Revista de Chimie
https://revistadechimie.ro
https://doi.org/10.37358/Rev. Chim.1949

Is There a Relation Between 25-Hydroxyvitamin D Deficiency and Gestational Diabetes?

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Abstract: *One of the essential roles of vitamin D is to maintain a good state of health, its actions being extremely complex. In the past years, the role and involvement of vitamin D have been intensively discussed in a variety of physiological or pathological conditions. To be effective, vitamin D requires binding to specific nuclear receptors (VDRs) that are found in multiple tissues. Therefore, there is a great interest in studies focused on vitamin D in order to evaluate the potential functions and relations with gestational diabetes mellitus (GDM). This disease is defined by glucose intolerance with onset or first recognition during pregnancy. It presents an increased risk of later progression to type 2 diabetes. Now, gestational diabetes represents a global public health problem due to its increasing incidence and possible severe complications of pregnancy. This article centralizes recent studies focused on a possible link between vitamin D deficiency and gestational diabetes, knowing that in pregnant women the insufficiency or deficiency of that vitamin is a common thing.*

Keywords*: gestational diabetes mellitus, pregnancy, vitamin D deficiency*

1. Introduction

In the scientific literature, it is known the classical role of vitamin D in regulating calcium and phosphorus homeostasis [1]. Vitamin D increases intestinal calcium uptake and phosphorus reabsorption at the tubular level, stimulates mineralization of osteoid tissue, promotes calcium and phosphorus deposition in the form of hydroxyapatite crystals [2]. Its action is focused on the three target organs, intestine, kidney, and bone, in which specific nuclear receptors *(*VDRs) are well expressed [3]. The studies and experiments conducted *in vitro* and *in vivo* have shown that vitamin D exerts other "non-calcium" actions also [1-6]. It was demonstrated that vitamin D receptors are located in the entire body tissues [1]. Recent studies have indicated that receptors of vitamin D are also located in cells that may regulate glucose metabolism, in pancreatic beta-cells, respectively [7-11]. It is still hard to demonstrate the link between vitamin D deficiency and gestational diabetes, based on the results provided by scientific literature. There are papers published in this area aiming this aspect, but the results are diverse and unclear. If this relation exists, the diagnostic and therapeutic implications could be significant, reducing the risk of developing gestational diabetes mellitus (GDM).

2. Materials and methods

For this review, we performed a literature search for 65 articles using the terms "gestational diabetes mellitus", "vitamin D deficiency", "pregnancy". The references of those articles were then checked and further publications were evaluated. The time period assessed was from 1999 to 2019.

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2.1 Metabolism of vitamin D during the pregnancy

The best indicator of vitamin D status in the body is considered to be serum 25-hydroxyvitamin D, 25-[OH]D [1-2]. This is known to be the renal and nonrenal synthesis precursor for 1,25-dihydroxyvitamin D, 1,25-[OH]2D (calcitriol) which, opposed to the previous, has a greater biological half-life of three weeks and higher circulating levels [3-7]. Serum 1,25-[OH]2D is the biologically active form of vitamin D that is responsible for most of the vitamin D actions and it does not cross the placenta [2]. Also, the plasmatic level of 1,25-[OH]2D is provided by the activity of two enzymes, 1-alpha-hydroxylase and 24-hydroxylase [2]. It is necessary to underline that 1-alpha-hydroxylase is a product encoded in the CYP27B1 gene and is expressed in kidneys, deciduas, and placenta during pregnancy [3]. Another compound encoded in the CYP24A1 gene is 24-hydroxylase that is responsible for producing less potent vitamin D metabolites [3,4]. During pregnancy the levels of 1,25-[OH]2D increase by 100% or more, possibly due to the methylation of the CYP24A1 catabolic gene [3,4]. In this case, the activity of this gene decreases automatically with the activity of 24-hydroxylase [4]. The serum calcium level in the mother does not change despite of the 100% rise in content of 1,25-[OH]2D [5]. It has been proved recently that, in the placenta, the production of 20-hydroxyvitamin D, 20-[OH]D is higher than 25-[OH]D [7]. However, these metabolites of hydroxyvitamin D are not regularly tested to indicate the vitamin D pool of the body. Vitamin D needs are assessed by dosing the 25-[OH]D in the blood. A concentration below 50 nmol/L (20 ng/mL) of circulating 25-[OH]D determines vitamin D deficiency, the optimal level being equal to or greater than 75 nmol/L (30 ng/mL) [8].

The actions of vitamin D in regulation of calcium and phosphorus homeostasis are well known. There is a debate, in the same time, about the role of antioxidant, anti-inflammatory and immunomodulatory, in reducing proteinuria, in inhibiting the renin-angiotensin system or in the anti-proliferative effect [8]. Vitamin D also modulates the activity of pancreatic beta-cells, protects beta-cells from immune attacks, immunoregulatory and anti-inflammatory effects resulting in insulin sensitization and stimulation of its secretion [9]. There are evidences to support the role of vitamin D in preserving normal homeostasis of glucose, even if the studies that have prospectively examined the risk of circulating 25-hydroxyvitamin D 25-[OH]D are controversial [10-12]. The pancreas possesses the vitamin D receptor (VDR) and the genes encoding 1-alpha-hydroxylase and thus can convert circulating 25-[OH]D to 1,25-[OH]2D to work as a paracrine or autocrine hormone [13]. As a result, vitamin D deficiency was associated with the development of cardiovascular, neurodegenerative and autoimmune illnesses, diabetes and even cancer [14-17].

2.2 Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a frequent disorder in pregnancy. It defined as a disease that first appears during pregnancy, without being present before [18]. GDM is mostly identified during the second or third trimester of pregnancy [18]. Women diagnosed with diabetes mellitus during first trimester are classified as pre-existing type 1 or type 2 diabetic patients rather than GDM [17]. GDM is an increasingly prevalent condition that leads to possible complications, for both mother and baby during pregnancy, including here preeclampsia, high fetal birth weight above 4000 grams and shoulder dystocia [19]. Between 2-14% of the pregnant women are affected by this disease, but this is related with the patient's demographics, screening strategies and diagnostic thresholds [20-22]. Therefore, a genetic predisposition to type 2 diabetes mellitus due to humoral changes can be easily observed during pregnancy [23-25]. Gestational diabetes mellitus is caused by a metabolism disorder of at least three aspects: insulin secretion, resistance to insulin and increased production of glucose [26]. Pancreatic hyperplasia of beta cells arises from the stimulation of prolactin and human chorionic somatomammotropin (HCS) in a normal pregnancy, resulting in higher insulin levels [26-27]. Placental secretion of diabetogenic hormones, such as growth hormone, HCS, corticotropin-releasing hormone, and progesterone, increases progressively insulin resistance until delivery [26]. The inability to repress insulin resistance in pregnancy despite beta-cell hyperplasia leads to GDM. Rapid

reduction of insulin resistance after birth suggests a major contribution of placental hormones. Thus, the routine glucose screening that is conducted during pregnancy serves as a useful tool for early detection of GDM [27].

3. Results and discussions

Globally, vitamin D deficiency has been identified during pregnancy, but it is not clear whether or not this is physiological [28-32]. Some studies proved that low plasma vitamin D rates in the first 28 weeks of amenorrhea may be correlated to a higher risk of developing diabetes after the second trimester of pregnancy [33]. In everyday practice 25-[OH]D is tested, which is a free fraction that during pregnancy reaches the cells and is transformed into an activated hormone through a placenta receptor by placenta 1-alpha-hydroxylase enzyme [34]. Overall, 25-[OH]D levels decrease in the last trimester of pregnancy [35]. It has been noted that 1,25-[OH]2D has significant effects and greater biological availability in pregnancy [36-37].

However, the link between this deficiency and the risk of GDM might be explained by several mechanisms. Firstly, by connecting 1,25-[OH]2D, the active form to the beta-cell receptors of vitamin D may, in different ways, adjust the endocrine activity of pancreatic beta-cell [38]. It also maintains the equilibrium between the extracellular and intracellular calcium concentrations from beta-cell and, secondly can enhance insulin sensitivity and reactivity for carrying glucose. [38]. This was linked with hereditary gene heterogeneity involving vitamin D- binding protein. Also, it also have been described a link between vitamin D receptor and alpha-hydroxylase gene to insulin resistance [38]. This will enable a normal extracellular calcium level, and in this way regulating the normal influx of calcium in the cells at the level of both, the membranes and cytosols [38]. Likewise, the reverse association of serum 25-[OH]D with the risk of GDM may suggest the role of other components in main internal or external sources of vitamin D on glucose normal levels [39]. For example, outdoor physical activity could diminish the risk of GDM, by stimulating the production of vitamin D from the skin as a result of sun exposure[39,40].

It is not sure if there is or not a relation between vitamin D deficiency and GDM. Data of practical relevance and clinical involvement of these associations are not established. Some studies concluded that GDM was associated with vitamin D deficiency [41-49], whereas other studies found no major GDM correlations [50-52]. All studies showed diminished levels of vitamin D in patients with gestational diabetes [41-52]. In a cross-sectional research on 741 pregnant women from Iran, Maghbooli *et al*. [53] revealed a prevalence of 70.6% of the deficiency of 25-[OH]D (< 25 nmol/L). In GDM cases, the incidence of serious deficiencies in vitamin D (< 12.5 nmol/L) was greater than in normoglycemic pregnancies. The analysis of regression showed a significant correlation between the HOMA index and the values of vitamin D. Results show a strong correlation between vitamin D concentrations and insulin sensitivity, so a lack in vitamin D could indicate insulin resistance.

In a prospective study, Muthukrishnan *et al.* [54] included 70 Indian pregnant women, with a pregnancy age of less than 28 weeks. All were tested for diabetes by glucose tolerance test. There were confirmed 51 cases with GDM (2 h post-glucose> 140 mg/dl), the remaining 19 with normal glucose tolerance (NGT) were included as controls. A number of 19 cases with NGT was taken as controls. Serum vitamin D levels in diabetes group were markedly decreased 24.7 (± 17.6) ng/ml compared with the group with NGT (45.8 ± 28 ng/ml) (P = 0.0004). It was not observed a important difference between the group with low 25-[OH]D (67%) and the group with normal 25-[OH]D (42%) (P = 0.0004).

Lu *et al.* [55], published a meta-analysis including a total of 20 observational studies containing 16515 individuals, with the aim to evaluate the link between vitamin D level and the chances of developing gestational diabetes. The result revealed a possible link between the insufficiency of vitamin D and an increased risk of gestational diabetes (RR 1.45; 95% CI 1.15-1.83; P < 0.001).

A meta-analysis of 29 observational studies, conducted by Hu *et al*. [56] was published. There have been involved 28982 participants, from these 4634 were diagnosed with GDM. Maternal low levels of

vitamin D deficiency have increased the risk of diabetes during pregnancy by 39 %. Furthermore, in cases of gestational diabetes, 25-[OH]D level was noticeably lower by 4.79 nmol/L compared to the control batch.

Robinson [57], after examining 112 studies, involving 2445 women, concluded that there is 85% higher risk of GDM when levels of vitamin D are low. Moreover it was described an inverse correlation between plasma levels of 25-[OH]D and maternal glycemic status.

Also many studies from developing countries showed an important association between the level of vitamin D and the risk of GDM.

Cho GJ *et al.* [58] examined the liaison between maternal 25-[OH]D values and gestational diabetes by studying the variations in vitamin D receptor (VDR), CYP24A and CYP27B1 correlated with placental development. In their study, 40 non-diabetic pregnant women and 20 women with GDM of Korean origin were investigated. The results revealed that 27.5% of non-diabetic group and 85% of diabetic group had level of vitamin D under <20 ng/mL. This insufficiency was significantly observed in diabetic group versus non-diabetic group ($P < .01$).

Analyzing the secretion of CYP24A1 protein and mRNA in placenta it was noted that they were highly expressed in diabetic group versus non-diabetic group. At the same time, the secretion of CYP27B1 and messenger RNA expression was similar in all women included in the study. Summarizing, the activity of CYP24A1 in the placenta is responsible for a deficit of vitamin D in GDM.

In a study conducted by Zhang *et al.* [59] it has been suggested that there is a strong correlation between maternal vitamin D low levels at the beginning of the pregnancy and the risk of diabetes appearance ($P<0.001$). 33% of the women with GDM had a low level of vitamin D (<20 ng/ml), compared to only 14% of the normal pregnant women ($P<0.001$). Several factors as age, race, obesity and hereditary diabetes did not change the results. The risk of GDM fluctuates depending on the concentrations of vitamin D, a decrease of 5 ng/ml in 25-[OH]D being linked to a 1.29-fold increase in GDM risk.

In a similar research carried by Lacroix *et al.* [60] on 655 pregnant Canadian women, the vitamin D was tested in the first trimester and insulin and glucose 3 times in the second trimester, suggesting that low levels 25-[OH]D in early pregnancy are acting as a non correlated factor for the development of GDM or insulin resistance in late pregnancy.

As mentioned earlier, some studies did not revealed a significant correlation between low level of vitamin D and the risk of developing GD, although this hypothesis was the starting point.

A study published by Kramer *et.al.* [61], demonstrated that vitamin D level in pregnancy was not linked with insulin sensitivity, secretory activity of beta-cells or glucose tolerance. Instead, increased PTH was associated with dysglycemia, the women in the highest tertile of PTH had an 82% increased risk of GDM. The status for PTH may be a relevant factor for future studies on the effects of vitamin D on GDM. It is possible that 1-alpha-hydroxylation of vitamin D in the kidney may lead to the formation of the physiologically active metabolite 1,25-[OH]2D, which is normalized by PTH [62].

Schneuer *et al.* [63] conducted in Australia a study involving 5109 pregnant women in the first trimester. Their results show that low plasma levels of Vitamin D between 10^{th}-14^{th} weeks of pregnancy was not related to diverse pregnancy complications such as: preeclampsia, GDM, preterm birth, intrauterine growth restriction. Also, low Vitamin D cannot be considered a more conclusive predictor for these complications, compared with the known obstetrical common risk factors.

A similar study was conducted by Farrant *et al.* [64] in South India, on 559 pregnant women with a gestational age of 30 weeks. Vitamin D low levels were found in most pregnant women. 66% of women had concentrations lower 50 nmol/l and 31% under 28 nmol/l, with seasonal variations ($P <0.0001$). According to these authors, there was no correlation between maternal vitamin D and gestational diabetes, the incidence being the same in both groups. The metanalysis of Rodrigues et al, performed on six studies showed no clear benefit of vitamin D supplements versus placebo when was administered to women wit gestational diabetes [65].

Hauta-Alus *et.al.* [66] conducted a study in Finland that included 723 pregnant women, from which 11% were diagnosed with GDM, and 97% had sufficient vitamin D. No difference has been noted between the concentration of vitamin D in diabetic and non-diabeti patients (82 versus 82 nmol/L, P = 0.99). Also no correlation was established between oral glucose tolerance test and maternal serum level of vitamin D (P> 0.53). The evidence of a link between GDM and vitamin D level is considered to be doubtful. Also Eggemoen et al observed the existence of no link between GDM and vitamin D deficiency after they study 784 pregnant women in the second or third trimester of pregnancy [67].

A level of vitamin D higher than 50 nmol/L can be a limit that pregnancy can normally flow above. The results could be influenced by the fact that, due to national health policies, the plasma level of maternal vitamin D in Finland has improved significantly.

Most studies have shown that vitamin D insufficiency during pregnancy can promote gestational diabetes. Gestational diabetes may also be induced by low vitamin D levels in early pregnancy, but is most often detected in the late pregnancy. There are questions about the impact of other variables on the risk of developing GDM in pregnant women with deficiency of 25-[OH]D: age of mother, race, diabetes family history, and pre-pregnancy body mass index, socioeconomic status of the country in which she lives or supplementation of vitamin D by national health programs. The literature, therefore, comes with evidence that supports this causal relation between vitamin D deficiency and gestational diabetes, although there is still a need for strong clinical studies to reinforce hypotheses so far. Some authors found a negative correlation between vitamin D and ferritin levels in women, with no relationship with different parameters as age or adipose mass and maybe it will interesting to study this link in pregnant women with gestational diabetes [68].Another interesting direction for future research would be represented by gut microbiota in patients with vitamin D deficiency and gestational diabetus. It is now recognized that gut microbiota is an important actor in nutrients absorption and also inflammation and a picture of the pattern of these women would be beneficial in order to clarify the subject [69].

4. Conclusions

In recent years, vitamin D deficiency during pregnancy has become more and more common. At the same time, the incidence of gestational diabetes increases, having a negative maternal-fetal outcome. The correlation between vitamin D deficiencies with the risk of GDM is a topic of special interest, being the start point for many studies. Some of them indicate a substantial association, whereas others mention contradictory evidence, which is why there is no concrete conclusion in this matter. In order to benefit from strong evidence, several large, randomized controlled clinical trials are necessary. Clarifying the physiological support that underlay the interaction between vitamin D deficiency and gestational diabetes will enable to develop new therapeutic strategies in order to lessen the risk of developing GDM and its complications.

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Manuscript received: 26.02.2020