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Systematic Review

The Association between Vitamin D Intake and Gestational Diabetes Mellitus: A Systematic Review

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Abstract

Background: Several studies have focused on the role of vitamin D in preventing gestational diabetes mellitus (GDM) but also in improving or preventing the unwanted perinatal outcomes of GDM. Even today, efforts to clarify the relationship between vitamin D deficiency (VDD) in pregnancy and GDM continue. **Methods**: We conducted research to search for systematic reviews (SRs) of randomized controlled trials (RCTs), in databases at PubMed, Google Scholar, Web of Science, Science Direct, Embase, Cochrane, Crossref and CAS, published from 2016 to 2021. These concerned maternal vitamin D status or taking vitamin D supplements, alone or in combination with other vitamins or minerals in pregnancy and their association with GDM. We used the AMSTAR (assessment of multiple systematic reviews) scoring scale quality and scoring checklist, which assessed the quality of each SR, at low medium or high. **Results**: Seven SRs of RCTS involving 7902 participants were selected. The results suggest that if pregnant women with GDM take vitamin D supplements, they improve blood vitamin D levels, as well as biomarkers related to blood glucose. It was also shown that pregnant women with GDM who took vitamin D supplements (1000–4762 IU/day) improved the primary GDM outcome measurements such as fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), serum insulin and homeostasis model of assessment of insulin resistance (HOMA-IR). In addition, improvements were observed in their lipid profile markers, such as total cholesterol (TC), low-dense lipoprotein (LDL), high-dense lipoprotein levels (HDL) and high-sensitivity C-reactive protein (hs-CRP). Also, the adverse outcomes of GDM in both the mother and the newborn appear to have decreased. However, there are studies that do not support the therapeutic effect of vitamin D intake by pregnant women with GDM. **Conclusions**: In conclusion, taking vitamin D, during pregnancy, for the prevention or treatment of GDM, is controversial and the real benefit unclear. Further RCTs are necessary.

Keywords: pregnancy; vitamin D; GDM

1. Introduction

Vitamin D is a fat-soluble vitamin with numerous actions that are not only related to bone health and calcium metabolism. Vitamin D is enzymatically converted in the liver to 25-hydroxyvitamin D (25(OH)D), the main form of circulation of vitamin D [1]. There are two (commercially) available forms, D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D has a direct effect on the differentiation of chondrocytes and osteoblasts to bone formation, as well as the metabolism of calcium and phosphorus, with its more specific action on their intestinal and renal reabsorption [2]. Low levels of vitamin D in the blood have been associated with the pathogenesis or progression of various chronic diseases, such as diabetes mellitus (DM) type 2 [3,4], metabolic syndrome (MS), obesity [5], cardiovascular diseases [4,6], certain cancers [7], but also autoimmune diseases such as type 1 DM, multiple sclerosis, Crohn's disease, psoriasis vulgaris, etc. [8].

Several studies have associated the pregnant mother's low vitamin D with undesirable effects during pregnancy, such as preeclampsia, cesarean section (C-section), transient osteoporosis of the hip (TOH) [9,10], gestational diabetes mellitus (GDM) [3], premature birth [11], increased likelihood of birth of children with type 1 DM, Low Birth Weight (LBW), neonatal hypokalemia attacks, small for gestational age (SGA), low neonatal immunization, decreased pulmonary maturation [3], bronchial asthma, allergic rhinitis and others [12] in their newborns. At this point it is worth clarifying that not only low vitamin D but also pregnancy itself, especially during its last months, is responsible for transient osteoporosis of the hip [9,10].

GDM is a common medical condition in pregnancy, and its complications affect both the mother and the fetus. GDM is defined as any degree of glucose intolerance developing or first detected during pregnancy [13] and usually subsides after birth. A more contemporary definition of DM, from the American Diabetes Association (ADA), is "diabetes diagnosed in the 2nd or 3rd trimester of pregnancy" that was not clearly present prior to gestation [14,15]. More generally, GDM was called glucose intolerance, which is first initiated or diagnosed during pregnancy, regardless of its course after childbirth. However, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG), in 2010, proposed a change in terminology. Thus, according to the IADPSG, a diagnosis of GDM can be made in women who have any of the following crite-

ria: Fasting plasma glucose ≥92 mg/dL but <126 mg/dL at any gestational age [16] or glucose levels 153–199 mg/dL, which were measured 2 hours after charging 75 g of glucose [13].

The ADA/IADPSG diagnostic protocol recommends the following: (1) Investigation in the first trimester of pregnancy, to identify women with conspicuous, undiagnosed DM, with fasting glucose ≥126 mg/dL, glycosylated hemoglobin (HbA1c) ≥6.5% or accidental blood glucose ≥200 mg/dL [13]. A single confirmed positive test result is enough to diagnose overt diabetes. (2) Universal screening of all pregnant women, without a pre-existing diagnosis of obvious diabetes, between 24 and 28 weeks of pregnancy. Screening consists of a scheduled oral glucose tolerance test of 75 g (OGTT) and the collection of three glucose samples (fasting, 1 and 2 hours after glucose overload, respectively) where the normal ranges are, respectively, 92, 180 and 153 mg/dL. A single positive value, higher than the aforementioned limits, is sufficient to diagnose GDM [13]. This protocol was proposed by the ADA in January 2011 [13]. After a critical review, the World Health Organization (WHO) also proposed changes to the diagnostic protocol of maternal hyperglycemia, differentiating DM in pregnancy (DM during pregnancy) from GDM. According to the revised WHO guidelines, regardless of gestational age, the diagnosis of DM, during pregnancy, is made on the basis of fasting glucose ≥126 mg/dL, glucose ≥200 mg/dL measured 2 hours after loading glucose 75 g or a random blood glucose measurement ≥200 mg/dL, associated with clinical symptoms [13]. On the other hand, the diagnosis of GDM is confirmed with fasting glucose values of 92–125 mg/dL or glucose levels of 153–199 mg/dL, which were measured 2 hours after charging 75 g of glucose [16,17].

Among the main consequences of GDM are increased risks of preeclampsia, large-sized neonates for gestational age (LGA), C-section delivery and related morbidities [17]. GDM is closely related to the risk of pancreatic cancer. In fact, GDM may precede the diagnosis of pancreatic cancer for many years [18]. Other common side effects, in addition to those mentioned above, include an increased risk of birth trauma, macrosomy, neonatal hypoglycaemia episodes and respiratory distress syndrome and/or prematurity, which increase the risk of perinatal death. Children of mothers with GDM have a higher risk of developing obesity and metabolic syndrome (MS), which also affects adulthood. Also, mothers with GDM are at increased risk of developing type 2 DM, MS, as well as preeclampsia in later life [13].

In most cases, hyperglycemia is the result of reduced glucose tolerance, due to dysfunction of pancreatic beta cells, against the background of chronic insulin resistance [19]. The prevalence of GDM has increased by more than 30% within the last two decades, in some countries, including developing countries [20]. It is estimated that 16.5% of pregnancies worldwide are complicated with GDM, a figure that is burdened by the escalating increase in obesity [19]. Maternal overweight/obesity, advanced gestational age, previous history of GDM, family history of type 2 DM and ethnicity are key risk factors for GDM [21].

Maternal concentrations of 25(OH)D have been positively associated with insulin sensitivity and preprandial and postprandial glucose concentrations in the middle of pregnancy [22]. Vitamin D deficiency in pregnancy has been associated with glucose intolerance and GDM, according to a recent meta-analysis, which assessed vitamin D deficiency with the risk of GDM [23]. The result seems to be a two-way street, as low values of vitamin D concentrations appear to increase GDM and women with GDM were much more likely to experience vitamin D deficiency compared to pregnant controls [24]. In pregnancy, the placentas of women with GDM are characterized by increased expression of glucose transporters (GLUT) GLUT1 and GLUT3 in the basal syncytiotrophoblast [25]. In these cases the placenta acts as a glycemic buffer: once glucose enters the fetal circulation, it is used to meet acute fetal and energy requirements [25]. The proportion of glucose that is not metabolized is stored in various fetal tissues, mainly in the liver, heart and skeletal muscles. Excess glucose is converted to glycogen [25]. Maternal hyperglycemia and hyperinsulinemia lead to increased oxygen consumption in the tissues, which is responsible for the consequent chronic hypoxemia of the fetoplacental unit, the upward regulation of specific hormones and inflammatory cytokines that most likely lead to placental neoangiogenesis and hypervascularization [25].

Given that 25(OH)D is directly related to the parathyroid hormone (PTH), a recent study by Sirico *et al.* [25] investigated increased expression of parathyroid hormone-related protein (PTH-rP) and parathyroid hormone (PTH)/PTH-rP receptors and its placental receptor PTH/PTH-rP, receptor PTH-P1, in women with GDM. PTH-rp is produced by the uterus, placenta, fetal membranes (amnion and chorion) and developing fetus and plays an important role in fetal growth and development, through the stimulation of placental calcium transport, vasodilatation of the uteroplacental vasculature, and regulation of cellular growth and differentiation [25]. It proved that, in women with GDM, placental expression of PTH and PTH-rP are associated with adverse perinatal effects. PTH-rP positive placentas were characterized by a higher incidence of 1 min Apgar Score <7 and maternal obesity, while PTH-R1 positives, with a higher incidence of lower mean percentage weight, on the third trimester ultrasound and a lower fetal placental weight ratio [25].

However, there is also the opposite view, that maternal vitamin D levels are not correlated with the serum glucose or insulin levels of pregnant women or their newborns, as argued by the study of Naseh *et al.* [26], which aimed to determine the prevalence of vitamin D deficiency in pregnant women, but also to identify any correlations, between

maternal levels of vitamin D and plasma glucose and insulin of the mother and newborn. Because of these conflicting views regarding the relationship between low vitamin D and glucose metabolism, the aim of this systematic review is to research the existence or not of a correlation between 25(OH)D and GDM. Especially, this systematic review aims at evaluating the role of maternal vitamin D levels, in women with GDM, and the contribution of supplemental vitamin D, alone or in combination with other vitamin or mineral supplements, Calcium (Ca), Magnesium (Mg), Zinc (Zn) or even probiotics, in the prevention or improvement of unwanted perinatal effects of GDM, at any gestational age of the woman, thus helping health professionals make decisions on whether or not they need to administer vitamin supplements preventively in pregnancy, in order to avoid GDM or targeted to pregnant women with GDM, to reduce the undesirable effects on both the mother and the newborn.

2. Materials and Methods

This study concerns a systematic review of the most valuable systematic reviews (SRs), based on the AMSTAR (assessment of multiple systematic reviews) scoring criteria [27]. A literature search was carried out to identify systematic randomized controlled trials (RCTs) concerning the maternal status of vitamin D or the taking of vitamin D supplements, alone or in combination with other vitamins or minerals (Ca, Mg, Zn) in pregnancy and their association with GDM. The data collected were evaluated by two researchers to enhance the quality of the research. In early September 2022, we conducted research to search for randomized SRs in databases in PubMed, Google Scholar, Web of Science, Science Direct, Embase, Cochrane, Crossref and CAS, published from 2016 to 2021. The keywords were: "pregnancy and vitamin D supplementation" and "GDM".

2.1 Inclusion - Exclusion Criteria

The criteria for participation in this study were SRs with RCT's, from 2016 to 2021, which cited data on the maternal status of vitamin D or the intake of vitamin D supplements, alone or in combination with other vitamins, minerals (Ca, Mg, Zn) or probiotics in pregnancy and their association with GDM. Exclusion criteria were studies that were not published in English, animal studies, studies on biological fluids other than blood, studies that were not the primary ones, case studies or editorials.

Two of the authors of this systematic review separately checked the titles, the summaries and the entire texts concerning studies that deal with the subject of the review, taking into account the predetermined participation criteria (Fig. 1). The same authors evaluated the SRs which were included in terms of their quality, using the AMSTAR scoring scale. In the researchers' view, the original and worthwhile SRs were evaluated, emphasizing the SRs whose rating was medium and high.

2.2 Eligibility of Studies

We included original SRs from RCTs, which evaluated taking a vitamin D supplement alone or in combination with other vitamins, at any gestational age. The effect of this intake on GDM was examined. The vitamin supplements administered to SRs involved taking any dose of vitamin D compared to placebo or other dosage and/or other type of vitamin, mineral (Ca, Mg, Zn) or probiotic. We evaluated and read the titles, summaries and entire texts where they were listed, to see which studies met the eligibility criteria.

2.3 Evaluation of the Quality of Studies

Using the AMSTAR quality control and scoring list [27], the scope of the study, the population, the type of intervention, the control group, the admission and exclusion criteria, the results and the timing of the survey were evaluated in each SR. The authors' bibliography search strategy (if, for example, they searched for data for the research question in at least two databases, whether they provided keywords, whether they searched within 24 months of completing the review, whether they set publication restrictions such as language) was also evaluated. Finally, the data analysis method was evaluated — whether quantitative data were used to reduce the bias of the study, whether there was a reference to sources of funding that were potential sources of conflicts of interest, whether reference was made to whether the authors provided a satisfactory explanation and discussion of any heterogeneity arising from the SR results, whether a meta-analysis was carried out, whether two or more authors of the study considered eligibility of the studies included in each SR concerned, whether they provided and justified a list of excluded studies and whether they assessed the risk of bias. The low quality of an SR was rated 0–4, the medium quality with 5–8 and the high quality with 9–11 [28]. The main results refer to measures concern maternal and neonatal concentrations of 25(OH)D, in umbilical cord blood samples and GDM.

3. Results

This SR compiles and evaluates the results of other SRs of randomised studies. These SRs addressed either the role of 25(OH)D in the prevention of GDM, or the role of 25(OH)D in improving the effects of GDM in pregnancy [29–34]. The improvement concerns any beneficial effect from taking vitamin D supplements, on the perinatal effects of both the mother and the newborn or the improvement of the glycemic profile of mothers with GDM. The prevention of GDM involves the association of low 25(OH)D levels, otherwise healthy pregnant women, with the development of GDM in pregnancy. In our SR the inclusion criteria were pregnant with GDM (normal or high risk of GDM), without taking into account gestational age. These pregnant women were taking any vitamin D supplement, with no dose limitation, (high or low)/(Daily doses typically ranged between 200–5000 international units (IU), no daily dosing

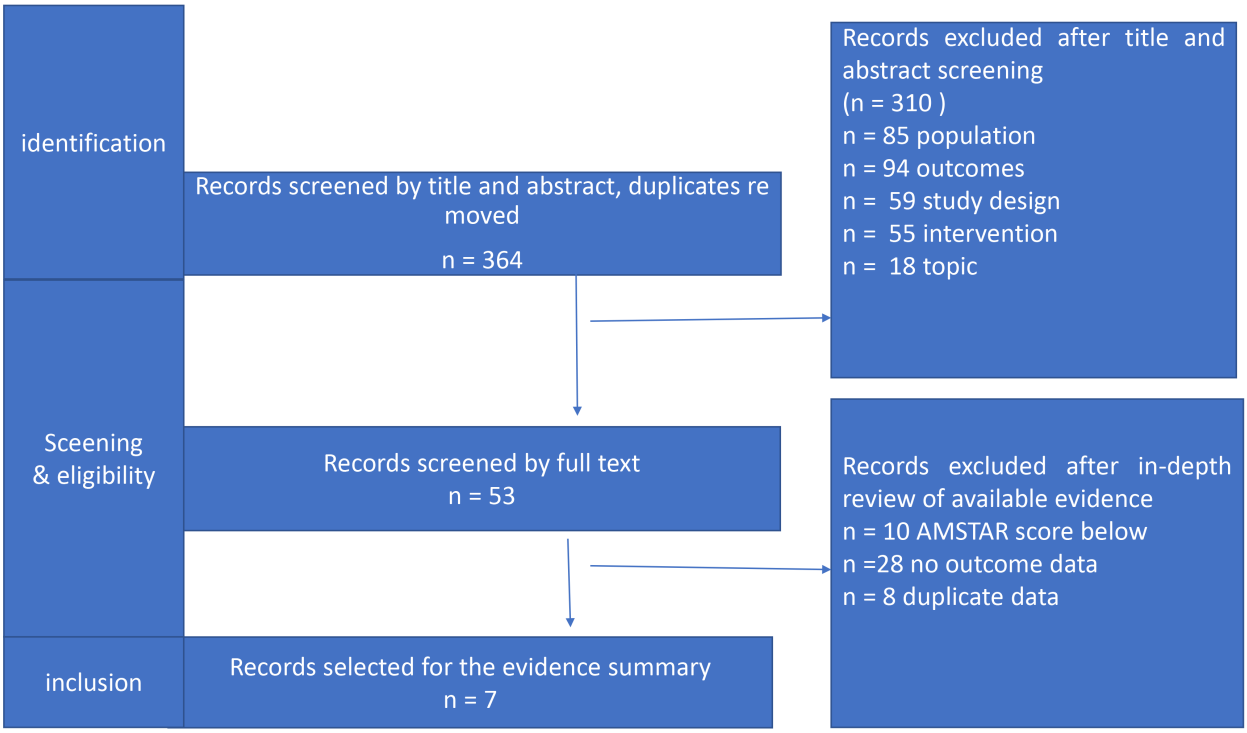

Fig. 1. Flow diagram of screening decisions.

(*e.g.*, daily, weekly) and no specific route of administration, compared to either a sample of pregnant women taking a placebo or any kind of vitamin D supplement.

Most of the SRs we included evaluated the role of 25(OH)D in improving the effects of GDM in pregnancy. The SR of Ojo *et al.* [29] showed that taking vitamin D supplements (1000–4762 IU/day) was enough to improve glycemic control in women with GDM (Table 1, Ref. [29–35]). Vitamin D intake was associated with a decrease in fasting blood glucose (FBG), on average (MD/Mean Deviation) 0.46 nmol/Lt (95% confidence inerval (95% CI): –0.68 to –0.25), glycosylated haemoglobin (HbA1c) by 0.37 (95% CI: –0.65 to –0.08) and serum insulin concentration by 4,10 μIU/ml (95% CI: –5.50 to –2.71) compared to the control group. Wang *et al.* [30], with a large-sized SR (including most of the SRs we evaluate in this SR) [29,31–33], and a very large number of participants evaluated the overall therapeutic effects of vitamin D intake in women with established GDM. It seemed that they also recognized the positive effect of vitamin D supplements on glycemic control, but also on the general improvement of the effects of GDM, on pregnancy and on both the mother and the newborn (Table 1). Overall, vitamin D intake by pregnant women with GDM significantly reduced both fasting plasma glucose (FPG) by mean deviation (MD): –10.20 mg/dL (95% CI: –13.43 to –6.96), and serum insulin concentration by MD: –5.02 (95% CI: –6.83 to –3.20), as well as homeostasis model of assessment of insulin resistance (HOMA-IR) by MD: –1.06 mg/dL (95% CI: –1.40 to –0.72). In addition, pregnant women with GDM who received vitamin D supplements had significantly fewer adverse maternal outcomes (Table 1), including cesarean section (CT) (relative risk (RR): 0.75, 95% CI: 0.63–0.89) and childbirth bleeding (RR: 0.47, 95% CI: 0.22–1.00). At the same time, several adverse neonatal complications were equally significantly reduced (Table 1), including neonatal hyperbilirubinemia (RR: 0.47, 95% CI: 0.33–0.67), very large in size children (RR: 0.58, 95% CI: 0.38–0.89), poly-hydramnium (RR: 0.42; 95% CI: 0.24–0.90) and preterm birth (RR: 0.43, 95% CI: 0.26–0.72). There appeared to be no statistically significant difference in the risk of hypoglycaemia in newborns (RR: 0.82, 95% CI: 0.52–1.29). This SR added that the intake of vitamin D by pregnant women with GDM, in addition to improving glycemic control, reduces both the adverse maternal and neonatal effects, compared to the control group that was given dummy vitamins, minerals or no vitamin supplements. Jahanjoo *et al.* [31] also evaluated the impact of vitamin D intake on both the maternal and the neonatal outcomes of pregnant women with GDM. Their SR compared taking a vitamin D supplement, by pregnant women with GDM, compared to taking placebo or without taking any supplement. It confirmed that vitamin D administered to pregnant women with GDM reduced neonatal hyperbilirubinaemia (Table 1), improved maternal serum levels of FPG, total cholesterol (TC), low-dense lipoprotein levels (LDL), high-dense lipoprotein levels (HDL), high-sensitivity C-reactive protein (hs-CRP) but it did not appear to affect insulin, serum thyroglobulin (TG) levels, the mother's HOMA-IR, or neonatal hypoglycemia. Finally, it in no way elucidated the role that vitamin D intake plays in

Table 1. Results of SRs of randomized studies.

Reviews	Number of studies/ individuals	Effect size - 95% Confidence Interval (95% CI)	Heterogeneity I squared (%)	Statistics significance	Quality research evaluation
		Risk ratio (RR), random effects			
SRs of RCTs		Odds Ratio (OR)		Calculated p homeostasis model of assessment robability (p values)	Level of evidence (GRADE)
		Mean Deviation (MD)			
Ojo *et al.* [29]	5/173 supplemented with vitamin D and 153 participants as control	Fusting blood glucose (FBG) (95% CI: –0.68 to –0.25)	0% to 41%	FBG ($p < 0.001$) (+)	Low
		Glycated Haemoglobin (GHb) (95% CI: –0.65 to –0.08)		GHb ($p < 0.01$) (+)	
		Serum Insulin (95% CI: –5.50 to –2.71)		Serum Insulin ($p < 0.01$) (+)	
Wang *et al.* [30]	19/1550	Fasting blood glucose (FBG) (95% CI: –13.43 to –6.96)	80%	FBG ($p < 0.001$) (+)	Medium
		Serum Insulin (95% CI: –6.83 to 3.20)	78%	Serum Insulin ($p < 0.001$) (+)	
		Model of Assessment of insulin resistance (HOMA-IR) (95% CI: –1.40 to –0.72)	74%	HOMA-IR ($p < 0.001$) (+)	
		MATERNAL RESULTS		MATERNAL RESULTS	
		Cesarean section (C-section) (RR: 0.75, 95% CI: 0.63 to 0.89)	43%	C-section ($p < 0.0001$) (+)	
		Childbirth Hemorrhages (RR: 0.47, CI: 0.22 to 1.00)	0%	Childbirth Hemorrhages ($p = 0.05$) (+)	
		Hospitalization after childbirth (RR: 0.13, 95% CI: 0.02 to 0.98)	0%	Hospitalization after Childbirth ($p = 0.05$) (+)	
		NEONATAL RESULTS		NEONATAL RESULTS	
		Neonatal Hyperbilirubinemia (RR: 0.47, 95% CI: 0.33 to 0.67)	0%	Hyperbilirubinemia ($p < 0.0001$) (+)	
		Large size newborns (RR: 0.58, 95% CI: 0.38 to 0.89)	0%	Large size newborns ($p = 0.01$) (+)	
		Poly-hydramnio (RR: 0.42, 95% CI: 0.24 to 0.90)	0%	Poly-hydramnio ($p = 0.002$) (+)	
		Pre-birth (RR: 0.43, 95% CI: 0.26 to 0.72)	0%	Pre-birth ($p = 0.002$) (+)	
		Fetal Dysphoria (RR: 0.46, 95% CI: 0.24 to 0.90)	0%	Fetal Dysphoria ($p = 0.02$) (+)	
		Hypoglycemia Risk (RR: 0.82, 95% CI: 0.52 to 1.29)	0%	Hypoglycemia Risk ($p = 0.39$) (–)	

Table 1. Continued.

Reviews	Number of studies/ individuals	Effect size - 95% Confidence Interval (95% CI)	Heterogeneity I squared (%)	Statistics significance	Quality research evaluation
		Risk ratio (RR), random effects			
SRs of RCTs		Odds Ratio (OR)		Calculated p homeostasis model of assessment robability (p values)	Level of evidence (GRADE)
		Mean Deviation (MD)			
Jahanjoo *et al*. [31]	5/310	MATERNAL RESULTS		MATERNAL RESULTS	Low
	3 tests with 223 participants	FBG	0%	FBG	
		MD: –12.54 (95% CI: –15.03 to –10.05)		($p < 0.001$) (+)	
	3 tests with 223 participants	Total cholesterol (TC)	78%	TC	
		MD: –24.77 (95% CI: –32.57 to –16.98)		($p < 0.001$) (+)	
	3 tests with 223 participants	Low-dense lipoprotein (LDL)	41%	LDL-Cholesterol	
		MD: –18.92 (95% CI: –24.97 to –12.88)		($p < 0.001$) (+)	
	3 tests with 223 participants	High-dense lipoprotein (HDL)	0%	HDL	
		MD: 3.87(95% CI: 1.20 to 6.55)		($p = 0.004$) (+)	
	2 tests with 126 participants	High-sensitivity C-reactive protein (hs-CRP)	0%	hs-CRP	
		MD: –1.35 (95% CI: –2.41 to –0.28)		($p = 0.01$) (+)	
		Homeostasis Model of Assessment of insulin resistance (HOMA-IR)	94%	HOMA-IR	
		MD: –1.19 (95% CI:–2.79 to 0.41)		($p = 0.14$) (–)	
		Fasting insulin	92%	Fasting insulin	
		MD: –3.79 μIU/mL (95% CI: –8.88 to 1.30)		($p = 0.14$) (–)	
		HOMA-IR	94%	HOMA-IR	
		MD: –1.19 (95% CI: –2.79 to 0.41)		($p = 0.14$) (–)	
		NEONATAL RESULTS		NEONATAL RESULTS	
	2 tests with 126 participants	Neonatal Hyperbilirubinemia	0%	Hyperbilirubinemia	
		(OR: 0.33, 95% CI: 0.13 to 0.80)		($p = 0.01$) (+)	
		Hypoglycemia Risk		Hypoglycemia Risk	
		MD: 0.02 (95% CI: –0.08 to 0.12)	31%	($p = 0.75$) (–)	

Table 1. Continued.

Reviews	Number of studies/ individuals	Effect size - 95% Confidence Interval (95% CI) / Risk ratio (RR), random effects / Odds Ratio (OR) / Mean Deviation (MD)	Heterogeneity I squared (%)	Statistics significance	Quality research evaluation
SRs of RCTs				Calculated *p* homeostasis model of assessment robability (*p* values)	Level of evidence (GRADE)
Akbari *et al*. [32]	6/371 184 pregnant with GDM and 187 pregnant as a control group	FBG (95% CI: –0.72 to 0.28)	82.3%	FBG ($p < 0.001$) (+)	Low
		Insulin (95% CI: –1.03 to 0.52)	87.1%	Insulin ($p < 0.001$) (+)	
		HOMA-IR (95% CI: –1.14 to –0.18)	57.4%	HOMA-IR ($p < 0.096$) (–)	
		HOMA-B (95% CI:–0.79 to –0.25)	0%	HOMA-B ($p = 0.594$) (–)	
		Glycosylated haemoglobin (HbA1c) (95% CI:–0.60 to 0.58)	76.6%	HbA1c	
		Quantitative intex of insulin sensitivity (QUICKI) (95% CI: 0.26 to 1.20)	64.9%	QUICKI ($p = 0.036$) (+)	
		TC (95% CI: –0.49 to 0.02)	16%	Total Cholesterol ($p = 0.312$) (–)	
		Triglycerides (95% CI: –0.63 to 0.28)	68.4%	Triglycerides ($p = 0.023$) (+)	
		LDL (95% CI: –0.58 to –0.10)	0%	LDL ($p = 0.413$) (–)	
		HDL (95% CI: –0.01 to 0.49)	0%	HDL ($p = 0.657$) (–)	
Zhang *et al*. [35]	25/2445 But also 87/55859 Observational studies	25(OH)D	38.56%	25(OH)D ($p < 0.001$) (+)	High
		Glutathione (GSH)	26.21%	GSH ($p = 0.003$) (+)	
		HDL MD: –0.188 (95% CI: –0.037 to –0.412)	6.62%	HDL ($p = 0.04$) (+)	
		Fasting insulin levels (FINS) MD: –0.613 (95% CI: –0.863 to –0.121)	68.64%	FINS ($p = 0.001$) (+)	
		HbA1C	0%	HbA1C	

Table 1. Continued.

Reviews	Number of studies/ individuals	Effect size - 95% Confidence Interval (95% CI) / Risk ratio (RR), random effects / Odds Ratio (OR) / Mean Deviation (MD)	Heterogeneity I squared (%)	Statistics significance	Quality research evaluation
SRs of RCTs				Calculated *p* homeostasis model of assessment robability (*p* values)	Level of evidence (GRADE)
		MD: –0.066 (95% CI: –0.262 to 0.135)		(*p* = 0.3) (–)	
		FINS	68.64%	FINS	
		MD: –0.487 (95% CI: –0.829 to 0.120)		(*p* = 0.001) (+)	
		Fasting plasma glucose (FPG)	40.25%	FPG	
		MD: –0.100 (95% CI: –0.166 to –0.033)		(*p* < 0.001) (+)	
		HOMA-IR	16.54%	HOMA-IR	
		MD: –0.351 (95% CI: –0.594 to –0.050)		(*p* < 0.001) (+)	
		C-reactive protein (CRP)	27.21%	CRP	
		MD: –0.705 (95% CI: –1.131 to –0.279)		(*p* = 0.02) (+)	
Zhang *et al.* [35]		TC	0%	TC	
				(*p* = 0.03) (+)	
		LDL	0%	LDL	
				(*p* = 0.003) (+)	
		Homeostasis Model of Assessment for B-cell function (HOMA-B)	29.17%	HOMA-B	
		MD: –0.664 (95% CI: –1.474 to –0.146)		(*p* = 0.2) (–)	
		Antioxidant Capacity (TAC)	60.79%	TAC	
				(*p* = 0.1) (–)	
		Blood triacylglycerol (TAG)	14.75%	TAG	
				(*p* = 0.09) (–)	
	13/2299	**MATERNAL RESULTS**			High
		Highest Circulating 25(OH)D intervention group versus control group	100%	(*p* < 0.00001) (+)	
		MD: 66.5 nmol/L (95% CI: 66.2 to 66.7)			
		Preeclampsia			
Pérez-López *et al.* [33]		RR: 0.88 (95% CI: 0.51 to 1.52)	24%	(*p* = 0.65) (–)	
		Gestational Diabetes Mellitus (GDM)			
		RR: 1.05 (95% CI: 0.50 to 1.21)	0%	(*p* = 0.86) (–)	
		Frequency of Appearance of C-section			
		RR: 0.94 (95% CI: 0.78 to 1.13)	0%	(*p* = 0.51) (–)	
		NEONATAL RESULTS			
		Higher Birth Weight of Intervention group *vs.* Control group			

Table 1. Continued.

Reviews	Number of studies/ individuals	Effect size - 95% Confidence Interval (95% CI)	Heterogeneity I squared (%)	Statistics significance	Quality research evaluation
		Risk ratio (RR), random effects			
SRs of RCTs		Odds Ratio (OR)		Calculated p homeostasis model of assessment robability (p values)	Level of evidence (GRADE)
		Mean Deviation (MD)			
Pérez-López *et al.* [33]		MD: 107.6 g (95% CI: 59.9 to 155.3)	0%	($p < 0.00001$) (+)	
		Small for Gestational Age (SGA)			
		RR: 0.78 (95% CI: 0.60 to 1.84)			
		Low Birth Weight	15%	($p = 0.27$) (–)	
		RR: 0.72 (95% CI: 0.44 to 1.16)			
		Pre-Birth	0%	($p = 0.18$) (–)	
		RR: 1.26 (95% CI: 0.60 to 2.63)			
		Length of Birth	0%	($p = 0.54$) (–)	
		MD: 0.3 cm (95% CI: 0.19 to 0.41)			
			84%	($p < 0.00001$) (+)	
Jin *et al.* 2020 [34]	13/754	FBG		($p = 0.341$) (–)	Medium
	96 Patients	Placebo versus (*vs.*) Omega-3	0%		
		MD: –5.93 (95% CI: –10.29 to –1.57)			
	110 Patients	Placebo *vs.* Magnesium	0%		
		MD: –10.59 (95% CI: –13.68 to –7.50)			
	151 Patients	Placebo *vs.* Vitamin D	0%		
		MD: –13.17 (95% CI: –15.95 to –10.39)			
	102 Patients	Placebo *vs.* Zn	0%		
		MD: –6.42 (95% CI: –10.18 to –2.65)			
	225 Patients	Placebo *vs.* probiotics	25%		
		MD: –5.49 (95% CI: –8.05 to –2.93)			
		Insulin		($p = 0.3678$) (–)	
	96 Patients	Placebo *vs.* Omega-3	28%		
		MD: –3.22 (95% CI: –6.21 to 0.24)			
	151 Patients	Placebo *vs.* Vitamin D	29%		
		MD: –6.23 (95% CI: –8.05 to –4.40)			

Table 1. Continued.

Reviews	Number of studies/ individuals	Effect size - 95% Confidence Interval (95% CI)	Heterogeneity I squared (%)	Statistics significance	Quality research evaluation
		Risk ratio (RR), random effects			
SRs of RCTs		Odds Ratio (OR)		Calculated *p* homeostasis model of assessment robability (*p* values)	Level of evidence (GRADE)
		Mean Deviation (MD)			
Jin *et al*. 2020 [34]	102 Patients	Placebo *vs.* Zn	62%	(p = 0.4532) (–)	
		MD: –4.61 (95% CI: –7.04 to –2.18)			
	165 Patients	Placebo *vs.* probiotics	0%		
		MD: –2.70 (95% CI: –3.46 to –1.94)			
		HOMA-IR			
	96 Patients	Placebo *vs.* Omega-3	17%		
		MD: –1.01 (95% CI: –1.81 to –0.21)			
	151 Patients	Placebo *vs.* Vitamin D	5%		
		MD: –1.97 (95% CI: –2.51 to –1.42)			
	102 Patients	Placebo *vs.* Zn	81%		
		MD: –0.97 (95% CI: –1.70 to –0.23)			
	165 Patients	Placebo *vs.* probiotics	33%		
		MD: –0.69 (95% CI: –0.88 to –0.50)			

The statistical significance is indicated in the table as positive (+) when the p value $\leq$ 0.05 and negative (–) if >0.05.

FBG, fusting blood glucose; GHb, glycated haemoglobin; HOMA-IR, homeostasis model of assessment of insulin resistance; HOMA-B, homeostasis model of assessment for B-cell function; C-section, cesarean section; TC, total cholesterol; LDL, low-dense lipoprotein; HDL, high-dense lipoprotein; hs-CRP, high-sensitivity C-reactive protein; QUICKI, quantitative intex of insulin sensitivity; HbA1c, glycosylated haemoglobin; FPG, fasting plasma glucose; GSH, glutathione; CRP, C-reactive protein; TAC, antioxidant capacity; TAG, blood triacylglycerol; GDM, gestational diabetes mellitus.

the prevention of GDM. Akbari *et al.* [32], in their attempt to summarize the effect of vitamin D supplementation on glucose homeostasis parameters and lipid metabolic profile of pregnant women with GDM, found no beneficial effect on the concentrations of FPG, insulin, hyperglycemia, HbA1c, triglycerides and total high-dense lipoprotein (HDL)-cholesterol levels. The only point it seemed to agree with the aforementioned meta-analyses was that it improved the levels of HOMA-IR [standarized mean difference (SMD): –0.66, 95% CI: –1.14 to –0.18]. What this SR probably added was that, there was a statistically significant increase in the quantitative index of insulin sensitivity (QUICKI-quantitative insulin sensitivity check index) (SMD: –0.73, 95% CI: 0.26 to 1.20), improvement of LDL cholesterol levels (SMD: –0.33, 95% CI: –0.58 to –0.07), but also a significant increase in the Homeostasis Model of Assessment for B-cell function (HOMA-B) (SMD: –0.52, 95% CI: –0.79 to –0.25). However, it is considered a low-reliability SR. Pérez-López *et al.* [33], with a fairly large SR (13RCTs/2299 participants), none of which are included in this SR, also evaluated the effect of vitamin D intake in pregnant mothers with GDM and the corresponding maternal and neonatal outcomes. They considered that although the intake of vitamin D by pregnant women significantly increased maternal 25(OH)D serum levels, compared to the control group, it did not seem to affect either maternal outcomes (preeclampsia, premature birth, GDM, C-section), or neonatal outcomes (SGA, LBW). It only supported the fact that infants born to mothers receiving vitamin D in pregnancy had significantly higher weight and birth length, compared to the control group (Table 1).

Jin *et al.* [34] studied the effect of other forms of dietary supplements compared to vitamin D intake, on glucose metabolism in women with GDM. They used 13 RCTs with 754 participants in their meta-analysis. They found that, compared to placebo, Ω3, Mg, vitamin D, Zn and probiotics were more beneficial in improving FBG, serum insulin and HOMA-IR. The analysis showed that vitamin D intake was superior to Ω3 (–3.64 ng/dL, 95% CI: –5.77 to –1.51), Zn (–5.71 ng/dL, 95% CI: –10.19 to –1.23), probiotics (–6.76 ng/dL, 95% CI: –10.02 to –3.50) but also placebo (–12.13 ng/dL, 95% CI: –14.55 to –9.70) to improve FPG, while Mg intake was more beneficial in reducing serum insulin compared to probiotics (–5.10 μIU/mL, 95% CI: –9.32 to –0.88) and placebo (–7.80 μIU/mL, 95% CI: –9.32 to –0.88). Thirteen studies were included in the Jin *et al.* (2020) [34] SR, most of which were conducted in Iran. Although it could be considered a high-quality SR, due to the number of participants and its novelty of comparing, for the first time, the effects of different nutritional strategies on the maintenance of metabolic glucose homeostasis, it is considered of medium quality. Although participants were asked to maintain their usual physical activity and dietary intake, each country has different dietary habits and different medications in pregnancy care. The participants were women with GDM, so the majority of intervention durations in the studies were around six weeks, which may have influenced the conclusion. Finally, most of the studies were placebo-controlled trials. In these, the number of clinical trials in the pairs studied and comparison of different dietary supplement strategies was limited, so more direct evidence of different dietary strategies is needed to further validate any conclusions in the future.

In the SR of Zhang *et al.* [35], vitamin D supplements were administered during pregnancy to prevent or treat GDM. They included an unprecedented large sample, with 25 RCTs, when the largest study of the past included a maximum number of studies of 20 RCTs. For the first time, biomarkers that had not been studied were evaluated. In addition, this study used RCTs, in which no research participant had been informed about the levels of vitamin D in her blood, to avoid the Hawthorne Phenomenon, which is the tendency of some people to work harder and perform more when observed. No statistically significant difference in the effect of vitamin D intake on HOMA-β, HbA1C, TAC and TAG concentrations was shown. While it appeared that vitamin D reduced the risk of GDM (RR = 0.718, 95% CI: 0.392–1.314), it was not clear whether vitamin D intake was effective in preventing it. This study reinforced the view that low levels of vitamin D, in the blood, are associated with a higher risk of GDM (OR: 1.850, 95% CI 1.471–2.328). On the other hand, in women with diagnosed GDM, the level of vitamin D was lower than in the control group. At this point it should be remembered that not even the SR of Jahanjoo *et al.* [31], that was not included in the SR of Zhang *et al.* [35], enlightened us about the role that vitamin D intake plays in the prevention of GDM. Finally, in this SR as well, vitamin D level was associated with FPG and HOMA-IR (r = –0.100 and r = –0.351 respectively), while the association between vitamin D level and fasting insulin may be obscured by publication bias. Taking vitamin D in pregnancy seemed to improve 25(OH)D blood levels, as well as biomarkers related to blood glucose, such as fasting insulin levels (FINS), FPG, HOMA-IR, but also other markers, such as glutathione (GSH), which is a marker of oxidative stress, the inflammatory index of C-reactive protein (CRP) and blood lipids.

4. Discussion

In conclusion, it appeared that pregnant women with GDM who took vitamin D supplements (1000–4762 IU/day) improved their glycemic indices [29]. Vitamin D intake was effective in the main outcome measures of GDM such as FBG [29,35], HbA1c, serum insulin [29] and HOMA-IR [30,35] (Table 2, Ref. [29–35]). In addition, improvements were shown in their lipid profile indices, such as TC, LDL, HDL and hs-CRP [31]. Furthermore, taking vitamin D supplements in women with diagnosed GDM, seems to significantly reduce both the adverse

Table 2. Results The role of vitamin D in preventing GDM and ameliorating the effects of GDM in pregnancy.

The role of vitamin D in the prevention of GDM	The role of vitamin D in reducing the negative effects on the mother	The role of vitamin D in reducing adverse effects in newborns	The role of vitamin D in reducing other indicators
FPG [30,31,35]	C-section [30]	neonatal hyperbilirubinemia [30,31]	CRP [35]
HOMA-IR [30,32,34,35]	childbirth bleeding [30]	very large in size children [30]	GSH [35]
FINS [35]		Fetal Dysphoria [30]	TC [31]
FBG [29,30,34]		poly-hydramnium [30]	LDL [31,32]
HOMA-B [32]		preterm birth [30]	HDL [31]
QUICKI [32]		higher birth weight [33]	hs-CRP [31]
HbA1c [29]		higher birth length [33]	blood lipids [35]
Serum insulin concentration [29,30,34]			

GDM, gestational diabetes mellitus; FPG, fasting plasma glucose; HOMA-IR, homeostasis model of assessment of insulin resistance; FINS, fasting insulin levels; FBG, fusting blood glucose; HOMA-B, homeostasis model of assessment for B-cell function; QUICKI, quantitative intex of insulin sensitivity; HbA1c, Glycosylated haemoglobin; C-section, Cesarean section; CRP, C-reactive protein; GSH, glutathione; TC, total cholesterol; LDL, low-dense lipoprotein; HDL, high-dense lipoprotein; hs-CRP, high-sensitivity C-reactive protein.

maternal and neonatal effects. A decrease in possible adverse maternal outcomes was observed (Table 1), including KT and childbirth bleeding [30], but also in adverse neonatal complications, including neonatal hyperbilirubinemia [30,31], very large children [30], poly-hydramnium [30] and preterm birth [30] (Table 2).

Despite the fact that remarkable reviews were included, at the same time each of them brought several disadvantages related to their methodological design. The SR of Ojo *et al.* [29] included a limited number of studies, with a small number of participants, therefore a greater probability of error and less accuracy. The SR of Wang *et al.* [30] was considered a fairly reliable study, as it included large sample size, medium quality, and relatively low heterogeneity of its RCTs. However, the RCTs it evaluated varied in the doses, route of administration and duration of intervention of the administered vitamin D supplements. The interventions involved either only the administration of vitamin D or in combination with other vitamin or mineral supplements, this was likely to create confusion in the interpretation of the results, about which of all the supplements creates any beneficial effects on GDM, but also in both the maternal and neonatal effects. In this study, a secondary analysis was carried out to see if vitamin D alone or in combination with other vitamins or minerals brought any beneficial effects, but nevertheless, there was still ambiguity. Pregnant women with GDM used different doses of vitamin D. The researchers divided their results into two groups, one group was administered a dose of 25(OH)D $<$800 IU/day while the second group was administered a dose of 25(OH)D $\geq$800 IU/day. In both test groups, vitamin D intake improved FPG, HOMA-IR, C-section risk and premature birth. However, when the dose was 25(OH)D $<$800 IU/day, there were no significant effects on neonatal hypoglycaemia and large neonates. The duration of the intervention, which was also varied, did not seem to influence the beneficial effects of vitamin D intake on FPG, insulin concentration, HOMA-IR and neonatal hypoglycemia. Finally, it appeared that, oral but not intramuscular administration (IM) of vitamin D could reduce FPG in participants. Of course, this may have been due to only two studies involving IM administration, but also to the fact that in the IM administration group, obese participants with body mass index (BMI): 28.9 $\pm$ 4.8, were enrolled in one study, which could affect the effect of taking vitamin D supplementation on glucose-insulin homeostasis in this group.

In addition, it is worth mentioning the effects of other forms of dietary supplements, vitamins or minerals, always compared to vitamin D intake, on glucose metabolism, in women with GDM. Omega 3, Mg, vitamin D, Zn and probiotics are much more beneficial in improving FBG, serum insulin and HOMA-IR, than a placebo [34]. Taking a vitamin D supplement is superior to Omega 3, Zn, probiotics, and placebo in improving FPG, while taking Mg is more beneficial in reducing serum insulin, compared to probiotics [34]. In conclusion, it was shown that taking vitamin D significantly reduces FPG and regulates HOMA-IR [34]. Mg intake is superior to other vitamins or minerals, in lowering serum insulin [34]. However, synergistically taking the aforementioned vitamins and minerals, simultaneously with vitamin D, opens up other horizons in the prevention of GDM, as it seems to have an effect on the maintenance of glucose homeostasis in patients with GDM and can be considered an adjunct therapy. Although participants were asked to maintain their usual physical activity and dietary intake, each country has different eating habits and different medications in pregnancy care. Undoubtedly, nutrition control is the main treatment and treatment of GDM [34]. Jin *et al.* [34] included thirteen studies, most of which were done in Iran. Although it could be considered a high-quality SR, due to the number of participants and its innovation to compare, for the first time, the effects of different dietary strategies on maintaining metabolic glucose homeostasis, it is considered of medium quality. The participants were

women with GDM, so the majority of the duration of intervention in the studies was around six weeks, which may have influenced the conclusion. Finally, most of the studies were trials, controlled with placebo. In these, the number of clinical trials in the pairs studied and comparing different dietary supplement strategies was limited, so more direct evidence of different dietary strategies is needed to further validate any conclusions in the future. In any case, studies such as Jin *et al.* [34], with a large number of participants, could potentially offer important information to the scientific community, for clinical practice applications, on condition that they are as homogeneous as possible. Differences in the physical activity, diet of pregnant women or taking different medicinal intake may cause significant differences in the regulation of glucose homeostasis, which may create uncertainty as to the clinical relevance of the results and potentially affect their universality. In addition, some of the studies have fewer samples and some others carry a high-risk bias, due to the lack of concealment of distribution and blindness in evaluating the results. There should be greater homogeneity in the inclusion criteria for GDM and the types and doses of dietary supplements in each study. In the future, more high-quality studies (more data provision), larger-scale (a larger number of studies) and better planning (to reduce heterogeneity) are needed to validate the data provided by the study. It is necessary to record important information, which is at the same time confounding factors and concerns either the mother (her diet, the time of gestation - childbirth, the increase in her body weight in pregnancy, the duration of pregnancy, the nationality of the pregnant woman and the characteristics of her skin) or the newborn. Furthermore, it is advisable to avoid differences in the quantification of 25(OH)D, which arise using another method. For example, the research of Pérez-López *et al.* [33], which lacked important information and used another method to quantify 25(OH)D. All of the Jahanjoo *et al.'s* [31] SRs involved pregnant women with GDM. Therefore, its effects cannot be generalized to pregnant women with normal glucose metabolism or normal 25(OH)D levels. Also the same SR had significant heterogeneity between its studies, had a fairly short duration of intervention and a very small sample size. An additional disadvantage is that vitamin D was administered either in the form of D2 or in the form of D3, in any dose, by any route of administration (oral or intramuscular) and at any frequency (*e.g.*, 3 times a day, 3 times a week, 3 times a month or even with a "bolus" administration of one or two times at most). Thus, the results obtained from each study should be thoroughly studied.

Other studies did not seem to endorse the therapeutic effect of vitamin D intake, by pregnant women with GDM, on parameters related to glucose homeostasis [32], lipid metabolic profile [32], but also adverse maternal and neonatal outcomes (preeclampsia, premature birth, GDM, C-section, SGA, LBW neonates). The SR of Akbari *et al.* [32] found no beneficial effect on either FPG, insulin, hyperglycaemia and HbA1c concentrations, nor triglycerides and total HDL only an improvement in LDL cholesterol levels, a statistically significant increase in QUICKI, an improvement in the levels of HOMA-IR, but also a significant increase in HOMA-B. Although this SR was a preliminary study, with a small sample size, it certainly needed more research in the future to confirm or reject its claims. It is considered a low reliability study, with high heterogeneity and very small sample size. The duration of administration of supplements to pregnant women ranged from 6 weeks to three months. The SR of Pérez-López *et al.* [33] only showed that neonates born to mothers who received vitamin D during pregnancy had a significantly higher birth weight and length, compared to the control group (Table 1), without any other clinical conclusion. But, although at first sight, it seemed quite remarkable, it bore several limitations. All RCTs included in the study differed in terms of doses, types of vitamin D supplements, duration of intake, gestational age at first administration, and heterogeneity. They administered either vitamin D2 or D3, alone or in combination with multivitamins, calcium or iron, against placebo or no intervention. All women received a standard prenatal multivitamin with 400 IU D3, with an additional vitamin D3 supplement with 0 IU (placebo), 1600 IU or 3600 IU, in order to be covered with a total of 400 IU, 2000 IU and 4000 IU vitamin D respectively. The start of vitamin D intake was between 8–28 weeks of gestation. Some RCTs started taking supplements in the second half of pregnancy, with the result that many clinical conditions (*e.g.*, preeclampsia and GDM) could practically not be avoided, as the various biochemical, metabolic and vascular changes had already occurred. Since many studies have been carried out in developing countries, in the population under study it was not possible to exclude the possibility of maternal and child malnutrition, with the natural consequence that the contribution of vitamin D supplementation was powerless to neutralize the basic nutritional status.

The administration of vitamin D to pregnant women to prevent GDM seems to be gaining ground. Low levels of vitamin D in the blood are associated with a higher risk of GDM. On the other hand, in women with diagnosed GDM, vitamin D levels appear lower compared to women who do not have GDM. Taking vitamin D in pregnancy seemed to improve blood vitamin D levels [33,35], but also biomarkers related to blood glucose FINS, FPG, HOMA-IR, as well as other markers, for example GSH (marker of oxidative stress), the inflammatory marker of CRP, but also blood lipids [35]. In the study of Zhang *et al.* (2018) [35], vitamin D supplements were administered during pregnancy to prevent or treat GDM. They included an unprecedented large sample, with 25 RCTs, when the largest study of the past included a maximum number of studies of 20 RCTs. For the first time, biomarkers that had not been studied and there were very minor errors were evaluated. In addition,

this study used RCTs, in which no research participant had been informed about the levels of vitamin D in her blood, to avoid the Hawthorne effect. Hawthorne effect is a phenomenon that reveals the tendency of some people to work harder and perform more when observed. In the current situation, pregnant women might have done the right thing in order to increase vitamin D.

Intervention by healthcare professionals in recommending vitamin D intake in pregnancy could improve blood vitamin D levels and therefore levels of blood sugar-related biomarkers FINS, FPG, HOMA-IR, but also other indicators such as GSH (an indicator of oxidative stress), CRP (an indicator of inflammation) and blood lipids.

5. Conclusions

In conclusion, taking vitamin D, during pregnancy, for the prevention or treatment of GDM, is controversial and the real benefit unclear. Further RCTs are necessary, with better methodology and design, which will improve the available data and clarify the advantages of taking it, in both any unwanted maternal and neonatal results, in pregnancy. The benefit, if any, of starting vitamin D supplements, prenatally or early in pregnancy, should be clarified, using stable doses of vitamin D. Finally, to determine the ideal beneficial dose of vitamin D for the sensitive period of pregnancy, which will lead to the maximum benefits, in terms of its outcome, but also to the reduction of any side effects from its overdose.

Any clinicall conclusions should be interpreted with caution. Although taking vitamin D seems to have significant benefits in pregnant women with GDM [31], it is necessary, as said, to weigh the benefits of each intervention, given any side effects. Also, it is necessary to investigate the ideal Daily Intake (RDI) of vitamin D in women with GDM, by conducting further studies, knowing that the management of GDM so far is mainly pharmaceutical, with pharmaceutical preparations such as insulin or metformin. With a better understanding of the mechanism by which 25(OH)D affects GDM and glucose metabolism, it is possible that GDM can be prevented, especially in women with a history of GDM or with risk factors. The ultimate goal is to help the scientific community and the relevant health professionals, in making correct decisions. Larger, multinational studies are needed.

The recommendations of health professionals in the preventive administration of vitamin D in pregnancy, could improve the levels of vitamin D in the blood and therefore prevent the occurrence of GDM, improve the levels of biomarkers related to blood sugar, such as FINS, FPG and HOMA-IR, but also other beneficial indicators such as GSH (an indicator of oxidative stress), CRP (an indicator of inflammation) and blood lipids. Ideally, the vitamin D dose should be defined or at least delimited so as to not only provide the optimum benefit to minimize or eradicate possible side effects of GDM for the expectant mother and newborn child but also pave the way for the prevention of GDM. Finally, it could constitute a new therapeutic approach to GDM, ideally together with a balanced and appropriate diet for GDM.

Abbreviations

VDD, vitamin D deficiency; GDM, gestational diabetes mellitus; SRs, systematic reviews; RCTs, randomized controlled trials; 25(OH)D, 25-hydroxyvitamin D; D2, ergocalciferol; D3, cholecalciferol; DM, diabetes mellitus; MS, metabolic syndrome; C-section, cesarean section; TOH, transient osteoporosis of the hip; GLUT, glucose transporters; LBW, low birth weight; SGA, small for gestational age; ADA, American Diabetes Association; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; HbA1c, glycosylated hemoglobin; OGTT, oral glucose tolerance test; WHO, World Health Organization; LGA, large-sized neonates for gestational age; Ca, Calcium; Mg, Magnesium; Zn, Zinc; AMSTAR, assessment of multiple systematic reviews; CI, confidence interval; RR, risk ratio; OR, odds ratio; MD, mean deviation; FBG, fasting blood glucose; FPG, fasting plasma glucose; HOMA-IR, homeostasis model of assessment for insulin resistance; CRP, C-reactive protein; IM, intramuscular administration; BMI, body mass index; TC, total cholesterol; LDL, low-dense lipoprotein levels; HDL, high-dense lipoprotein levels; hs-CRP, high sensitivity C-reactive protein; FINS; fasting insulin levels; QUICKI, quantitative insulin sensitivity check index; HOMA-B, homeostasis model of assessment for B-cell function; RDI, reference daily intake.

Author Contributions

AK conceived the topic; AK, MD and GI retrieved the literature; AK wrote the paper; MD, AL and GI provided relevant methodological support and supervision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

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References

[1] Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. Vitamin D Sources, Metabolism, and Deficiency: Available Compounds and Guidelines for Its Treatment. Metabolites. 2021; 11: 255.

[2] Bikle DD. Vitamin D and the skin: Physiology and pathophysiology. Reviews in Endocrine & Metabolic Disorders. 2012; 13: 3–19.

[3] Lo TH, Wu TY, Li PC, Ding DC. Effect of Vitamin D supplementation during pregnancy on maternal and perinatal outcomes. Ci Ji Yi Xue Za Zhi. 2019; 31: 201–206.

[4] Mousa A, Naderpoor N, Teede HJ, De Courten MPJ, Scragg R, De Courten B. Vitamin D and cardiometabolic risk factors and diseases. Minerva Endocrinologica. 2015; 40: 213–230.

[5] Echida Y, Mochizuki T, Uchida K, Tsuchiya K, Nitta K. Risk factors for vitamin D deficiency in patients with chronic kidney disease. Internal Medicine (Tokyo, Japan). 2012; 51: 845–850.

[6] Skaaby T, Thuesen BH, Linneberg A. Vitamin D, Cardiovascular Disease and Risk Factors. Advances in Experimental Medicine and Biology. 2017; 996: 221–230.

[7] Brown RB. Vitamin D, cancer, and dysregulated phosphate metabolism. Endocrine. 2019; 65: 238–243.

[8] Murdaca G, Tonacci A, Negrini S, Greco M, Borro M, Puppo F, *et al*. Emerging role of vitamin D in autoimmune diseases: An update on evidence and therapeutic implications. Autoimmunity Reviews. 2019; 18: 102350.

[9] Fattah A, Abounoori M. Transient osteoporosis of the hip: Physicians the occupation of at risk. Clinical Case Reports. 2021; 9: e04968.

[10] Asadipooya K, Graves L, Greene LW. Transient osteoporosis of the hip: review of the literature. Osteoporosis International. 2017; 28: 1805–1816.

[11] Amegah AK, Klevor MK, Wagner CL. Maternal vitamin D insufficiency and risk of adverse pregnancy and birth outcomes: A systematic review and meta-analysis of longitudinal studies. PLoS ONE. 2017; 12: e0173605.

[12] Urrutia RP, Thorp JM. Vitamin D in pregnancy: current concepts. Current Opinion in Obstetrics & Gynecology. 2012; 24: 57–64.

[13] Sirimarco MP, Guerra HM, Lisboa EG, Vernini JM, Cassetari BN, de Araujo Costa RA, *et al*. Diagnostic protocol for gestational diabetes mellitus (GDM) (IADPSG/ADA, 2011): influence on the occurrence of GDM and mild gestational hyperglycemia (MGH) and on the perinatal outcomes. Diabetology & Metabolic Syndrome. 2017; 9: 2.

[14] American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021; 44: S15–S33.

[15] American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care. 2015; 38: S8–S16.

[16] Iatrakis G. Gestational Diabetes. In: High Risk Pregnancy. Zevelekakis Medical Editions: Athens. 2021.

[17] Durnwald C, Nathan DM, Werner EF, Barss VA. UpToDate. Gestational diabetes mellitus: Screening, diagnosis, and prevention. UpToDate 2020. Available at: https://www.medilib.ir/uptodate/show/6797 (Accessed: 18 January 2023).

[18] Perrin MC, Terry MB, Kleinhaus K, Deutsch L, Yanetz R, Tiram E, *et al*. Gestational diabetes as a risk factor for pancreatic cancer: a prospective cohort study. BMC Medicine. 2007; 5: 25.

[19] Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH. The Pathophysiology of Gestational Diabetes Mellitus. International Journal of Molecular Sciences. 2018; 19: 3342.

[20] Ramasammy R, Munisammy L, Sweta K, Selvakumar S, Velu K, Rani J, *et al*. Relationship between GCK gene polymorphism and gestational diabetes mellitus and its pregnancy outcomes. Meta Gene. 2021; 28: 100856.

[21] McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nature Reviews. Disease Primers. 2019; 5: 47.

[22] Clifton-Bligh RJ, McElduff P, McElduff A. Maternal vitamin D deficiency, ethnicity and gestational diabetes. Diabetic Medicine: a Journal of the British Diabetic Association. 2008; 25: 678–684.

[23] Wang L, Zhang C, Song Y, Zhang Z. Serum vitamin D deficiency and risk of gestational diabetes mellitus: a meta-analysis. Archives of Medical Science: AMS. 2020; 16: 742–751.

[24] Maghbooli Z, Hossein-Nezhad A, Karimi F, Shafaei AR, Larijani B. Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. Diabetes/metabolism Research and Reviews. 2008; 24: 27–32.

[25] Sirico A, Dell'Aquila M, Tartaglione L, Moresi S, Farì G, Pitocco D, *et al*. PTH-rP and PTH-R1 Expression in Placentas from Pregnancies Complicated by Gestational Diabetes: New Insights into the Pathophysiology of Hyperglycemia in Pregnancy. Diagnostics (Basel, Switzerland). 2021; 11: 1356.

[26] Naseh A, Ashrafzadeh S, Rassi S. Prevalence of vitamin D deficiency in pregnant mothers in Tehran and investigating its association with serum glucose and insulin. The Journal of Maternal-fetal & Neonatal Medicine. 2018; 31: 2312–2318.

[27] Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, *et al*. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. Journal of Clinical Epidemiology. 2009; 62: 1013–1020.

[28] Pieper D, Koensgen N, Breuing J, Ge L, Wegewitz U. How is AMSTAR applied by authors - a call for better reporting. BMC Medical Research Methodology. 2018; 18: 56.

[29] Ojo O, Weldon SM, Thompson T, Vargo EJ. The Effect of Vitamin D Supplementation on Glycaemic Control in Women with Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. International Journal of Environmental Research and Public Health. 2019; 16: 1716.

[30] Wang M, Chen Z, Hu Y, Wang Y, Wu Y, Lian F, *et al*. The effects of vitamin D supplementation on glycemic control and maternal-neonatal outcomes in women with established gestational diabetes mellitus: A systematic review and meta-analysis. Clinical Nutrition (Edinburgh, Scotland). 2021; 40: 3148–3157.

[31] Jahanjoo F, Farshbaf-Khalili A, Shakouri SK, Dolatkhah N. Maternal and Neonatal Metabolic Outcomes of Vitamin D Supplementation in Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. Annals of Nutrition & Metabolism. 2018; 73: 145–159.

[32] Akbari M, Moosazaheh M, Lankarani KB, Tabrizi R, Samimi M, Karamali M, *et al*. The Effects of Vitamin D Supplementation on Glucose Metabolism and Lipid Profiles in Patients with Gestational Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Hormone and Metabolic Research. 2017; 49: 647–653.

[33] Pérez-López FR, Pasupuleti V, Mezones-Holguin E, Benites-Zapata VA, Thota P, Deshpande A, *et al*. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials. Fertility and Sterility. 2015; 103: 1278–88.e4.

[34] Jin S, Sha L, Dong J, Yi J, Liu Y, Guo Z, *et al*. Effects of Nutritional Strategies on Glucose Homeostasis in Gestational Diabetes Mellitus: A Systematic Review and Network Meta-Analysis. Journal of Diabetes Research. 2020; 2020: 6062478.

[35] Zhang Y, Gong Y, Xue H, Xiong J, Cheng G. Vitamin D and gestational diabetes mellitus: a systematic review based on data free of Hawthorne effect. BJOG: an International Journal of Obstetrics and Gynaecology. 2018; 125: 784–793.