulting in cervical dilatation or effacement before 37 weeks' gestation [49]. In 2020, preterm birth affected 1 of every 10 infants born in the United States. The preterm birth rate declined 1% in 2020, from 10.2% in 2019 to 10.1% in 2020 [49]. In 2020, the rate of preterm birth among African-American women [14.4%] was about 50 percent higher than the rate of preterm birth among white or Hispanic women [9.1% and 9.8% respectively] [50]. Preterm delivery can be associated with immediate and long-term neonatal complications. Long-term morbidity includes cerebral palsy, neurodevelopmental delay and chronic lung disease. The newborn outcome is influenced by the gestational age at delivery and other factors including nutrition and infection. The risk of mortality and morbidity increases with decreasing gestational age. However, studies have shown a link between low levels of maternal serum vitamin D and a higher risk of premature birth [51] . Vitamin Dplays a significant role in modulating an effective coordination of anti-inflammatory and

antimicrobial responses within the fetoplacental unit processes which help in maintaining a healthy term pregnancy [52]. A study by MehrdadShakiba et al.2013,that involved a total of 51 healthy pregnant women were supplemented with vitamin D and they reported a low rate of prematurity among neonates born to women who have been supplemented with vitamin D. Only 1 [2% of the total] neonate born to the 51 women who got vitamin D supplements was preterm [53]. Additionally, a meta-analysis that only considered longitudinal studies revealed that mothers who had 25(OH)D concentrations below 30 ng/mL had an 83 percent higher risk of having a child early [54].

Recently, a prospective observational study also determined the association between maternal serum vitamin D levels and spontaneous preterm delivery in 161 pregnant women and found that vitamin D deficiency was strongly associated with preterm birth and Vitamin D level was positively correlated with gestational age at delivery [55]. The proposed mechanism of action of Vit. D is its role in promoting cytokine inhibition and the expression of potent antimicrobial peptides in various immune cells, such as macrophages and dendritic cells, and also its action on placental tissue by modulating anti-inflammatory effects. All these might be implicated in the activities leading to preterm birth[56]. Also, preterm labour might arise from a switch of the myometrial quiescence to the coordinated contractility prior to fetal maturation. Myometrial contractility depends on vitamin D-regulated calcium release within the muscle cell. Therefore, the possible role of vitamin D in reducing the risk of spontaneous preterm birth might be by maintaining myometrial quiescence [57]. Furthermore, vitamin D has immunmodulatory and anti-inflammatory effects, such as the regulation of production and function of cytokines and neutrophil degranulation products that is important and relevant to prevent microbial invasion which may be a protective effect on SPB risk [58].

5.Vitamin D and Low Birth Weight

Low birth weight [LBW] refers to term or preterm neonates with birth weight < 2.5kg. Any infant weighing less than 2.5 kg or 1.5 kg at birth is a low-birth-weight or very-low-birth-weight infant, respectively, regardless of gestational age [59]. At 29 weeks' gestation, more than 90% of fetuses weigh less than 1.5 kg. These neonates may be small for gestational age or have intrauterine growth restriction. Mortality rate in such neonates is 40 times more than those with normal weight [59]. Perez-Lopez et al. [60] confirmed that vitamin D supplementation alone, but not in combination with other micronutrients, significantly increased birth weight, birth length, and head circumference and that newborns from women supplemented with vitamin D alone had a lower risk of LBW. A previous study demonstrated that Mice raised on vitamin D deficient diets have placentas with narrower fetal vessels in the placental labyrinth compared to mice fed vitamin D sufficient diets, indicating dysregulated vascularization, thereby establishing that there is an inverse relationship between maternal 25(OH)D and risk of placental vascular lesions in pregnancies with male fetuses[60] . It was found in the study of 4000 expectant moms that babies of mothers with low vitamin D levels had smaller bodies, shorter statures, and were more likely to develop SGA [33]. Other researchers have also documented associations between vitamin D and biomarkers of angiogenesis [61].

The positive effect of maternal vitamin D supplementation on birth size and risk of LBW and SGA might be mediated by changes in fetal cell mass and function, skeletal mineralization, and metabolism [48]. The active form of vitamin D attaches to vitamin D receptors in numerous fetal organs, controlling the genes necessary for the placenta's correct implantation [62], which is important for fetal growth. Moreover, vitamin D could influence the maternal immune response to the placenta and the expression of human chorionic gonadotropin and sex steroids [37]. The

influence of vitamin D in glucose and insulin metabolism, might affect the bio-availability of energy to the fetus [39], as well as musculoskeletal growth [60].A plausible mechanism for the impact of maternal vitamin D on fetal growth is placental vascularization which is linked to vitamin D status [63].

Conclusion

Inadequate or deficient Vitamin D status in pregnancy is related to the development of pregnancy related complications. Vitamin D inadequacy has not been considered as a serious health issue by physicians and patients in developing countries. However, recent researches have reported strong associations between vitamin D status and pregnancy complications. It is therefore important that widespread awareness of the importance of Vitamin D and supplementation in diet during pregnancy is highly recommended.

Further studies on the influence of Vitamin D at the level of genetic expression of proteins important for healthy pregnancy and delivery are also encouraged.

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Legends

Figure 1: Graphical Abstract

Figure 2: Role of Vitamin D deficiency in the development of GDM