International Journal of Research and Reports in Gynaecology

5(3): 161-171, 2022; Article no.IJRRGY.92019

Hypovitaminosis D in Pregnancy: Implication for the Risk of Development of Pregnancy Complications

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/92019

Review Article

Received 11 July 2022
Accepted 16 September 2022
Published 12 October 2022

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. Scientific evidence have shown that Vitamin D insufficiency is global problem and has been linked with several disease conditions, acute or chronic. Vitamin D has been shown to be involved in the control of endocrine and immune pathways, gene regulation and balance of various body metabolic processes. In fact its deficiency had been linked with chronic metabolic disorders and major pregnancy complications increasing fetal and maternal morbidity and mortality. Recent works have proven that Vitamin D might be a promising therapeutic and preventive tool in the management of these complications. Therefore, this review discusses the possible mechanisms in which Vitamin D deficiency or insufficiency can contribute to the development of pregnancy complications in order to encourage more studies even at molecular level to find probable solutions.

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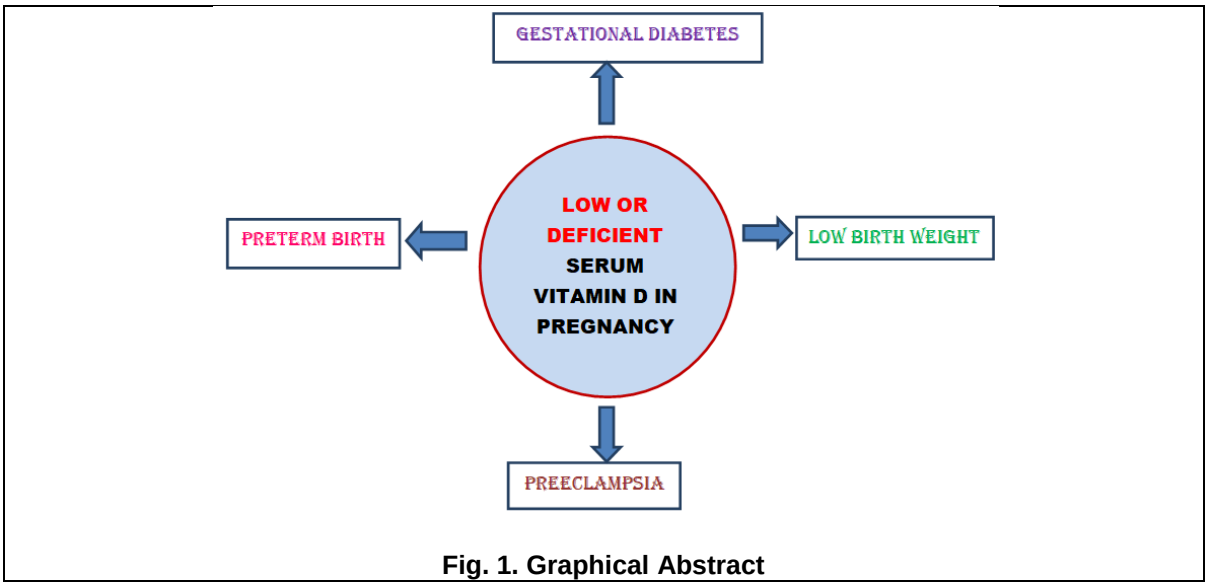

Fig. 1. Graphical Abstract

Keywords: Pregnancy; vitamin D; preeclampsia; gestational diabetes; preterm birth.

1. INTRODUCTION

Vitamin D is classified as a fat-soluble vitamin which is originally known to be involved in metabolism of the bone and teeth via its influence on the bioavailability of calcium and phosphate within the body [1]. However, recently studies have been able to establish strong evidences to support the hypothesis that Vitamin D has numerous and priceless roles within the human body. Vitamins D_2 and D_3 are the two major forms, and D_2 differs from D_3 in having a double bond between the C22 and C23 with a methyl group at C24 in its side chain and it is rapidly cleared from the circulation due to its poor affinity with DBP. Humans get their vitamin D_3 [cholecalciferol] either from 7-dehydrocholesterol via effect of UV-light on the skin or through the consumption of animal products; while vitamin D_2 [ergocalciferol] is mostly derived from plants, such as mushrooms and used often for fortification [2]. Rich sources of vitamin D include egg yolk, oily fish such as salmon, mackerel and herring, cod liver oil, and dietary supplements etc. The amount of vitamin D synthesized from the skin is highly dependent on amount of UVB light getting to the dermis and quantity of available 7-dehydrocholesterol [3]. Other factors influencing the vitamin production include time of year, skin color, latitude, use of sunscreen, type of clothes, and amount of exposed skin etc. 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].

"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]; and the D3 synthesized is transported to the liver bound to DBP. The dietary vitamin D2 and D3 are transported by chylomicrons to the liver, where it is further processed in chylomicron remnants" [5,6]. "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]. "Then the 25(OH) D3 is activated by the addition of another hydroxyl group in a reaction catalyzed by 1alpha-hydroxylase [1alpha-OHase] enzyme in the kidney to form the active [1, $25(OH)_2$ D]" [8].

"Serum 25 (OH) vitamin D concentration is mainly used to assess Vitamin D status because of its longer half life of 2 weeks compared to the active form, therefore it represent both endogenous (cutaneous) and exogenous (food and supplements)source of the vitamin. According to available evidence a serum 25-OH-D ≥32 ng/ml is found to be adequate, levels <32 ng/ml is insufficient and <20 ng/ml indicate deficiencies" [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].

54% of pregnant women have been shown to have insufficient vitamin D status while deficiencies has been reported in 18% of these group of women globally [11] and "evidence from basic science to clinical applications have highlighted a strong association of insufficient/deficient status with chronic diseases, and several pregnancy complications. Vitamin D play major functional roles in gene regulation and expression in early placental development during pregnancy, feto-maternal immune tolerance, and placental antimicrobial and anti-inflammatory responses" [12]. "Worldwide, 14% of maternal deaths in pregnancy has been attributed mainly to gestational hypertension, pre-eclampsia and eclampsia" [13]. "Recent researches suggests that there might be associations between vitamin D deficiency and preterm birth, fetal intrauterine growth restriction, low birth weight, and hypertension in pregnancy" [14,15].

This review therefore aims to discuss the recent justifications that establish the effects of Vitamin D status in the development of various pregnancy complications.

2. VITAMIN D AND GESTATIONAL DIABETES

It is known that insulin resistance is present in normal pregnancy especially at second and third trimesters because of the associated increased counter regulatory hormones production. However, GDM might develop as a result of maladaptation of β cells to increased insulin demands or reduced reserve of β cells [16]. Other factors increasing the risk of GDM are advanced maternal age, obesity, positive family history of diabetes mellitus and previous adverse pregnancy outcomes. Insulin resistance is the pathologic factor attributed to impaired glucose tolerance occurrence in pregnancy and might lead to the development of GDM as pregnancy progresses. It has been shown that 7-14% of pregnant women in the United States of America develop GDM as pregnancy progresses [17]. "GDM had been linked with several maternal and fetal adverse pregnancy outcomes including pregnancy induced hypertension, pre-eclampsia, increased rate of caesarean section and perinatal morbidity/mortality, macrosomia, sudden intra uterine death and traumatic birth injuries" [18]. In fact, research has shown that pregnancies complicated with GDM are more likely to progress to full blown type II diabetes mellitus later in life and more likely to be delivered via caesarian section [19]. Recently vitamin D has increasingly been fingered to contribute greatly to the GDM development in pregnancy [20]. "Available evidences have shown that there is positive relationship between vitamin D deficiencies and risk of developing GDM. Recent work by Sayid et al. determined the Vitamin D Status of 234 Turkish women with gestational diabetes mellitus and 168 controls. They reported that women with GDM had significantly lower 25-hydroxyvitamin D levels compared to controls (30.8±16.3 *vs*.36.0±16.2 nmol/L)" [21]; "similar findings was stated by Farhana and colleagues involving 18 GDM women and 54 controls found that Majority (83.3%) of the GDM patients had insufficient or deficient serum vitamin D level (<30 ng/mL) as compared to 57.4% of the control group. The risk of having GDM in pregnant women with insufficient or deficient serum vitamin-D was estimated to be almost 4-fold (95% CI = 1.1 – 14.3) higher (p = 0.047) than that in the pregnant women with normal serum vitamin-D level". [22]. A study conducted among Nigerian pregnant women by Sonuga and Sonuga 2020, also found that those with gestational diabetes had significantly low levels of serum 25 (OH) D [14]; this was also similar to the work of Jain M et al. 2015 [23]. Wang et al., 2001 reported "96.25% and 52.75% prevalence of vitamin D insufficiency and deficiency respectively in pregnant women with GDM compared to normoglycaemic pregnant group despite controlling for age and pre-pregnancy BMI" [13].

"These studies buttresses the possible relationship between vitamin D status and development of gestational diabetes mellitus and this possibly could be due to the functional role that the vitamin play in glucose metabolism, and modulation of gene expression for insulin secretion. Vitamin D has been shown to regulate glucose metabolism influencing insulin release and action via its involvement in gene expression regulation upon coupling with vitamin D receptor" [24]. "Also vitamin D is involved in glucose homeostasis as a result of the expression of 1α-hydroxylase enzymes in the pancreatic islet β cells, this process is driven by the presence of a vitamin D response element in the human insulin gene promoter" [25]. It has also been postulated that vitamin D alters the synthesis of calbindin, a vitamin D-dependent calcium-binding protein, and decreases intracellular calcium influx across the pancreatic cell membrane thereby influencing insulin secretion by the pancreas and insulin action at the tissue level [Fig. 2] [26]. Vitamin D stimulates insulin responsiveness at the tissues

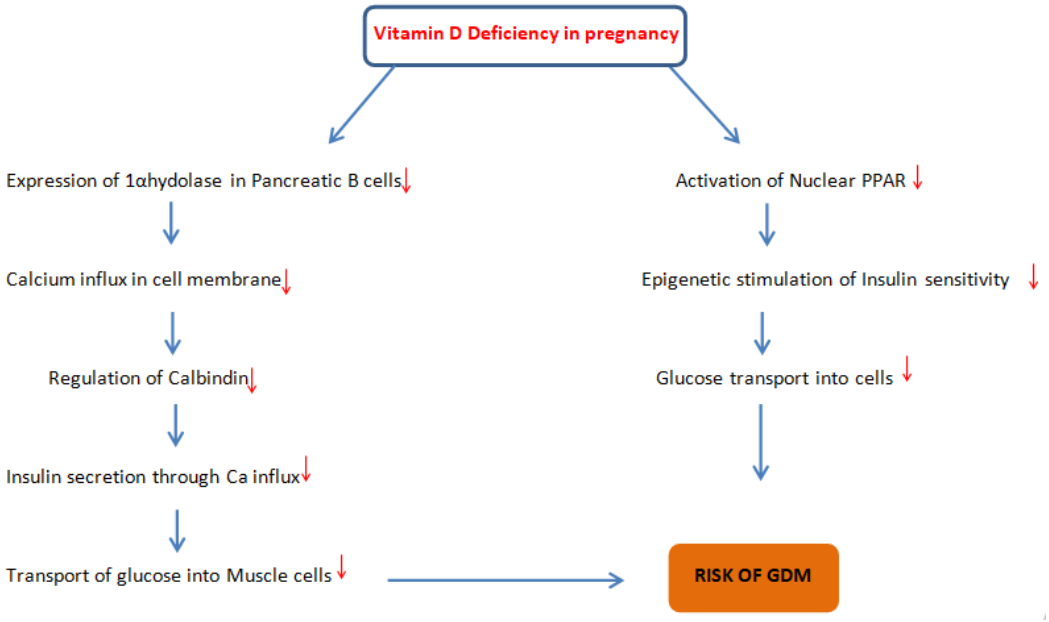

Fig. 2. Role of Vitamin D deficiency in the development of GDM

most especially in the muscle [27] by enhancing insulin mediated glucose transport at the cellular level, this effect has been associated with the increased intracellular calcium influx into the pancreatic islet *B* cells under the influence of the vitamin and the activation of peroxisome proliferator-activated receptors [nuclear PPAR] [Fig. 2] [28].

3. VITAMIN D AND PREECLAMPSIA

"Preeclampsia is diagnosed in pregnant women with hypertension (defined as BP ≥140/90 mmHg on two separate occasions ≥4 hours apart) in the presence of significant proteinuria (defined as at least 300 mg per 24-hour urine collection, a protein-to-creatinine ratio of at least 0.3 mg per dL, or urine dipstick test result of 2+)" [29]. "It can also be diagnosed in the absence of proteinuria, if hypertensive pregnant women have new-onset thrombocytopenia; renal insufficiency; impaired liver function combined with right upper quadrant or epigastric pain unresponsive to medication and not attributed to other etiologies; pulmonary edema; headache not amenable to treatment or that cannot be attributed to another etiology; or vision problems" [29]. "If preeclampsia is left untreated it can progress development of eclampsia, which is defined as new-onset seizures not attributed to other etiologies (e.g., epilepsy).Gestational hypertension is diagnosed in pregnant women with the hypertension criteria for preeclampsia without the proteinuria or any of the above mentioned severe clinical features [30]. Available report shows that preeclampsia complicates 2-8% of all pregnancies and has been linked with poor maternal and perinatal outcomes" [30]. Pre-eclampsia had been linked with generation ROS, decreased placental/maternal immune response, endothelial cell and trophoblast injury, altered vascular reactivity, DIC and increased production of lipid peroxides [31].

There is compelling evidence that an improperly implanted placenta is a primary factor contributing to pregnant women susceptibility to pre-eclampsia [32]. Poor uterine and placental perfusion caused by this improperly placed placenta leads to hypoxia, increased generation of anti-angiogenic proteins and free radicals, and inflammatory response in the maternal circulation [32]. "A major consequence of all these is generalized endothelial dysfunction. Therefore summarizing from a study that demonstrates lack of developed immunological tolerance in pregnancy, the aberrant implantation characterizing preeclampsia is assumed to be due to the mother's immune system's reaction against the placenta. Endothelial dysfunction results in hypertension and many of the other symptoms and complications associated with pre-eclampsia" [33]. The main pathological change linked with development of preeclampsia and its characteristic clinical features is the incomplete transformation of the placental spiral arteries resulting in release of several

inflammatory factors leading to systemic inflammation, oxidative stress, generalized endothelial dysfunction and cell death [34].

"A study carried out among 120 pregnant women (normotensive and preeclamptic) in South-Western Nigeria reported low serum 25 (OH) D levels in preeclampsia compared to normotensive pregnant women at second and third trimesters of cyesis. Conversely, following oral vitamin D supplementation in the preeclamptic group, there is a significant improvement in the levels of their serum vitamin D and antioxidant status" [35]. "The authors of this study therefore suggested that preeclampsia might result from the reduced/lack of functional vitamin D actions in immunosuppression, in reducing ROS generation and in enhancing adequate placental development" [36]. "Again the suggestion that adequate vitamin D levels might protect against the development of preeclampsia is reiterated in a study which reported that vitamin D administration in pregnancy was associated with a reduced risk of preeclampsia (odd ratio [OR] 0.37, 95% confidence interval [CI]: 0.26, 0.52; I2 = 0%). If the vitamin D supplementation was started up to 20 weeks' gestation, the odds was a little lower (OR 0.35, 95% CI: 0.24, 0.50, $p < 0.001$)" [37]. "A recent meta analysis involving a total of 22 studies with 25,530 participants included for analysis. Women with VitD insufficiency or deficiency had a higher preeclampsia rate compared to women with normal VitD levels (OR 1.58, 95% CI 1.39–1.79)" [38]. "Vitamin D supplementation in the first year of life in females has been shown to reduce the risk of developing preeclampsia in first pregnancy by 50%" [39]. "It is known that fetus is dependent on the mother for nourishment and that 25(OH) D readily crosses the human placenta, therefore vitamin D supplementation in pregnancy enhances the quantity that gets to the fetus" [37].

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]. "It has been proposed that the low levels of vitamin D associated with majority of preeclampsia cases might be as a result of decreased circulatory levels and activity of 1α-hydroxylase enzyme" [41]. Also it has been reported that alteration in vitamin D metabolism at the placental tissues may lead to abnormal trophoblastic invasion characteristic of these pregnancies [42]; hence it can be suggested that active vitamin D directly influence implantation of blastocyst, placental invasion and neovascularization [43]. Vitamin D increases the activity of regulatory T-cells (Tregs), which are essential for promoting immunological tolerance to facilitate placental implantation [44]. "It is also involve in the regulation blastocyst implantation, fetomaternal immune tolerance, and placental antimicrobial and anti-inflammatory responses" [45]. "It is also involve in the regulation blastocyst implantation, fetomaternal immune tolerance, and placental antimicrobial and anti-inflammatory responses" [45]. Autophagocytosis can be stimulated in the presence of stressful cell conditions such as hypoxia, infection etc and it has been shown in a study that adequate serum vitamin D can protect against it [46].

Mechanism by which vitamin D deficiency can be a causative factor in the development of preeclampsia include impairment of the balance between Th1 and Th2 cytokines, with higher Th1 expression adversely affecting the immunological tolerance of embryo implantation [47]; and disruption of V-ATPase activity, which have been found to be fundamental in the pathogenesis of pre-eclampsia [47]. Other mechanism include abnormal trophoblastic invasion as a result of altered vitamin D metabolism by placental tissue [37]. As stated earlier vitamin D modulates gene expression in trophoblastic cells of the placenta [48], and also regulates cell proliferation, differentiation, and immune responses [7] via binding to Vitamin D receptor. Therefore vitamin D deficiency result in loss of the regulatory action which 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 and by altering the transcription of the VEGF gene, 1, 25(OH) 2 D may control the angiogenesis process" [45].

4. VITAMIN D AND PRETERM BIRTH

"World Health Organization (W.H.O) has defined preterm labor as that which onset starts before the completion of 37 weeks of gestation, in a pregnancy beyond 20 weeks of gestation. Labor is a regular uterine contractions occurring at least once every 10 minutes and resulting in cervical dilatation or effacement" [49]. It was reported that the prevalence of preterm birth in United States as at 2020 is 1 in 10 [49]. The prevalence of preterm birth is about 50% higher among African-

American population (14.4%) compared to White (9.1%) or Hispanic population (9.8%) according to report in 2020 [49]. There are several acute and chronic adverse neonatal outcomes associated with preterm birth, such as chronic lung disease, cerebral palsy and neuro-developmental delay. 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 [50].

"However, studies have shown a link between low levels of maternal serum vitamin D and a higher risk of premature birth" [51]. "Vitamin D plays a significant role in the modulation of effective anti-inflammatory and antimicrobial responses within the fetoplacental units, which help in maintaining a healthy term pregnancy" [52,53]. Mehrdad Shakiba et al. in 2013 studied 51 healthy pregnant women who were given vitamin D supplements and found that the prevalence of preterm birth in them was very low; 1 out the 51 participants (2%) studied had premature delivery [54]. "A meta-analysis of several longitudinal studies revealed that the risk of preterm birth is 83% in pregnant women who had serum 25(OH)D concentrations below 30 ng/mL" [54]. "In another research where association between maternal serum vitamin D levels and spontaneous preterm delivery in pregnant women were studied, it was reported that vitamin D deficiency is significantly associated with preterm birth and Vitamin D level was positively correlated with gestational age at delivery" [55].

"There are several proposed mechanisms by which vitamin D deficiency might lead to preterm birth. These mechanisms might be associated with the role of the vitamin D in promoting cytokine inhibition, stimulating antimicrobial peptides in various immune cells, such as macrophages and dendritic cells, and also in modulation of anti-inflammatory effects by its action on placental tissue". [56]. "It has also been shown that myometrial contractility depends on vitamin D-regulated calcium release within the muscle cell such that vitamin D deficiency results in increase coordinated contraction of the uterus (preterm contraction), inducing preterm birth". [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 spontaneous preterm birth 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]. Maugeri 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" [61]. "Other researchers have also documented associations between vitamin D and biomarkers of angiogenesis" [62].

"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" [63]. "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" [64], "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" [65,66].

6. 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Jeon SM, Shin EA. Exploring vitamin D metabolism and function in cancer. Exp Mol Med. 2018;50(4):1-14.
   DOI: 10.1038/s12276-018-0038-9
2. Tiwari A, Singh G, Singh U, Sapra L, Rana V, Sharma V, et al. Edible mushrooms: the potential game changer in alleviating vitamin D deficiency and improving human health. Int J Food Sci Technol. 2022; 57(3):1367-77.
   DOI: 10.1111/ijfs.15410
3. Wacker M, Holick MF. Sunlight and vitamin D: A global perspective for health. Dermatoendocrinol. 2013;5(1):51-108.
   DOI: 10.4161/derm.24494, PMID 24494042.
4. Gallagher JC. Vitamin D and aging. Endocrinol Metab Clin North Am. 2013;42(2):319-32.
   DOI: 10.1016/j.ecl.2013.02.004, PMID 23702404.
5. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academies Press; 2011.
6. Chen TC, Lu Z, Holick MF. Photobiology of vitamin D. In: Holick M, editor. Vitamin D: physiology, molecular biology, and clinical applications. 2nd ed. New York: Humana Press; 2010.
7. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol. 2014;21(3): 319-29.
   DOI: 10.1016/j.chembiol.2013.12.016, PMID 24529992.
8. Sugimoto H, Shiro Y. Diversity and substrate specificity in the structures of steroidogenic cytochrome P450 enzymes. Biol Pharm Bull. 2012;35(6):818-23.
   DOI: 10.1248/bpb.35.818, PMID 22687469.
9. Quraishi SA, Camargo CA. Vitamin D and major chronic illness. J Restor Med. 2012; 1(1):9-23.
   DOI: 10.14200/jrm.2012.1.1001, PMID 30197839.
10. Girgis CM, Mokbel N, Cha KM, Houweling PJ, Abboud M, Fraser DR, et al. The vitamin D receptor (VDR) is expressed in skeletal muscle of male mice and modulates 25-hydroxyvitamin D (25OHD) uptake in myofibers. Endocrinology. 2014; 155(9):3227-37.
    DOI: 10.1210/en.2014-1016, PMID 24949660.
11. Jones KS, Meadows SR, Schoenmakers I, Prentice A, Moore SE. Vitamin D status increases during pregnancy and in response to vitamin D supplementation in rural Gambian women. J Nutr. 2020;150(3):492-504.
    DOI: 10.1093/jn/nxz290, PMID 31834380, PMCID PMC7056615.
12. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated humanantimicrobial response. Science. 2006;311(5768):1770-3.
    DOI: 10.1126/science.1123933, PMID 16497887.
13. Cecil RL, Goldman L, Schafer AI. Goldman's Cecil medicine. 24th ed. Philadelphia: Elsevier Saunders; 2012.
14. Sonuga AA, Sonuga OO. Hypovitaminosis D is associated with some metabolic indices in gestational diabetes mellitus. Biomed Hub. 2020;5(2):1177-90.
    DOI: 10.1159/000508207, PMID 32884931, PMCID PMC7443670.

15. Tamblyn JA, Hewison M, Wagner CL, Bulmer JN, Kilby MD. Immunological role of vitamin D at the maternal–fetal interface. J Endocrinol. 2015;224(3):R107-21.
DOI: 10.1530/JOE-14-0642, PMID 25663707.
16. Janus A, Szahidewicz-Krupska E, Mazur G, Doroszko A. Insulin resistance and endothelial dysfunction constitute a common therapeutic target in cardiometabolic disorders. Mediators Inflamm. 2016;2016:3634948.
DOI: 10.1155/2016/3634948, PMID 27413253.
17. Etminan-Bakhsh M, Tadi S, Hatami M, Darabi R. Prevalence of gestational diabetes mellitus and its associated risk factors in boo-Ali Hospital, Tehran. Galen Med J. 2020;9:e1642.
DOI: 10.31661/gmj.v9i0.1642, PMID 34466559.
18. Committee on Practice Bulletins. Practice Bulletin No. 180. Practice Bulletin No. 180: Gestational Diabetes Mellitus. Obstet Gynecol. 2017;130(1):e17-37.
DOI: 10.1097/AOG.0000000000002159, PMID 28644336.
19. Mathieu IP, Song Y, Jagasia SM. Disparities in postpartum follow-up in women with gestational diabetes mellitus. Clin Diabetes. 2014;32(4):178-82.
DOI: 10.2337/diaclin.32.4.178, PMID 25646944.
20. Dror DK. Vitamin D status during pregnancy: maternal, fetal, and postnatal outcomes. Curr Opin Obstet Gynecol. 2011;23(6):422-6.
DOI: 10.1097/GCO.0b013e32834cb791, PMID 21986726.
21. Zuhur SShafi, Erol RS, Kuzu I, Altuntas Y. The relationship between low maternal serum 25-hydroxyvitamin D levels and gestational diabetes mellitus according to the severity of 25-hydroxyvitamin D deficiency. Clinics (Sao Paulo). 2013; 68(5):658-64.
DOI: 10.6061/clinics/2013(05)13, PMID 23778416.
22. Naznin F, Jesmin S, Akter N, Sharmin S, Khatun MR. Vitamin D status in patients of gestational diabetes mellitus in comparison to that of normal pregnancy. Ibrahim Card Med J. 2021;11(1):41-7.
DOI: 10.3329/icmj.v11i1.58704.
23. Jain M, Kapry S, Jain S, Singh SK, Singh TB. Maternal vitamin D deficiency: A risk factor for gestational diabetes mellitus in North India. Gynecol Obstet (Sunnyvale). 2015;5:264.
DOI: 10.4172/2161-0932.1000264.
24. Upreti V, Maitri V, Dhull P, Handa A, Prakash MS, Behl A. Effect of oral vitamin D supplementation on glycemic control in patients with type 2 diabetes mellitus with coexisting hypovitaminosis D: A parallel group placebo controlled randomized controlled pilot study. Diabetes Metab Syndr. 2018, Jul;12(4):509-12.
DOI: 10.1016/j.dsx.2018.03.008, PMID 29580871.
25. Yousefi Rad E, Djalali M, Koohdani F, Saboor-Yaraghi AA, Eshraghian MR, Javanbakht MH, et al. The effects of vitamin D supplementation on glucose control and insulin resistance in patients with diabetes type 2: a randomized clinical trial study. Iran J Public Health. 2014; 43(12):1651-6. PMID 26171357.
26. Maestro B, Campión J, Dávila N, Calle C. Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. Endocr J. 2000;47(4):383-91.
DOI: 10.1507/endocrj.47.383, PMID 11075718.
27. Dzik KP, Kaczor JJ. Mechanisms of vitamin D on skeletal muscle function: oxidative stress, energy metabolism and anabolic state. Eur J Appl Physiol. 2019; 119(4):825-39.
DOI: 10.1007/s00421-019-04104-x, PMID 30830277.
28. Dunlop TW, Väisänen S, Frank C, Molnár F, Sinkkonen L, Carlberg C. The human peroxisome proliferator-activated receptor δ gene is a primary target of 1α,25-dihydroxyvitamin D3 and its nuclear receptor. J Mol Biol. 2005;349(2): 248-60.
DOI: 10.1016/j.jmb.2005.03.060, PMID 15890193.
29. The Task Force on Hypertension in Pregnancy. ACOG. Hypertens Preg; 2013.
30. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. National High Blood Pressure Education Program Working Group. Am J Obstet Gynecol. 2000;183:0.
31. Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376(9741):631-44.

DOI: 10.1016/S0140-6736(10)60279-6, PMID 20598363.

32. Al-Jameil N, Aziz Khan F, Fareed Khan M, Tabassum H. A brief overview of preeclampsia. J Clin Med Res. 2014;6(1):1-7.
DOI: 10.4021/jocmr1682w, PMID 24400024.
33. McElwain CJ, Tuboly E, McCarthy FP, McCarthy CM. Mechanisms of endothelial dysfunction in pre-eclampsia and gestational diabetes mellitus: Windows into future cardiometabolic health? Front Endocrinol (Lausanne). 2020 Sep 11;11:655.
DOI: 10.3389/fendo.2020.00655, PMID 33042016, PMCID PMC7516342.
34. Gathiram P, Moodley J. Pre-eclampsia: its pathogenesis and pathophysiolgy. Cardiovasc J Afr. 2016;27(2):71-8.
DOI: 10.5830/CVJA-2016-009, PMID 27213853, PMCID PMC4928171.
35. Sonuga AA, Asaolu MF, Oyeyemi AO, Oyeboloa OO. Effects of vitamin D3 supplementation on antioxidant status and lipid peroxidation product in preeclamptic women. J Gynecol. 2019;4(1): 000169.
36. Fischer D, Schroer A, Lüdders D, Cordes T, Bücker B, Reichrath J et al. Metabolism of vitamin D3 in the placental tissue of normal and pre-eclampsia complicated pregnancies and premature births. Clin Exp Obstet Gynecol. 2007;34(2):80-4. PMID 17629157.
37. Fogacci S, Fogacci F, Banach M, Michos ED, Hernandez AV, Lip GYH, et al. Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials. Clin Nutr. 2020;39(6):1742-52,ISSN 0261-5614.
DOI: 10.1016/j.clnu.2019.08.015, PMID 31526611.
38. Hu KL, Zhang CX, Chen P, Zhang D, Hunt S. Vitamin D levels in early and middle pregnancy and preeclampsia, a systematic review and metaanalysis. Nutrients. 2022;14(5):999.
DOI: 10.3390/nu14050999, PMID 35267975.
39. Saraf R, Morton SM, Camargo CA Jr., Grant CC. Global summary of maternal and newborn vitamin D status—a systematic review. Matern Child Nutr. 2016;12(4):647-68.
DOI: 10.1111/mcn.12210, PMID 26373311.
40. Poniedziałek-Czajkowska E, Mierzyński R. Could vitamin D be effective in prevention of preeclampsia? Nutrients. 2021 Oct 28;13(11):3854.
DOI: 10.3390/nu13113854, PMID 34836111.
41. Liu NQ, Hewison M. Vitamin D, the placenta and pregnancy. Arch Biochem Biophys. 2012;523(1):37-47.
DOI: 10.1016/j.abb.2011.11.018, PMID 22155151.
42. Díaz L, Noyola-Martínez N, Barrera D, Hernández G, Avila E, Halhali A, et al. Calcitriol inhibits TNF-alpha-induced inflammatory cytokines in human trophoblasts. J Reprod Immunol. 2009; 81(1):17-24.
DOI: 10.1016/j.jri.2009.02.005, PMID 19501915.
43. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J. 2008;156(5):918-30.
DOI: 10.1016/j.ahj.2008.06.042, PMID 19061708.
44. Ganguly A, Tamblyn JA, Finn-Sell S, Chan SY, Westwood M, Gupta J et al. Vitamin D, the placenta and early pregnancy: effects on trophoblast function. J Endocrinol. 2018;236(2):R93-R103.
DOI: 10.1530/JOE-17-0491, PMID 29109081.
45. Li X, Zhou J, Fang M, Yu B. Pregnancy immune tolerance at the maternal-fetal interface. Int Rev Immunol. 2020;39(6):247-63.
DOI: 10.1080/08830185.2020.1777292, PMID 32530719.
46. Høyer-Hansen M, Nordbrandt SPS, Jäättelä M. Autophagy as a basis for the health-promoting effects of vitamin D. Trends Mol Med. 2010;16(7):295-302.
DOI: 10.1016/j.molmed.2010.04.005, PMID 20488750.
47. Kim HA, Perrelli A, Ragni A, Retta F, De Silva TM, Sobey CG, et al. Vitamin D deficiency and the risk of cerebrovascular disease. Antioxidants (Basel). 2020; 9(4):327.
DOI: 10.3390/antiox9040327, PMID 32316584.
48. Novakovic B, Sibson M, Ng HK, Manuelpillai U, Rakyan V, Down T, et al. Placenta-specific methylation of the vitamin D 24-hydroxylase gene: implications for feedback autoregulation of

active vitamin D levels at the fetomaternal interface. J Biol Chem. 2009;284(22): 14838-48.
DOI: 10.1074/jbc.M809542200, PMID 19237542.

49. Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion. Preterm birth; 2020.
50. Oluwole AA, Okunade KS, Okojie OE. Maternal serum vitamin D levels and preterm delivery among low-risk parturients in Lagos, Nigeria. Int J Gynaecol Obstet. 2019;144(2):216-20.
DOI: 10.1002/ijgo.12719, PMID 30461011.
51. Singh D, Hariharan D, Bhaumik D. Role of vitamin D in reducing the risk of preterm labour. Int J Reprod Contracept Obstet Gynecol. 2015;4(1):86-93, ISSN 2320-1789.
DOI: 10.5455/2320-1770.ijrcog20150217.
52. World Health Organization. international statistical classification of diseases and related health problems. 10th revision. 2010;ICD-10.
53. Amegah AK, Nsoh M, Ashley-Amegah G, Anaman-Togbor J. What factors influences dietary and non-dietary vitamin D intake among pregnant women in an African population? Nutrition. 2018;50:36-44.
DOI: 10.1016/j.nut.2017.11.003, PMID 29522981.
54. Shakiba M, Iranmanesh MR. Vitamin D requirement in pregnancy to prevent deficiency in neonates: a randomised trial. Singapore Med J. 2013;54(5):285-8.
DOI: 10.11622/smedj.2013110, PMID 23716156.
55. Wagner CL, Baggerly C, McDonnell S, Baggerly KA, French CB, Baggerly L, et al. Post-hoc analysis of vitamin D status and reduced risk of preterm birth in two vitamin D pregnancy cohorts compared with South Carolina March of Dimes 2009-2011 rates. J Steroid Biochem Mol Biol. 2016;155(B):245-51.
DOI: 10.1016/j.jsbmb.2015.10.022, PMID 26554936.
56. Qin LL, Lu FG, Yang SH, Xu HL, Luo BA. Does maternal vitamin D deficiency increase the risk of preterm birth: A meta-analysis of observational studies. Nutrients. 2016;8(5):301.
DOI: 10.3390/nu8050301, PMID 27213444.
57. Tribe RM. Regulation of human myometrial contractility during pregnancy and labour: are calcium homeostatic pathways important? Exp Physiol. 2001;86(2): 247-54.
DOI: 10.1113/eph8602180, PMID 11429641.
58. Chesney RW. Vitamin D and the Magic Mountain: the anti-infectious role of the vitamin. J Pediatr. 2010;156(5): 698-703.
DOI: 10.1016/j.jpeds.2010.02.002, PMID 20385316.
59. Maugeri A, Barchitta M, Blanco I, Agodi A. Effects of vitamin D supplementation during pregnancy on birth size: A systematic review and meta-analysis of randomized controlled trials. Nutrients. 2019 Feb;11(2):442.
DOI: 10.3390/nu11020442, PMID 30791641.
60. Maugeri A, Barchitta M, Blanco I, Agodi A. Effects of vitamin D supplementation during pregnancy on birth size: A systematic review and meta-analysis of randomized controlled trials. Nutrients. 2019 Feb 20;11(2):442.
DOI: 10.3390/nu11020442, PMID 30791641, PMCID PMC6412248.
61. Liu NQ, Ouyang Y, Bulut Y, Lagishetty V, Chan SY, Hollis BW, et al. Dietary vitamin D restriction in pregnant female mice is associated with maternal hypertension and altered placental and fetal development. Endocrinology. 2013; 154(7):2270-80.
DOI: 10.1210/en.2012-2270, PMID 23677931.
62. Wei SQ, Audibert F, Luo ZC, Nuyt AM, Masse B, Julien P, et al. Maternal plasma 25-hydroxyvitamin D levels, angiogenic factors, and preeclampsia. Am J Obstet Gynecol. 2013;208(5):390:e1-6.
DOI: 10.1016/j.ajog.2013.03.025, PMID 23618499.
63. Karras SN, Fakhoury H, Muscogiuri G, Grant WB, van den Ouweland JM, Colao AM et al. Maternal vitamin D levels during pregnancy and neonatal health: Evidence to date and clinical implications. Ther Adv Musculoskelet Dis. 2016 Aug;8(4): 124-35.
DOI: 10.1177/1759720X16656810, PMID 27493691.
64. Kaur J, Kamboj K, Yadav AK, Kaur P, Kumar V, Jha V. Cholecalciferol supplementation and angiogenic markers in chronic kidney disease. PLOS ONE. 2022;17(6):e0268946.

DOI: 10.1371/journal.pone.0268946, PMID 35657784.

65. McDonnell SL, Baggerly KA, Baggerly CA, Aliano JL, French CB, Baggerly LL, et al. Maternal 25(OH)D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. PLOS ONE. 2017;12(7):e0180483. DOI: 10.1371/journal.pone.0180483, PMID 28738090.

66. Purswani JM, Gala P, Dwarkanath P, Larkin HM, Kurpad A, Mehta S. The role of vitamin D in pre-eclampsia: a systematic review. BMC Preg Childbirth. 2017; 17(1):231. DOI: 10.1186/s12884-017-1408-3, PMID 28709403.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/92019