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Maternal Vitamin D Deficiency and Risk of Development of Gestational Diabetes Mellitus: A Scoping Review

Yureka Demini Wimalajeewa[1*], Usha Pushkala Kumari Hettiaratchi[2], Thamara Dilhani Amarasekara[3], Shamini Prathapan[4], Mathota Arachchilage Madura Mangala Jayawardane[1]

[1]Department of Obstetrics & Gynaecology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka
[2]Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka
[3]Department of Nursing & Midwifery, Faculty of Allied Health Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka
[4]Department of Community Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka
Email: *deminiwimalajeewa@gmail.com

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Abstract

Background: Maternal vitamin D status is a critical determinant during pregnancy, because it plays an important role in the body not only in calcium homeostasis and bone remodeling, but also in the glucose metabolism. Vitamin D deficiency is associated with adverse pregnancy outcomes including gestational diabetes mellitus. **Objective:** To review evidence on the association between maternal vitamin D deficiency and incidence of gestational diabetes mellitus (GDM). **Methods:** PRISMA for scoping review guideline and scoping review guidelines of Arksey & O'Malley (2005) was followed in methodological process. A comprehensive search strategy was carried out across the Google Scholar and PubMed from January 2012 to December 2022, using the search terms of "gestational diabetes mellitus/pregnancy outcomes" combined with "vitamin D", "cholecalciferol" or "25-hydroxyvitamin D" and/or "deficiency". Articles were screened at the title and the abstract level and at full text by three co-investigators of the study independently with a fourth reviewer resolving discrepancies. Research studies published only in English language were selected. Research using pregnant mothers with multiple pregnancy and chronic diseases was excluded. **Results:** After screening 134 titles and abstracts, finally 55 original research articles were selected. It involved 48 observational studies and 7 Randomized Control Trials (RCT). Only 30 research articles had found an association between maternal vitamin D deficiency and GDM. **Conclusion:** As results of previous studies are mixed and inconclusive, further research including more RCTs is needed to clarify the exact mechanism of vitamin D on glucose metabolism during pregnancy.

Keywords

Gestational Diabetes Mellitus, Maternal, Vitamin D Deficiency

1. Introduction

The growing fetus cannot synthesize its own vitamin D, and depend on the placenta to transfer the metabolite 25(OH)D from maternal bloodstream. This compound is transported into the fetus by passively diffusing across the placenta. Foetal calcium level is normally higher than the maternal level throughout the gestation, while foetal vitamin D level is usually 20% lower than maternal levels [1]. Vitamin D deficiency is common among people due to multiple risk factors such as lack of sun exposure, inadequate dietary intake, darker skin pigmentation, usage of sunscreen, clothing covering the whole body and latitude of residence and ethnicity [2]. Vitamin D contributes to several extra skeletal functions in the body including cardiovascular and pulmonary functions, regulation of blood pressure and inflammation, modulation of the immune system, metabolic and cellular functions, and cell proliferation. In addition, vitamin D helps to modulate gene expression, second messenger systems, hormonal actions, and the cell cycle and induce apoptosis [3].

A recent study conducted with pregnant mothers in Colombo Medical Officer of Health area shows that maternal vitamin D deficiency in third trimester is 18.8% among pregnant mothers [4]. Normal pregnancy is physiologically characterized by a progressive increase in insulin resistance, which acts as a physiological adaptation aimed at ensuring the adequate supply of glucose to the rapidly growing fetus [5] while, pancreatic beta cells increase their insulin production to compensate pregnancy-induced insulin resistance in healthy women [6]. When insulin secretion is insufficient to overcome insulin resistance and maintain glucose homeostasis in the body, maternal hyperglycaemia may develop [7]. C peptide is produced in equal amounts to insulin and is the best measure of endogenous insulin secretion in patients with diabetes mellitus [8].

GDM has become a public health concern in the world not only because of its high prevalence but also serious maternal and fetal outcomes associated with the disease. It has become a common metabolic disorder in the globe and affects up to 12.9% of all pregnancies worldwide [9]. The pooled global standardized prevalence of GDM was 14.0% [10] The regional standardized prevalence of GDM was 7.1% (7.0% - 7.2%) in North America and Caribbean, 7.8% (7.2% - 8.4%) in the Europe, 10.4% (10.1% - 10.7%) in South America and Central America, 14.2% (14.0% - 14.4%) in Africa, 14.7% (14.7% - 14.8%) in Western Pacific, 20.8% (20.2% - 21.4%) in South East Asia, and 27.6% (26.9% - 28.4%) in Middle East and North Africa [10]. The standardized prevalence of GDM in low-, middle- and high-income countries were 12.7% (11.0% - 14.6%), 9.2% (9.0% - 9.3%) and 14.2 .1% (7.0% - 7.2%) in North America and Caribbean (NAC), 7.8% (7.2%

- 8.4%) in Europe (EUR), 10.4% (10.1% - 10.7%) in South America and Central America (SACA), 14.2% (14.0% - 14.4%) in Africa, 14.7% (14.7% - 14.8%) in Western Pacific, 20.8% (20.2% - 21.4%) in South-East Asia and 27.6% (26.9% - 28.4%) in Middle East and North Africa [10]. In Sri Lanka, the current prevalence of GDM (2014) is 13.9%, and it is a 65.5% rise when compared with the prevalence of GDM reported in 2004 (8.4%) [11] [12].

Universal screening for GDM is done with the 75 g Oral Glucose Tolerance Test (OGTT) performed at 24 - 28 weeks of gestation while screening for pregestational diabetes is advocated at the booking visit in women not known to have preexisting diabetes [13]. According to the guidelines of International Association of Diabetes and Pregnancy Study Group (IADPSG), GDM is diagnosed with a 75 g OGTT when one or more following diagnostic threshold are met; Fasting ≥ 92 mg/dl (5.1 mmol/l), 1-hour ≥ 180 mg/dl (10.0 mmol/l), 2-hour ≥ 153 mg/dl (8.5 mmol/l) [14]. Common perinatal and neonatal complications of GDM include fetal macrosomia, shoulder dystocia, birth injuries, hypoglycemia, polycythemia, hyperbilirubinemia, increased rate of perinatal mortality, still births, neonatal deaths and congenital malformations. Moreover, a systematic review describes that there is a slightly higher risk of major congenital malformations in women with gestational diabetes than in the reference group [15]. While, the offspring of mothers with GDM are at a greater risk of developing childhood obesity and early onset of type 2 diabetes mellitus (T2DM) later in their life [16] [17]. In addition, it has been found that cord blood C peptide from newborns of women with GDM is higher than those with normal glucose tolerance [18]. Further, women with GDM had a 10-fold higher risk of developing T2DM within 10 years after controlling other confounding variables [19]. The known risk factors for GDM include family history of T2DM, maternal overweight and obesity, advanced maternal age, history of GDM, history of having macrosomic babies and multigravida [9] [20] [21]. In addition to these risk factors, recent studies have reported that maternal vitamin D deficiency may also be associated with a higher risk of GDM. Many observational studies have reported that a relationship between low level of vitamin D and increased risk of GDM. In addition to GDM, low levels of vitamin D during pregnancy are associated with preterm deliveries, bacterial vaginosis, anemia and small-for-gestational-age babies and preeclampsia [22]. When the mother is vitamin D deficient during pregnancy their babies are also predisposed to vitamin D deficiency during early infancy and, they can have negative health outcomes including delayed milestones, rickets etc. [1].

The American College of Obstetrics and Gynecology (ACOG) do not recommend routine screening for 25(OH)D level in pregnancy nor vitamin D supplementation beyond what is contained in a prenatal vitamin. However, ACOG suggests that when vitamin D deficiency is identified during pregnancy 1000 - 2000 international units per day of vitamin D is safe [23]. The current scoping review is aimed to map the existing literature on the association between maternal 25(OH)D deficiency and incidence of developing GDM.

2. Methods

2.1. Overview

PRISMA for scoping review presentation guidelines [24] and scoping review guidelines proposed by Arksey & O'Malley (2005) [25] was followed in articles' screening and methodological process.

2.2. Search Strategy

Comprehensive literature survey was carried out using two search engines including Google Scholar and Pub Med. Original research studies published in English in Google Scholar and PubMed from January 2012 to December 2022 were selected using the search terms of "gestational diabetes mellitus/pregnancy outcomes" combined with "vitamin D", "cholecalciferol" or "25-hydroxyvitamin D" and/or "deficiency".

2.3. Inclusion and Exclusion Criteria

Original research articles which have been published only in English language in Google Scholar and PubMed from January 2012 to December 2022 were included in the study.

Research using subjects with multiple pregnancy, chronic diseases including pre-existing diabetes mellitus, thyroid deficiencies and, review articles, case reports, systematic reviews and meta-analysis, studies designed on animal models, studies with missed data & duplicate publications and studies published in languages other than English were excluded.

2.4. Data Extraction

The screening process was conducted using the PRISMA extension for scoping reviews [24] (**Figure 1**). Overall, 136 original research articles were initially identified through data base searching using above mentioned key words, and 2 additional articles were identified through screening of references in relevant systematic reviews. Selected articles were screened initially in title and abstract level to remove duplicates. Thereafter, articles were screened in full text level to select relevant studies based on the inclusion and exclusion criteria of this scoping review. Finally, altogether 55 original research articles (48 observational studies & 7 RCTs) were selected to the present review article (**Figure 1**). It involved 48 observational studies (9 cross sectional studies, 18 prospective cohort studies, 4 retrospective cohort studies, 9 nested case control studies, 8 case control studies) and 7 Randomized Control Trials (RCT). Articles were screened at the title and the abstract level and at full text by three co-investigators of the study independently with a fourth reviewer resolving discrepancies.

Extracted data included study design, nation, number of study participants, sampling timing for 25(OH)D, publication year and results (odds ratios with confidence intervals for the association between vitamin D deficiency and the diagnosis of GDM). Additionally, from RCTS data on treatment group, sample

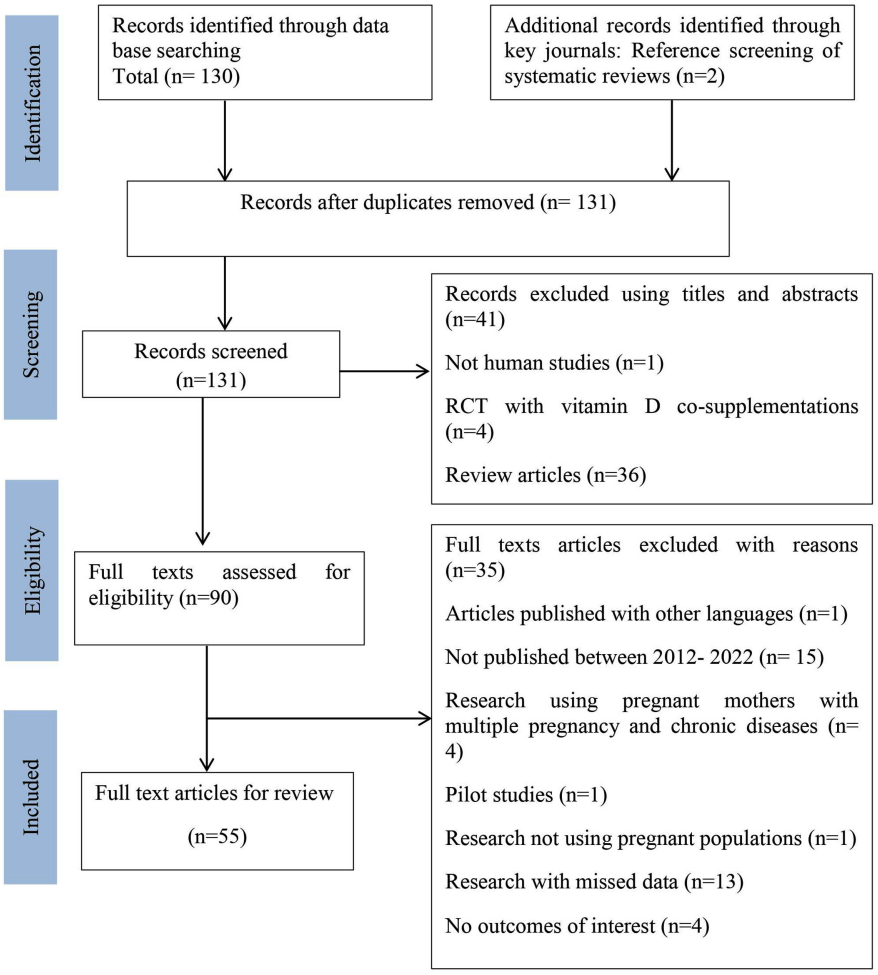

Figure 1. Flow chart of the review process.

size, dosage/intervention, treatment duration, timing of vitamin D intervention were included.

3. Results

3.1. Article Characteristics

The present scoping review comprising 48 observational studies and 7 RCTs published between January 2012 and December 2022. Observational studies involved 8 cross sectional studies, 18 prospective cohort studies, 4 retrospective cohort studies, 10 nested case control studies and 8 case control studies. Several studies in the world have been conducted to explore the association between GDM and maternal vitamin D deficiency. This review included altogether 55 original research articles published in different areas such as Finland, Turkey, Saudi, Spain, USA, Canada, India, Australia, Korea, Egypt, Russia, China, Iran, Malaysia, New Zealand, Taiwan (China), Istanbul, Norway, Central Europe, Iceland, Brazil, Belgium & France. Among them, most of the studies had been conducted in China (9 out of 55).

The majority of the studies exploring the relationship between GDM and ma-

ternal vitamin D deficiency were prospective cohort studies (18 out of 55 studies) (Table 1).

Table 1. Summary of observational studies on maternal vitamin D status and incidence of GDM.

S/N	Study design	No. of subjects (Nation)	Sampling for serum 25(OH)D (Trimester/Weeks)	Cut off value for 25(OH)D deficiency/ insufficiency	Results(Maternal vitamin D level vs. incidence of GDM)	Reference
1	Cross sectional	886 (Spain)	Second trimester	<20 ng/mL	Vitamin D deficiency is associated with GDM, independent of BMI.	[26]
2	Cross sectional	80 (Turkey)	Second trimester	10 - 20 ng/mL	Serum vitamin D levels in women with GDM are significantly lower than the controls.	[27]
3	Cross sectional	90 (Iran)	20 - 30 weeks	10 - 20 ng/ml	Serum 25(OH)D level is significantly low in GDM group.	[28]
4	Cross sectional	78 (Malaysia)	Third trimester	<12 ng/ml	Women with GDM had lower vitamin D status which was associated with ethnicity and less outdoor activity.	[29]
5	Cross sectional	228 (Philippine)	Second & third trimesters	≤20 ng/ml.	An association found between low level of (≤30 ng/ml) maternal serum vitamin D level and GDM (OR = 0.28; 95% CI = 0.09 - 0.88) but none was evident after adjusting for possible confounders (OR = 0.66; 95% CI = 0.18 - 2.36).	[30]
6	Cross sectional	723 (Finland)	11 weeks	<50 nmol/L	No association found.	[58]
7	Cross sectional	1400 (Turkey)	24 - 28 weeks	<20 ng/mL (Severe deficiency)	No association found.	[59]
8	Cross sectional	80 (Iran)	24 - 28 weeks	<20 ng/dL	No association found.	[60]
9	Prospective cohort	1314 (USA)	26 - 28	25 - 50 nmol/L	Pregnant mothers with 25(OH)D levels of 25 nmol/L may have higher odds of experiencing GDM (OR: 2.2, 95% CI: 0.8 - 5.5).	[31]
10	Prospective cohort	515 (Saudi)	First trimester	<50 nmol/L	GDM risk was significantly higher among vitamin D deficient group (OR: 2.87; Confidence Interval: 1.32 - 6.25; P = 0.008	[32]
11	Prospective cohort	655 (Canada)	06 - 13	<50 nmol/L	Lower first trimester 25(OH)D level is associated with higher risk of developing GDM (OR = 1.48; 95% CI = 1.03 - 2.12), and higher HOMA-IR (r = −0.08; P = 0.03).	[33]
12	Prospective cohort	392 (South India)	12 weeks	<50 nmol/L	Vitamin D deficiency in early pregnancy is significantly associated with developing GDM.	[34]
13	Prospective cohort	890 (Australia)	18 weeks	<30 nmol/L	Second trimester low maternal 25(OH) D levels (<30 nmol/L) are associated with GDM (OR = 14.63, 95% CI = 1.59 - 134.78).	[35]

Continued

14	Prospective cohort	2800 (Australia & New Zealand)	15 ± 1 weeks	<50 nmol/L	GDM risk was observed with high (>81 nmol/L) "standardised" vitamin D status when compared to moderate-high (63 - 81 nmol/L)	[36]
15	Prospective cohort	64 (Turkey)	24 - 28	<10 ng/l (Severe deficiency)	25(OH)D levels were negatively correlated with HOMA-IR ($P < 0.001$).	[37]
16	Prospective cohort	3318 (China)	8 - 14 weeks	<20 ng/ml	Vitamin D deficiency in T_2 was associated with an increased risk of GDM with increased FBG of OGTT.	[38]
17	Prospective cohort	674 (USA)	<16	<50 nmol/L	There was a negative association between 25(OH)D and maternal hyperglycaemia among smokers (OR = 0.30; 95% CI = 0.13 - 0.68) while no association found among non-smokers.	[39]
18	Prospective cohort	1710 (New Zealand)	15	<50 nmol/l	No association found.	[40]
19	Prospective cohort	523 (Korea)	24 - 28 20 - 22 32 - 34	<25 nmol/L	No association found.	[61]
20	Prospective cohort	80 (Egypt)	24 - 28	<20 ng/mL	No association found.	[62]
21	Prospective cohort	785 (Australia)	6 - 14 & 14 - 18	<12.5 nmol/L (Severe deficiency)	No association found.	[63]
22	Prospective cohort	524 (Canada)	17 - 18	<50 nmol/L	No association found.	[64]
23	Prospective cohort	785 (Norway)	15 - 28 weeks	<50 nmol/L	No association found.	[65]
24	Prospective cohort	3110 (China)	First trimester	<20 ng/ml	No association found.	[66]
25	Prospective cohort	938 (Iceland)	11 - 14 weeks	<30 nmol/L	No association found.	[67]
26	Prospective cohort	1516 (China)	11 - 14 weeks	<50 nmol/L	No association found.	[68]
27	Retrospective cohort	8468 (China)	<20 weeks	<20 ng/ml	Vitamin D level > 20 ng/mL can reduce the risk of GDM (OR = 0.90).	[41]
28	Retrospective cohort	2814 (China)	≤20 weeks	<50 nmol/L	A protective association was found between higher serum 25(OH)D concentrations and GDM ($P = 0.003$).	[42]
29	Retrospective cohort	7816 (China)	6 - 14 weeks	<20 ng/ml	No association found.	[69]
30	Retrospective cohort	235 (USA)	5 - 12 weeks	<20 ng/ml	No association found.	[70]
31	Nested case control	400 (China)	26 - 28	<25 nmol/L	Subjects with 25(OH)D deficiency had 1.8-fold higher risk of GDM (OR: 1.800, 95% CI: 1.209 - 2.678, $P = 0.004$).	[43]
32	Nested case control	210 (India)	<20	<20 ng/mL	Women with vitamin D deficiency in early pregnancy were eleven times more likely to have GDM compared to controls ($P = 0.001$)	[44]

Continued

33	Nested case control	335 (Canada)	15 - 18	<75 nmol/l (Insufficient)	Vitamin D insufficiency in early pregnancy is associated with a greater than twofold increase in subsequent gestational diabetes, even after matching and adjusting for race, age, season and weight.	[45]
34	Nested case control	321 (USA)	10 - 14 23 - 31 33 - 39	<50 nmol/L.	Women with persistent vitamin D deficiency at 10 - 14 and 15 - 26 weeks of gestation had a 4.46-fold elevated risk for GDM.	[46]
35	Nested case control	2320 (Canada)	<20 weeks	<30 nmol/L	In smokers, significant increased odds of developing GDM was seen among women with 25(OH)D < 30 nmol/L [aOR = 3.73, 95% CI 1.9, 7.14] compared to non-smokers with 25(OH)D concentration ≥50 nmol/L.	[47]
36	Nested case control	652 (USA)	16	<20 ng/mL or <50 nmol/L	No association found.	[48]
37	Nested case control	180 (USA)	11 - 14	<50 nmol/L.	No association found.	[71]
38	Nested case control	1191 (Belgium & France)	11 - 15	<10 ng/mL (deficiency) <20 ng/mL (insufficiency)	No association found.	[72]
39	Nested case control	318 (Russia)	8 - 14 & 24 - 32	<20 ng/mL	No association found.	[73]
40	Nested case control	5109 (Australia)	First trimester	<25 nmol/L	No association found.	[74]
41	Case control	120 (Turkey)	26 - 28	<25 ng/mL	Vitamin D deficiency in the second trimester was inversely correlated with fasting and 1-h plasma glucose after 75 g glucose challenge test ($P < 0.001$), also low 25 OHD3 levels were associated with insulin resistance.	[49]
42	Case control	60 (Korea)	Third trimester	<20 ng/mL	Serum levels of 25(OH)D were lower in women with GDM ($P < 0.01$).	[50]
43	Case control	70 (India)	<28 weeks	<20 ng/ml	Vitamin D deficiency is more frequently associated with GDM than the controls.	[51]
44	Case control	80 (Egypt)	<28 weeks	<10 ng/ml	Serum 25 (OH)D had a significant negative correlation with fasting insulin level ($P = 0.05$).	[52]
45	Case control	40 (Turkey)	24 - 28	<10 ng/mL	No association found.	[75]
46	Case control	157 (Brazil)	Third trimester	<10 ng/ml	No association found.	[76]
47	Case control	76 (Central Europe)	24 - 30 weeks	<50 nmol/L	No association found.	[77]
48	Case control	122 (Istanbul)	24 - 28	≤20 ng/ml	No association found.	[78]

3.2. Cross Sectional Studies

Out of 8 cross sectional studies involved in this literature survey, only 5 studies had found an association between maternal vitamin D deficiency and GDM [26] [27] [28] [29] [30]. [26] further showed that vitamin D deficiency is associated with GDM independent of maternal BMI. A study conducted in Iran reported a negative significant correlation between 25(OH)D and, fasting blood sugar (P = 0.009) and pre-pregnancy BMI in their population [28]. Another cross sectional study conducted in Malaysia found that women with GDM had lower vitamin D status which was associated with ethnicity and less outdoor activity while, they further reported that there was no correlations between serum 25(OH)D and parameters of hyperglycaemia or insulin sensitivity in GDM pregnancies [29]. Although, [30] reported an association between maternal vitamin D level and incidence of GDM, they found no association between two variables after adjusting for possible confounders like age, parity, history of GDM and pre-pregnancy BMI (**Table 1**).

3.3. Prospective Cohort Studies

Out of 18 prospective cohort studies included in the current study, only 9 studies have reported an association between maternal 25(OH)D deficiency and GDM [31]-[39]. [32] described that low levels of 25(OH)D at first trimester is an independent risk factor for developing GDM and is associated with insulin resistance at second trimester. [33] further reported that the strength of association between vitamin D levels and the risk of GDM was enhanced by adding potential confounders of vitamin D (OR = 1.37; 95% CI = 1.04 - 1.81 in unadjusted model increasing to 1.47 after adjustment for factors influencing vitamin D). A prospective cohort study conducted among 890 Australian pregnant mothers reported that participants with 25(OH)D levels < 30 nmol/L were had a 10.7- fold higher risk of developing GDM (OR = 14.63, 95% CI = 1.59 - 134.78), and that association was stronger (OR 12.52, 95% CI = 1.27 - 23.75), when maternal age, family history of diabetes, pre-pregnancy BMI and gestational weight were considered as [35]. Another study conducted in Turkey also reported that 25(OH)D levels are negatively correlated with HOMA-IR [37]. Another study showed that maternal vitamin D deficiency in second trimester was associated with an increased risk of GDM (OR = 2.87; CI = 1.32 - 6.25) with increased fasting blood glucose (FBG) values of OGTT [38]. A prospective cohort study carried out among 674 pregnant mothers in USA found that serum 25(OH)D level was lower among smoking women with maternal hyperglycaemia, and a negative association was found between 25(OH)D at <16 weeks and the likelihood of maternal hyperglycaemia, while no association found among non-smokers [39]. A same type of study conducted in New Zealand showed maternal 25(OH)D levels < 30 ng/mL at 15 weeks of gestation were associated with the development of GDM, but after adjustment with body mass index (BMI) and ethnicity, the association was not significant [40] (**Table 1**).

3.4. Retrospective Cohort Studies

Two out of four retrospective cohort studies conducted in China had found an significant protective association between higher maternal serum 25(OH)D concentration and incidence of GDM [41] [42] (**Table 1**).

3.5. Nested Case Control Studies

With regards to nested case control studies, 5 out of 10 studies had found an association between maternal 25(OH)D level and GDM [43] [44] [45] [46] [47]. A study conducted in China reported that pregnant mothers with 25(OH)D deficiency has 1.8-fold higher risk of GDM [43], while a study conducted in India reported that women with vitamin D deficiency in early pregnancy were eleven times more likely to have GDM compared to controls [44]. Another nested case control study conducted in Canada reported that vitamin D insufficiency in early pregnancy is associated with a greater than twofold increase in subsequent gestational diabetes, even after matching and adjusting for race, age, season and weight [45]. While, [46] showed that women with persistent vitamin D deficiency at 10 to 14 and 15 to 26 weeks of gestation had a 4.46-fold elevated risk for GDM. Another study conducted in Canada reported that women who smoked during pregnancy and had 25(OH)D concentrations < 30 nmol/L had an adjusted Odds Ratio = 3.73 [95% CI 1.95, 7.14] compared to nonsmokers with 25(OH)D concentrations ≥ 50 nmol/L [47]. Accordingly, the authors had detected an additive interaction between smoking status and 25(OH)D level [47]. A study conducted in the United States of America (USA) reported that GDM cases had lower mean total 25(OH)D and 25(OH)D3 but, total 25[OH]D concentrations were not significantly associated with GDM risk [48] (**Table 1**).

3.6. Case Control Studies

Out of 8 case control studies, only 4 studies had found that maternal 25(OH)D deficiency is associated with incidence of developing GDM [49] [50] [51] [52]. A study conducted in Turkey reported that vitamin D deficiency in the second trimester was inversely correlated with fasting and 1-h plasma glucose after 75 g glucose challenge test, and low 25OHD3 levels were associated with insulin resistance [49]. A study conducted in Egypt reported that serum 25 (OH)D had a significant negative correlation with fasting insulin level (P = 0.05) [52] (**Table 1**).

3.7. Randomized Controlled Trials (RCTs)

With regard to the previous RCTs, 5 out of 7 RCTs have found that a significant relationship between vitamin D supplementation and incidence of GDM [53] [54] [55] [56] [57]. A study conducted in Iran administered 50,000 IU of vitamin D3 to their test group twice during the pregnancy (at baseline & at day 21) and control group was given a placebo. They found that vitamin D supplementation significantly deceased concentrations of FPG (P < 0.001), serum insulin (P = 0.01) & HOMA-IR (P < 0.001) among their study population [54]. Similar study

conducted in China divided their control group into three groups (low dose, medium dose and high dose) based on the dose of vitamin D supplement [55]. They administered 200 IU of calciferol daily as the low dose until the delivery (n = 38) while, 2000 IU daily for 25 days as the medium dose (n = 38), and 4000 IU daily for 12.5 days as the high dose (n = 37) [55]. Their results revealed that high and medium doses of vitamin D supplementation reduces Insulin and HOMA-IR levels in mothers with GDM ($P < 0.01$) [55]. Another study conducted in China reported that vitamin D supplements (vitamin D3) statistically reduce FPG ($P = 0.04$), serum insulin (0.03) & HOMA-IR ($P = 0.01$) [57]. Results of RCTs are displayed in Table 2.

Table 2. Summary of RCTs on vitamin D supplementation and incidence of GDM.

S/N	Nation	Treatment group	Sample size	Dosage/ Intervention	Treatment Duration	Timing of vitamin D intervention	Results	Reference
1	Europe	Vitamin D Placebo	70 70	50,000 IU/2 weeks	10 weeks	14 - 16	No association found between vitamin D supplementation and developing GDM.	[79]
2	Iran	Vitamin D Placebo	46 45	5000 Units/week	Until the 26th week	First trimester	Incidence of GDM in intervention group was statistically lower than in control group ($P < 0.001$)	[53]
3	Iran	Vitamin D_3 Placebo	36 36	50,000 IU/2 weeks	10 months	24 - 28 weeks	Vitamin D supplements were associated with a significant decrease in fasting glucose ($P = 0.01$) and HbA1c ($P = 0.02$).	[54]
4	China	Calciferol Low dose Medium dose High dose Placebo	38 38 37 20	200 IU/daily 2000 IU/daily 4000 IU/daily	Until the delivery 25 days 12.5 days	24 - 28 weeks	High and medium doses of vitamin D supplementation reduces Insulin and HOMA-IR levels in mothers with GDM ($P < 0.01$).	[55]
5	Australia	Vitamin D_3 High dose Low dose Nonrandomized	89 90 24	5000 IU/daily 400 IU/daily	Until the delivery (from <20 weeks)	<20 weeks	No association found between vitamin D supplementation and developing GDM.	[80]
6	Iran	Vitamin D_3 Placebo	27 27	50,000 IU twice (at baseline & day 21)	6 weeks	24 - 28 weeks	Vitamin D supplementation significantly decreases concentrations of FPG ($P < 0.001$), serum insulin ($P = 0.01$) & HOMA-IR ($P < 0.001$).	[56]
7	China	Plain yogurt with vitamin D_3 Plain yogurt without vitamin D_3	52 51	Two servings (200 g) of supplemented yogurt per day (500 IU vitamin D3 per serving)	16 weeks	13 weeks	Vitamin D supplements statistically reduce FPG ($P = 0.04$), serum insulin (0.03) & HOMA-IR ($P = 0.01$).	[57]

4. Discussion

Out of 55 research articles included in the current scoping review, only 30 research articles had found an association between maternal vitamin D status and incidence of GDM. The majority of research articles were based on prospective cohort studies (18 out of 55). Among all research articles only one prospective cohort study has reported that GDM risk is high with high "standardized" vitamin D status (>81 nmol/L) when compared to moderate-high (63 - 81 nmol/L) [35]. Some studies had found that maternal vitamin D deficiency is an independent risk factor for developing GDM among pregnant mothers even after adjusting to some contributing factors such as race/ethnicity, body mass index [44] while, some studies had reported that there was no association found after adjusting for possible confounding factors such as smoking status, indoor activity, ethnicity and age [29] [38] [46].

Moreover, studies had reported that maternal 25(OH)D deficiency is associated with higher HOMA-IR [32], and vitamin D supplementation during pregnancy has an effect on decreasing fasting plasma glucose, HbA1c, insulin and HOMA-IR in the body [53] [54] [55] [56].

5. Conclusion

Vitamin D level of pregnant mothers with GDM is significantly lower than the normoglycaemic mothers and maternal vitamin D deficiency is associated with increased risk of developing GDM. Maternal vitamin D level is negatively correlated with HOMA-IR and vitamin D deficiency contributes to increase fasting plasma glucose level in OGTT. A protective association was found between higher serum 25(OH)D concentrations and GDM. In conclusion, the present study suggests that early detection and treatment of vitamin D deficiency during pregnancy is necessary in preventing GDM.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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