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BIBLIOGRAPHIC REVIEW ON THE INVOLVEMENT OF SERUM VITAMIN D IN PROPER PREGNANCY DEVELOPMENT

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Abstract. Maternal nutrition is a determining factor in the proper development of pregnancy. One of the micronutrients that becomes especially important during this stage is vitamin D. The primary role of vitamin D is the regulation of calcium homeostasis, although it also plays a significant role in pregnancy development. It has been reported that vitamin D deficiency during this stage is associated with adverse outcomes such as preterm birth, fetal problems, or preeclampsia. The aim of this bibliographic review is to analyze the implication of vitamin D in the proper development of pregnancy. Articles from scientific journals indexed with an impact factor ≥ 1.5 , published in English or Spanish in the last 5 years, were selected. PubMed, Sciencedirect, and Cochrane were consulted. Low concentrations of serum vitamin D were associated with adverse outcomes such as gestational diabetes or preeclampsia. Adequate levels showed beneficial effects on offspring development, improving the immune system or preventing bone fractures; however, they did not show benefits in neonatal growth. High doses of vitamin D supplementation were found to be safe. It was also concluded that vitamin D supplementation with doses of up to 4000 IU/day would be safe for both the mother and the fetus.

Keywords: Vitamin D. Pregnancy. Preeclampsia. Supplementation.

IMPLICACIÓN DE LA VITAMINA D SÉRICA CON EL CORRECTO DESARROLLO DEL EMBARAZO: REVISIÓN BIBLIOGRÁFICA

Resumen. La nutrición materna es un factor determinante en el correcto desarrollo del embarazo. Uno de los micronutrientes que cobran especial importancia en esta etapa es la vitamina D. El papel principal de la Vitamina D es la regulación del homeostasis del calcio, aunque, también ejerce un papel importante en el desarrollo del embarazo. Se ha descrito que la deficiencia de Vitamina D durante esta etapa está asociada con resultados adversos como parto prematuro, problemas en el feto o preeclampsia. El objetivo de esta revisión bibliográfica es analizar la implicación de la vitamina D en el correcto desarrollo del embarazo. Se seleccionaron artículos pertenecientes a revistas científicas, indexadas y con un factor de impacto $\geq 1,5$, en inglés o en español y publicados en los últimos 5 años. Se consultó en Pubmed, Scienedirect y Cochrane. Se asociaron las bajas concentraciones de vitamina D sérica con resultados adversos como diabetes gestacional o preeclampsia. Niveles adecuados mostraron efectos beneficiosos en el desarrollo de la descendencia, mejorando el sistema inmune o previniendo fracturas óseas, sin embargo, no han mostrado beneficios en el crecimiento del neonato. Dosis altas de suplementación con esta vitamina mostraron ser seguras. También se concluyó que la suplementación con vitamina D con dosis de hasta 4000 UI/día resultaría seguro tanto para la madre como para el feto.

Palabras clave: Vitamina D. Embarazo. Preeclampsia. Suplementación.

Introduction

Numerous factors determine the appearance of complications during this stage, such as maternal stress (1), existing health problems (HTN, diabetes, renal disease, etc.), age, and lifestyle-related problems such as alcohol and tobacco consumption (2) and maternal nutrition (1), the latter being of particular importance.

Women's nutritional needs change during pregnancy and lactation (3). In particular, nutritional needs vary for some micronutrients, which are vital for improving pregnancy outcomes (4).

The role of vitamin D as a regulator of calcium and phosphorus homeostasis is well known (5), however, there is increasing evidence of the role of this vitamin in the development of pregnancy, preventing the onset of complications typical of this stage, such as preeclampsia. (6, 7)

There is a high prevalence of vitamin D deficiency in the world (8, 9), including in pregnant women, which opens the door to further research on the effects of this vitamin in pregnancy, as well as the benefits and safe doses of supplementation.

Vitamin D in pregnancy:

Pregnancy is a time of physical, metabolic and hormonal changes. To ensure that all these changes take place properly, the nutritional needs of women vary, especially the micronutrient requirements. The one to be highlighted in this article is vitamin D.

Vitamin D is fat-soluble and is obtained mainly after skin exposure to ultraviolet radiation from the sun. It can also be obtained through diet or by taking supplements. Some of the foods rich in vitamin D are egg yolks, oily fish, liver and fortified foods (10).

Its main function, as mentioned above, is to maintain calcium and phosphorus homeostasis, in addition to preserving bone integrity (11). However, it also plays a crucial role in the modulation of the immune system (12) and in the regulation of female reproductive function (13). This is because the vitamin D receptor (VDR) is present on monocytes/macrophages, T cells, B cells, natural killer (NK) cells and dendritic cells (12, 14, 15), as well as on all cells of the female reproductive tract. (13) Effects on the immune system are especially relevant during pregnancy, particularly during embryo implantation. By modulating the immune response, vitamin D helps prevent a reaction by the mother's body to the embryo, which contains paternal genes. (12, 16)

This vitamin also plays other roles, such as the regulation of gene transcription and expression, participation in glucose metabolism, as well as in the nervous and muscular systems (17-19). During pregnancy, it helps the formation of the baby's bones and teeth by facilitating the absorption of calcium (20).

Deficiency of this micronutrient during gestation has been associated with various problems of fetal development such as intrauterine growth retardation, neonatal rickets, and alterations in dental enamel (21, 22). In addition, it has been observed that this deficiency could be associated with adverse pregnancy outcomes such as gestational diabetes, preeclampsia (10), preterm delivery or low birth weight (23).

In the systematic review with meta-analysis by Akbari S et al. (24), which included 23 articles, showed a significant correlation between low vitamin D levels (<20 ng/ml) during pregnancy and the risk of preeclampsia.

Similar result was obtained in the open-label trial by Xiaomang J et al. (25) whose objective was to demonstrate that high-dose vitamin D supplementation in vitamin D-deficient pregnant women reduces the prevalence of preeclampsia. This study divided 450 pregnant women into 3 vitamin D supplementation groups; a low dose group (400 IU/day); a medium dose group (1500 IU/day) and a high dose group (4000 IU/day). Supplementation was administered from week 12 of pregnancy, and was followed up until week 12 postpartum. As a result, the prevalence of preeclampsia cases was significantly lower in the high-dose vitamin D supplementation group.

In the cohort study by Raia-Barjat T et al. (26) aimed to evaluate the relationship between vitamin D status and the occurrence of placenta-mediated complications in a high-risk population. To do so, they recruited 182 women at risk for placenta-mediated complications. At the end of the study it was concluded that patients with vitamin D deficiency at 32 weeks of pregnancy have a higher risk of developing placenta-mediated complications, which include preeclampsia, eclampsia, placental abruption, hemolysis, elevated liver enzymes, low platelet syndrome, intrauterine growth retardation, intrauterine fetal death or recurrent miscarriages.

Hornsby E et al. (27) conducted a double-blind, randomized, controlled clinical trial to evaluate the efficacy of daily vitamin D supplementation in pregnant women on the immune system of the newborn, in relation to the development of asthma. For this purpose, they recruited umbilical cord blood from 51 pregnant women who were taking vitamin D supplements (26 of them with 4400 IU/day and 25 with 400 IU/day). As a result, it was found that newborns born to mothers supplemented with 4400 IU/day of vitamin D had higher innate cytokine responses. Thus, by improving the immune

response, there is a lower probability of developing asthma.

In general, the prevalence of vitamin D deficiency in Europe is estimated to be approximately 40% (28); it ranges from 40% to 98% among pregnant women worldwide (4).

However, despite the importance of this vitamin, especially during the gestation phase, there is currently no consensus on its supplementation.

Although several studies (28-32) have shown that doses of up to 4000 IU per day are safe during pregnancy.

The objective of this review is to analyze the available literature to determine the role of vitamin D in the pregnancy period.

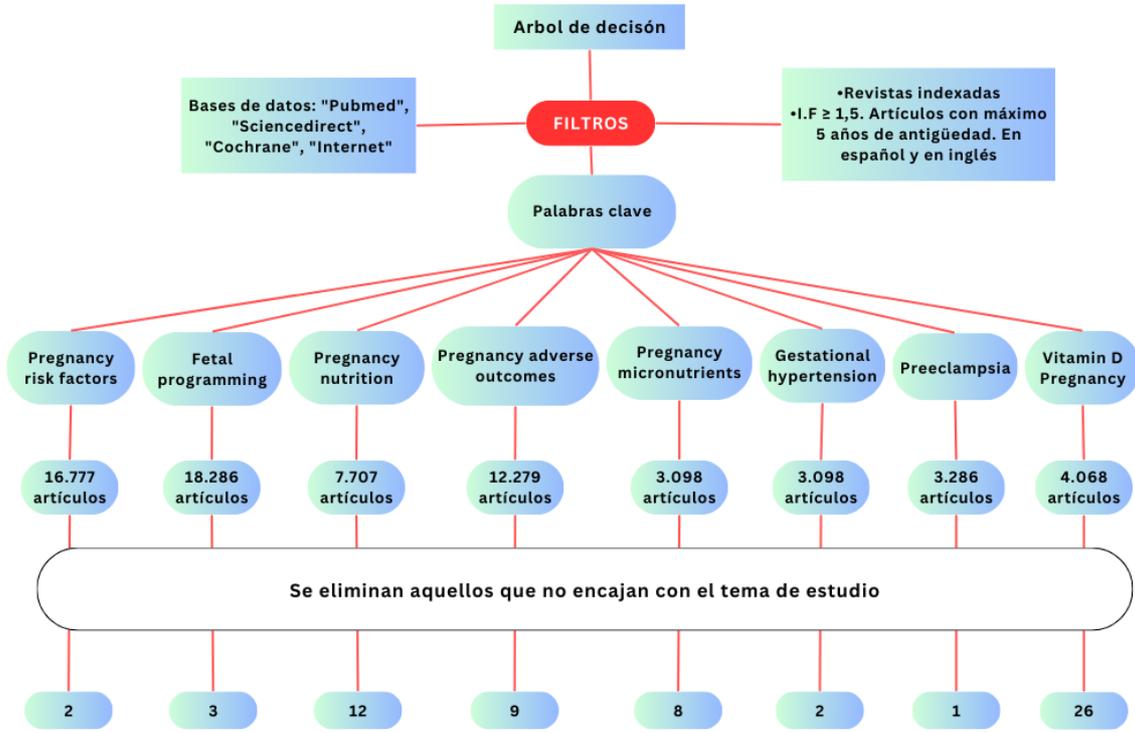
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Method

The article presented here consists of a bibliographic review in which the available scientific literature is brought together in order to determine the role of vitamin D in the correct development of pregnancy, as well as to try to establish the need or not of supplementation of this vitamin during the gestational stage. For this purpose, clinical trials, systematic reviews and meta-analyses, online books, guidelines and dictionaries were included. It was taken into account that these articles had been published in the last 5 years. They should be in English or Spanish, and belong to indexed journals with an impact factor of $1.5 \geq 1,5$. This literature search for the elaboration of the state of the art began in November 2022 and ended in April 2023. The following is a detailed explanation of the different databases that have been used for this purpose:

Figure 1.
Decision tree for conducting the literature review



Eleven experimental articles were used for the discussion section.

Results

Table 1 below shows in detail the characteristics of the studies used.

Table 1. Table summarizing the characteristics of the studies included in this discussion

AUTHOR S	TYPE OF STUDY	POPULATION	METHODOLOGY	OBJECTIVE	RESULTS
Xiaomang Janet al 2021. (25)	Open randomized trial	450 pregnant women between 20 and 40 years of age, with maternal treatment and a diagnosis of vitamin D deficiency.	Women were divided into 3 vitamin D supplementation groups: low dose (400 IU/day), medium dose (1500 IU/day) and high dose (4000 IU/day). Supplements were administered from week 13 of pregnancy and followed up to 12 weeks postpartum. Serum vitamin D levels were measured before and after supplementation.	The hypothesis was that high-dose vitamin D supplementation reduces the incidence of preeclampsia.	The incidence of preeclampsia was significantly lower in the high-dose vitamin D supplementation group. In addition, high-dose supplementation did not demonstrate any adverse effects.
Raia-Barjat T et al. 2021. (26)	Prospective multicenter cohort study	182 pregnant women at risk for PMC. With diabetes, chronic hypertension, obesity, <18 years or >38 years, among	A total of 5 blood samples were collected per patient, at 20, 24, 28, 32 and 36 weeks of pregnancy. Vitamin D deficiency was defined as a 25 (OH) D level <20 ng/ml and vitamin D insufficiency <30 ng/ml.	Primary outcome: appearance of PMC. Secondary outcomes: occurrence or recurrence of preeclampsia without intrauterine growth retardation, occurrence or	At 32 weeks, the risk of occurrence of PMC (especially late PMC) was 5 times higher in patients with vitamin D deficiency than in patients with normal vitamin D levels.

		other factors.	risk		recurrence of early (before 34 weeks) or late (after 34 weeks) PMC.	
Díaz-López A et al. 2020 (33)	Cross-sectional analysis	793 healthy pregnant women before the 12th week of pregnancy, over 18 years of age.		Blood was drawn from all participants before 12 weeks of pregnancy and total serum vitamin D concentrations were determined.	Objective: to determine the prevalence of vitamin D deficiency in pregnant women from the Mediterranean coast.	High prevalence of vitamin D deficiency in pregnant women on the eastern Mediterranean coast, especially in overweight women, Arab ethnic group and dark skin, low social class, low exposure to sunlight and less efficient dermal synthesis of vitamin D during winter and spring, low consumption of dairy products and low physical activity.
Vestergaard AL et al. 2021. (34)	Prospective cohort study	225 Danish pregnant women, \geq 18 years.		Blood samples were taken from all patients to determine serum vitamin D levels and placentas were sampled for genetic analysis.	To characterize vitamin D status in women in the 1 st trimester of gestation and correlate it with pregnancy outcomes and placental biology.	Forty-two percent did not reach the vit level. $D \geq 75$ nmol/L, 10 % showed a concentration < 50 nmol/L and 2 % suffered from severe vitamin D deficiency (< 25 nmol/L). Women with a higher BMI are at increased risk

					for vitamin deficiency. Vitamin D insufficiency in the first trimester was associated with lower placental growth factor expression
Hornsbury E et al. 2018. (35)	Randomized, double-blind, placebo-controlled trial	51 pregnant women between 10 and 18 weeks of gestation. Vitamin D deficient.	Subjects were divided into 2 vitamin D supplementation groups: low dose (400 IU/day) and high dose (4400 IU/day). Cord blood was collected and cultures were performed.	The main hypothesis was that supplementation with high doses of vitamin D in pregnancy would stimulate the innate immune system of the newborn, through the production of proinflammatory cytokines, preventing the onset of asthma.	In the high-dose vitamin D supplementation group, blood levels of vitamin D returned to normal, and the neonates of these women demonstrated increased innate cytokine responses. Doses up to 4000 IU/day appear safe for both the pregnant woman and the baby.
Roth DE et al. 2018. (36)	Randomized, double-blind, placebo-controlled trial	1,300 pregnant women, 18 years of age or older and between 17 and 24 weeks of gestation. Residents in Bangladesh.	Five groups were made and each woman was randomly assigned to one of them. A different dose of vitamin D was administered in each group: 0 IU/week postpartum ("placebo"); 4200 IU/week prenatal and 0 IU/week	The primary outcome was length-for-age z-score (LAZ) at 1 year (364-420 days) of age. As a secondary outcome, weight-for-age z-score was measured.	Vitamin D supplementation from mid-pregnancy to delivery or 6 months after delivery did not show significant effects on offspring growth. However, it proved that its supplementation is safe.

			postpartum; 16800 IU/week prenatal and 0 IU/week postpartum; 28000 IU/prenatal and 0 IU/week postpartum; or, 28000 IU/week prenatal and postpartum.		
Brustad N et al. 2022 (37)	Randomized clinical trial	623 pregnant women with 26 or less weeks of gestation, a daily intake of vitamin D <600 IU/day and no endocrine, cardiac or renal disorders.	The sample was randomly divided into two vitamin D administration groups: high dose 2400 IU/day or placebo group (0 IU/day); from week 24 of pregnancy until week 1 postpartum.	Relationship of prenatal vitamin D supplementation and fracture risk, as well as bone mineralization of the offspring.	Significantly lower incidence of 60% of fractures in children born to mothers who had received high-dose vitamin D during pregnancy, compared to those whose mothers belonged to the placebo group.
Yin W-J et al. 2020. (38)	Prospective cohort study	6821 pregnant women aged ≥18 years, residents of Hefei, singleton pregnancy and no assisted conception. Who were in the second trimester of pregnancy.	Serum vitamin D concentration was measured and at 24-28 weeks of gestation, diagnostic tests for gestational diabetes mellitus were performed.	In this study we sought to estimate the relationship of vitamin D with gestational diabetes mellitus.	Low vitamin D concentrations were significantly associated with an increased risk of gestational diabetes mellitus. The risk was significantly reduced only in those women taking supplementation and whose serum vit.D levels approached 50 nmol/L.

Bakleic heva M et al. 2021. (39)	Prospective randomized multicenter study	88 pregnant women in the first trimester of gestation, aged 20-44 years, singleton pregnancy, BMI ≤ 30 kg/m ² and known serum vitamin D level.	Patients were divided into 3 groups depending on the initial serum vitamin D level (group 1: < 10 ng/ml, group 2: 10-30 ng/ml, group 3: >30 ng/ml).	Objective: to evaluate the characteristics of the course of pregnancy in women with different serum vitamin D levels in the first trimester.	In the group with pronounced vitamin D deficiency (< 10 ng/ml) the risk of miscarriage was 2 times higher than in the group with normal vitamin D levels (>30 ng/ml).
Liu C-C et al. 2023. (40)	Retrospective observational study	1048 women with known vitamin D levels with a delivery ≥ 20 weeks gestation; 746 women who were vitamin D deficient (<20 ng / ml) and received the same vitamin D supplementation ; and 3654 women with unknown vitamin D levels and delivery \geq	Vitamin D supplementation with 2000 IU/day was initiated at 12-16 weeks of pregnancy if vitamin D was present. If the level exceeded ≥ 20 ng/ml, maintenance doses were administered at 800 IU/day until birth. If vitamin D level remained <20 ng/ml, supplementation of 2000 IU/day was continued until levels were ≥ 20 ng/ml or delivery.	We sought to study the correlation between serum vitamin D levels during gestation and the occurrence of adverse pregnancy outcomes.	Inverse correlation between initial vitamin D level and maternal BMI. Doses of up to 4000 IU/day of vitamin D are safe. And high serum vitamin D levels may protect against preterm delivery, low birth weight and postpartum hemorrhage.

20 weeks
gestation

Ogiji J et al. 2022 (41)	Retrospective observational study	161 pregnant women.	During the first trimester of pregnancy, blood samples were collected to determine serum vit.D concentrations. Vitamin D levels of women who developed postpartum depression (PPD) were compared with those who did not.	We sought to study the relationship between serum vitamin D levels during pregnancy and the occurrence of postpartum depression.	The occurrence of postpartum depression was significantly negatively correlated with prenatal vitamin D levels.
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Discussion and conclusions

Vitamin D deficiency is considered a very common condition or pathology among pregnant women, as seen in the studies of Diaz-Lopez A et al. (33) and Vestergaard AL et al. (34); in some areas of the world, it can reach 100% of the population.

Of the 11 studies, 3 of them studied the implication of vitamin D supplementation on different offspring developmental outcomes. All three were randomized, double-blind, controlled trials. The first of them (35) related it to the stimulation of the neonate's immune system development, decreasing the risk of asthma. Another (36) proposed the relationship of vitamin D with the growth of the newborn; and the third (37) proposed that supplementation with this vitamin during gestation decreases the risk of fractures in the offspring. Two of them concluded that vitamin D favorably influences newborn development.

As mentioned above, two of the studies used looked at the prevalence of hypovitaminosis D in a population of women from the Mediterranean coast (33) and in a population of Danish women (34), a cross-sectional study and a prospective cohort study, respectively. Both concluded that there was a significant vitamin D deficiency among pregnant women.

Four other studies used analyzed the relationship of vitamin D deficiency with different pregnancy outcomes. A 25 (OH) D level of less than 20 ng/ml was taken as the reference value for vitamin D deficiency. These were prospective multicenter cohort studies. The first analyzed this relationship with the risk of suffering placenta-mediated complications (26); the second posited this relationship with the risk of suffering gestational diabetes mellitus (39); and the third (40) studied the characteristics of the course of pregnancy according to different serum vitamin D levels. The last one (41) analyzed the relationship of serum vitamin D levels with the development of postpartum depression. All four studies concluded that the risk of adverse pregnancy outcomes was significantly higher in women with low serum vitamin D levels.

The remaining 2 studies examined the effect of vitamin D supplementation during gestation on the occurrence of adverse pregnancy outcomes. One of the studies was an open-label randomized trial (25) that proposed that high-dose vitamin D supplementation from early pregnancy reduces the incidence of preeclampsia. This one concluded that the incidence of preeclampsia was significantly lower in those women who were supplemented with high doses of vitamin D. The other article sought to study the association between serum vitamin D levels and the occurrence of adverse pregnancy outcomes (40), concluding that doses of up to 4000 IU/day of vitamin D supplementation were safe, and that high serum vitamin D levels were protective against preterm delivery, low birth weight and postpartum hemorrhage.

All the articles reviewed that studied the association of vitamin D levels with adverse pregnancy outcomes had favorable results. In the study by Yin W-J et al. (38) concluded that adequate levels of this micronutrient (>50 nmol/L) during pregnancy significantly reduced the risk of gestational diabetes mellitus.

Bakleicheva M et al. 2021. (39) demonstrated that women with severe vitamin D deficiency during pregnancy had a significantly increased risk of miscarriage. And the study by Ogiji J et al. (41) concluded that the occurrence of postpartum depression had a significant

inverse association with serum vitamin D levels during pregnancy.

The study by Raia-Barjat T et al. (26) concluded that there was a significant association between low serum vitamin D levels during pregnancy and the occurrence of placenta-mediated complications, preeclampsia being one of these complications.

As mentioned above, Vestergaard AL et al. (34) showed that there was a high prevalence of vitamin D deficiency among pregnant Danish women. In addition, in this study, vitamin D insufficiency during the first trimester of pregnancy was associated with low expression of placental growth factor, which is a biochemical marker predictive of risk of preeclampsia in the first trimester of pregnancy.

Thus, 3 of the articles analyzed demonstrated significant associations between low serum vitamin D levels during pregnancy and the occurrence of preeclampsia (25, 26, 35).

Of the studies analyzing the relationship of serum vitamin D concentrations during pregnancy to neonatal development, the one by Roth DE et al. (37) showed no significant differences between these concentrations and infant growth.

However, Liu C-C et al. (40) demonstrated that high serum levels of vitamin D during pregnancy protect against low birth weight.

In addition, adequate levels of this vitamin during pregnancy appear to protect offspring from health problems such as asthma by stimulating the innate immune system of the newborn, as demonstrated by Hornsby E et al. (35) in their clinical trial. They may also protect against fractures in the child, concluded Brustad N et al. (36).

Regarding supplementation with this vitamin, 4 of the studies (25, 36, 35, 40) showed that supplementation doses of up to 4000 IU/day are safe for both the mother and the fetus.

The evidence obtained so far suggests that correct serum levels of vitamin D can influence the correct development of pregnancy, both by protecting the mother against adverse pregnancy outcomes (such as diabetes mellitus, premature delivery or postpartum depression, among others), and by protecting the fetus from future bone fractures, or by reinforcing its immune system. And, in the opposite case, deficient levels of this vitamin during pregnancy may favor the appearance of problems characteristic of this stage such as preeclampsia or gestational diabetes mellitus.

Therefore, in conclusion, it can be stated that the role of vitamin D during pregnancy is not only to maintain calcium and phosphorus levels and bone health, but that its functions go beyond that. For example, by favoring the implantation of the fetus in the uterus by modulating the immune response, or by preventing the onset of preeclampsia. In addition, as mentioned above, the prevalence of vitamin D deficiency is widespread among pregnant women worldwide, so it would be very interesting to reach a consensus on the recommended vitamin D supplementation dose for all pregnant women. According to what was observed in this review, it could be stated that a dose of up to 4000 IU/day of vitamin D would be safe for both the mother and the fetus, in addition to being effective in normalizing maternal serum concentrations and preventing various pregnancy problems. Therefore, in order to prevent the occurrence of problems due to deficiency of this micronutrient, supplementation with 4000 IU/day, a dose that has been proven to be safe, should be recommended for all pregnant women. However, the evidence is still limited and much more research is needed

in this area as there is still no agreement on the optimal concentration of vitamin D, nor has its supplementation been standardized for all pregnant women, as has been done with other micronutrients such as folic acid.

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