The impact of vitamin D deficiency on maternal outcomes in pregnancy

Abstract. Results show vitamin D supplementation during pregnancy improves maternal and infant 25(OH)D concentrations and may play a role in maternal insulin resistance and fetal growth. Literature search was performed using PubMed Database of the National Library of Medicine, with date limits from January 2015 to November 2020. We used the keywords: Vitamin D, pregnancy, vitamin D supplementation, hypovitaminosis D, pre eclampsia, 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 outcomes. 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 pre eclampsia. The overall level of evidence is high for vitamin D supplementation playing no role in the prevention of gestational diabetes. 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 RCT to study the impact of vitamin D supplementation on C-section rates. 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. Though the level of evidence is moderate, our analysis shows no significant association between vitamin D and preterm deliveries. Many studies have been designed to investigate an association between postpartum depression and vitamin D. 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.

Keywords: vitamin D deficiency; pregnancy; maternal outcomes; review

Introduction
Vitamin D is a secosteroid, which is also considered an important prohormone [1]. Since vitamin D receptors (VDR) 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 [2]. During pregnancy, vitamin D plays a vital role in embryogenesis, especially fetal skeletal development and calcium homeostasis [3]. Vitamin D deficiency is a growing health concern worldwide in both adults and children [4]. 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 [5].

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 [6]. Given the low cost of vitamin D supplementation, if proven effective in pregnancy, it could bring about some major improvements in public health worldwide [7].

The impact of vitamin D deficiency during pregnancy has been discussed in a few recent reviews and meta-analyses [8, 9]; however, more randomized clinical trials (RCT) 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.

Literature search was performed using PubMed Database of the National Library of Medicine, with date limits from January 2015 to November 2020. 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 outcomes. References in these articles were searched for any other related articles. Duplicate articles were excluded.

**Vitamin D deficiency and pregnancy**

Vitamin D is a fat-soluble vitamin with two major physiological forms: ergocalciferol — vitamin D$_2$ and cholecalciferol — vitamin D$_3$ [10]. These two forms basically differ in their side chain structure. 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 hydroxylation reactions and the availability of active vitamin D are regulated by serum calcium and phosphorus and parathyroid hormone (PTH) [11].

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 [12]. The serum 25(OH)D is regarded as the best stable and circulating biomarker for vitamin D deficiency [13]. 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 [13].

During pregnancy, mobilization of maternal calcium increases to meet the demands of adequate fetal bone mineralization. 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 [14]. Maternal 25(OH)D crosses the placenta and is the main form of vitamin D for the fetus [15]. Calcitriol rises during pregnancy, almost doubled by the end of third trimester and then returns to normal levels after delivery. 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 [16]. Fetal serum calcium levels are higher than maternal serum calcium levels, thereby requiring specific transplacental carriers to transfer calcium against the concentration gradient. This is mediated by the expression of calcium binding proteins in placenta, including calbindin D-9k and D-28k [17].

The most important contribution of vitamin D during pregnancy is to escalate calcium absorption and placental calcium transport. Additionally, vitamin D also regulates immune system and inhibits inflammation by restraining inflammatory cytokines. 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 [18]. All these effects indicate the vital importance of vitamin D during gestation and the potential role of its deficiency on adverse maternal-fetal outcomes.

**Vitamin D deficiency and adverse maternal outcomes**

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 (> 300 mg/day), and other organ dysfunction, including liver involvement, hematological disturbance, neurological or renal complications [19]. 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 [20]. Vitamin D helps in maintaining the immune homeostasis and thus prevents placental vasoconstriction and ultimately, preeclampsia. 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 [21].

Several observational studies were recently performed to investigate an association between vitamin D deficiency and preeclampsia but the findings have been inconsistent. M. Achkar et al. [21] 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 [22–24]. On the contrary, D.A. Bomba-Opon et al. [25] measured the 25(OH)D 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 (PIGF), uterine artery pulsatility index and mean arterial pressure. Similarly, F.J. Schneuer et al. [26] reported no increased risk of preeclampsia in vitamin D deficient pregnant women in a nested case control study conducted in 5109 pregnant women.

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),
Gestational diabetes mellitus is defined as hyperglycemia from glucose intolerance that develops or is first diagnosed during pregnancy. Vitamin D plays a role in glucose homeostasis by multiple mechanisms [28]. It regulates the calcium levels, which in turn regulates insulin production and secretion by the endocrine pancreas. It also improves the sensitivity of the target cells like adipose tissue, liver and skeletal muscles to insulin. Vitamin D deficiency or the dysfunction of vitamin D receptors relates to the pathogenesis of type 1 and type 2 diabetes mellitus, but its role in GDM remains inconclusive [29].

Observational studies have been recently conducted to study the association of vitamin D with GDM. D.L. Arnold et al. [30] conducted a 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 GDM. A 5 ng/ml increase in vitamin D3 levels was associated with reduction in GDM risk by 14%. Similar effects were reported by other authors in a prospective observational study in Canada [31]. On the contrary, some studies failed to establish a role of vitamin D in the prevention of GDM [32].

To compare and contrast the efficacy of different dosing patterns of vitamin D on GDM, two clinical trials were undertaken. C. Yap et al. [32] conducted the study in women with 25(OH)D levels less than 32 ng/ml before 20 weeks and randomized them to receive oral vitamin D at 5,000 IU daily or 400 IU daily from 14 weeks until delivery, and found no difference in the outcomes. D. Mojibain et al. [33] randomized pregnant women with 25(OH)D 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. The overall level of evidence is high for vitamin D supplementation playing no role in the prevention of GDM.

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 [34]. Vitamin D deficiency, therefore, may decrease the strength of the contractile muscles, causing prolonged labor or obstructed labor, indicating the need for C-section [35]. Vitamin D deficiency has also been postulated to cause malformation of pelvis, which is yet another indication for C-section. Few studies have analyzed the association between vitamin D levels and cesarean sections. In a prospective cohort study conducted in Spain in 2,382 mother child pairs, A. Rodriques et al. [36] reported that adequate vitamin D level (25(OH)D ≥ 30 ng/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 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 [37]. 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 [31].

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 RCT to study the impact of vitamin D supplementation on C-section rates.

One of the most common causes for preterm delivery is infection [38]. Vitamin D, through its role in anti-inflammatory pathways via nuclear factor-κB inhibition, could play a role in decreasing the incidence of infections thereby, preterm births [39]. But the exact role of vitamin D in the pathogenesis of preterm birth has not yet been clearly defined. Observational and interventional studies have investigated their association with lack of consistency in the results. L.M. Bodnar et al. [39] conducted a case control study with 1,126 cases and 2,327 controls in Pittsburgh, PA, USA. Serum 25(OH)D 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. Other studies did not support the above findings [40].

Few recent interventional studies on vitamin D supplementation examined its role in the prevention of preterm births. N. Hossain et al. [41] carried out a RCT of routine care (200 mg ferrous sulfate and 600 mg calcium) vs vitamin D, 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). On the contrary, A. Sablok et al. [42] 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. C.L. Wagner et al. [43] carried out a post hoc analysis to measure the strength of association between serum 25(OH)D 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. Meta-analysis [8] 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.

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 [44]. 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 [45]. Such an effect of vitamin D supports its role in the immunoregulation during implantation. This hypothesis was examined by T. Ganchimeg et al. [46] 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 followed by in vitro experiments and significantly reduced 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 this association.

Postpartum depression is the most common psychiatric condition occurring in the postpartum period. Vitamin D is believed to be a neurosteroid and has been linked to the occurrence of depression [47]. There are various plausible mechanisms relating postpartum depression with vitamin D deficiency. VDR are located throughout the body including brain, so, in case of vitamin D-deficiency, the VDR in the brain may affect the hormones that are involved in the occurrence of mood disorders [48]. Vitamin D also plays a role in brain processes like neurotransmission, neuro-immunomodulation and neuroprotection. Vitamin D is involved in the synthesis of norepinephrine and dopamine, which gets imbalanced in mood disorders. 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 [49].

Many studies have been designed to investigate an association between postpartum depression and vitamin D. C. Fu et al. [48] 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 25(OH)D 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 25(OH)D levels (< 30 ng/ml). The levels of autoantibodies were measured. The 47.4 % of these women had low vitamin D deficiency: a critical review. Matern Child Health J. 2015 Jan;19(1):94-101. doi:10.1007/s10995-014-1499-7.

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Влияние дефицита витамина D на перепрібіг вагітності

Резюме. Установлено, що адекватне забезпечення вітаміном D під час вагітності сприяє нормальному її перебігу як для матері, так і для плода. Метою було вивчити вплив дефіциту вітаміну D на перебіг вагітності. Потрібно використовувати ключові слова: "витамін D", "вагітність", "дефіцит вітаміну D", "гестоз", "гестаційний діабет", "передчасні пологи" та інші суміжні терміни. Виконання аналізу орігінальних та обзора відбулось за допомогою бази даних PubMed за період від січня 2015 року по листопад 2020 року. За допомогою ключових слів використовувалися загальні позиції, які свідчать про те, що дефіцит вітаміну D знижує ризик гестозу. Не встановлено доказової бази щодо впливу додаткового призначення вітаміну D на профілактику гестаційного діабету. Можливі усуненнями вагітності при дефіциті вітаміну D є перспективи, гестаційний діабет, передчасні пологи тощо. Хоча ці стані досить добре відомі, зв'язок із вітаміном D є новим напрямком вивчення їх патогенетичних ланок.

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Влияние дефицита витамина D на течение беременности

Резюме. Установлено, что адекватное обеспечение витамином D во время беременности способствует нормальному ее течению как для матери, так и для плода. Целью было изучить влияние дефицита витамина D на течение беременности. Поиск литературы осуществляли с помощью базы данных PubMed за период с января 2015 года по ноябрь 2020 года. Использовали ключевые слова: «витамин D», «беременность», «дефицит витамина D», «гестоз», «гестационный диабет», «предвестнические роды» и другие смежные термины. Проведен анализ оригинальных и обзорных статей относительно влияния дефицита витамина D во время беременности и эффективности дополнительного назначения препаратов витамина D на результаты завершения беременности. Корреляционный обзор по этим исследованиям отмечает, что женщины, которые дополнительно получали витамин D, имели меньший риск гестоза (ОР 0,52, ДИ 0,25–1,05). В то же время назначение витамина D и кальция значительно уменьшало риск гестоза. Не установлена доказательная база о влиянии дополнительного назначения витамина D на профилактику гестационного диабета. Возможными осложнениями беременности при дефиците витамина D являются прэклампсия, гестационный диабет, преждевременные роды и т.д. Хотя эти состояния достаточно хорошо известны, связь с витамином D является новым направлением изучения их патогенетических звеньев. Доказано, что назначение витамина D во время беременности снижает вероятность этих осложнений, что, в свою очередь, снижает долю дородоразрешённых путем кесарева сечения. Прэклампсия — угрожающее состояние не только для матери, но и для плода, что может привести к преждевременным родам, как спонтанным, так и по угряктом по- казаниям. К тому же у матери с прэклампсиеей повышается риск рождения ребенка с гипотрофийю, что имеет последствия в разном возрасте. Прэклампсия чаще обнаруживают у беременных с дефицитом витамина D. Указанная роль витамина D в качестве универсального модулятора иммунной системы обосновывает снижение его уровня в контексте иммунного ответа беременных. Витамин D и плода играет важную роль в возникновении воспаления плаценты. Необходима дальнейшая оценка с помощью крупных многоцентровых двойных слепых рандомизированных контролируемых клинических исследований с акцентом на конкретные неблагоприятные исходы беременности для установления преимуществ дополнительного назначения витамина D во время беременности.

Ключевые слова: дефицит витамина D; беременность; осложнения; обзор